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IN SILICO STUDY OF SOME NATURAL FLAVONOIDS AS POTENTIAL AGENTS AGAINST COVID-19: PRELIMINARY RESULTS

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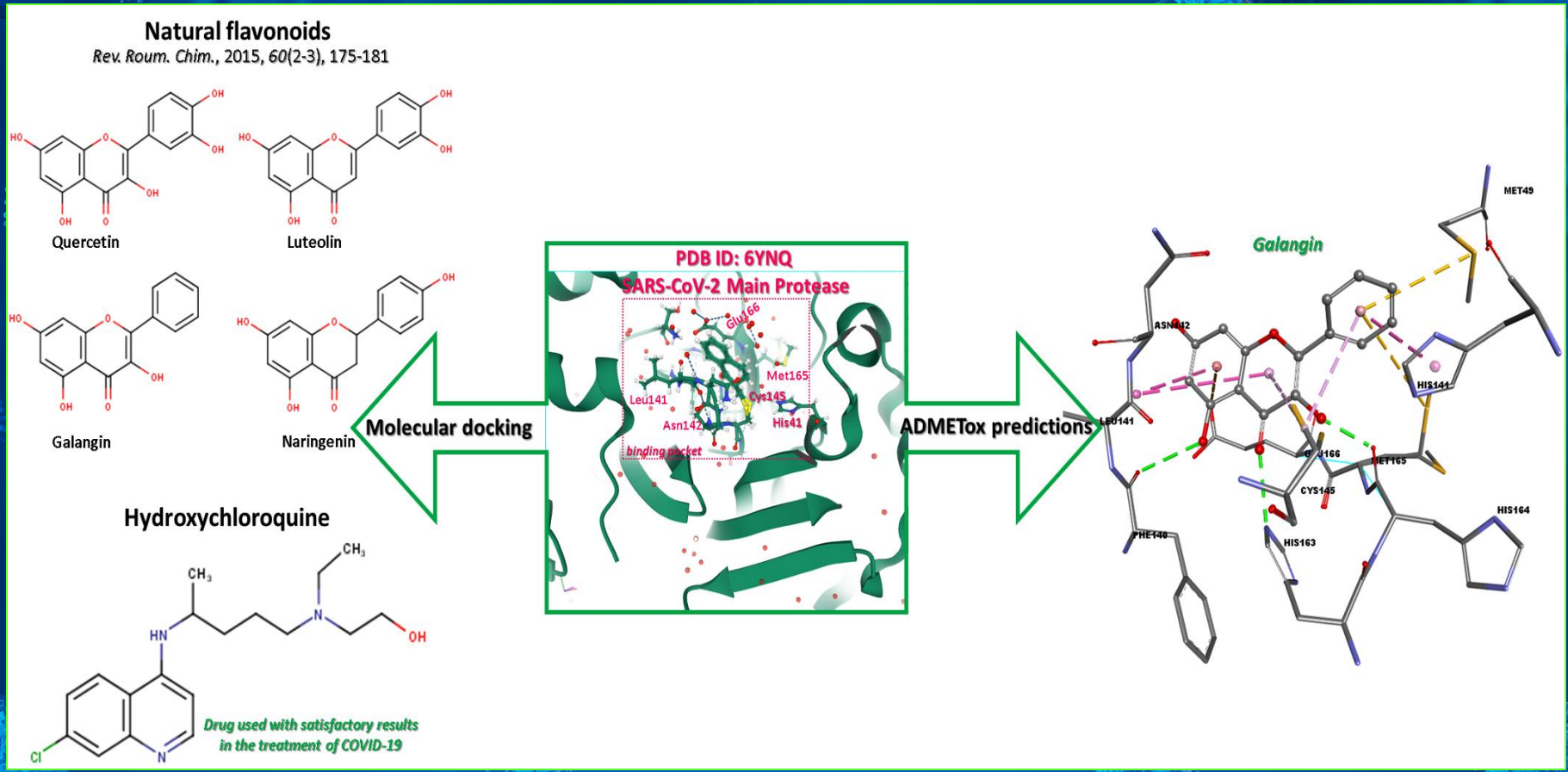
OVERVIEW

- Flavonoids, widely distributed in fruits, vegetables, and medicinal herbs, are compounds with multiple biological benefits to human health from anti-inflammatory, antioxidant, anticancer, antibacterial to antiviral activity.
- Coronavirus disease 2019 (Covid-19), a serious concern in the world today, is a disease of the respiratory tract involving moderate to severe symptoms of pneumonia, with a major incidence in older people and patients having chronic diseases. This emergency health situation led us to evaluate the possible use of natural products to prevent respiratory diseases.
- The present study aims to report the potential of four natural flavonoids, known to have anti-inflammatory and antiviral activity, as anti-SARS-CoV-2 through their binding on the 6YNQ protein receptor and pharmacokinetic profiles.
- Molecular docking study with the FRED program was chosen as an appropriate tool to analyze the interaction of natural flavonoids, quercetin, luteolin, galangin, and narigenin, with the SARS-CoV-2 main protease and to rank the conformations through a scoring function to predict their binding affinity.
- The preliminary results indicate the potential of the titled natural flavonoids to fight the new coronavirus, Covid-19, with galangin showing excellent inhibitory profile against SARS-CoV-2 compared with control, hydroxychloroquine.

Computational workflow scheme



METHODS

Ligands preparation

QUERCETIN, LUTEOLIN, NARINGENIN, GALANGIN, HYDROXYCHLOROQUINE

Ionization states/tautomers – **LigPrep** (Schrödinger; https://www.schrodinger.com)

Conformers – **Omega** (OpenEye; http://www.eyesopen.com)

Protein preparation

6NYQ - SARS-CoV-2 main protease (Mpro) bound to 2-methyl-1-tetralone (P6N)

active site box of 2400Å^3

outer/inner contours of 1088Å^3 /113Å^3 → **Make Receptor** (OpenEye; http://www.eyesopen.com)

Molecular docking

Quercetin, Luteolin, Naringenin
Galangin, Hydroxychloroquine

6NYQ

→ **FRED** (OpenEye; http://www.eyesopen.com)

- default parameters
- CG4 (Chemgauss 4 to score ligads pose placement in 6NYQ active site)

Prediction of pharmacokinetic profile

QPPCaco, QPPMDCK, QPlogKhsa,
QlogBB , CNS , PSA, %HOA

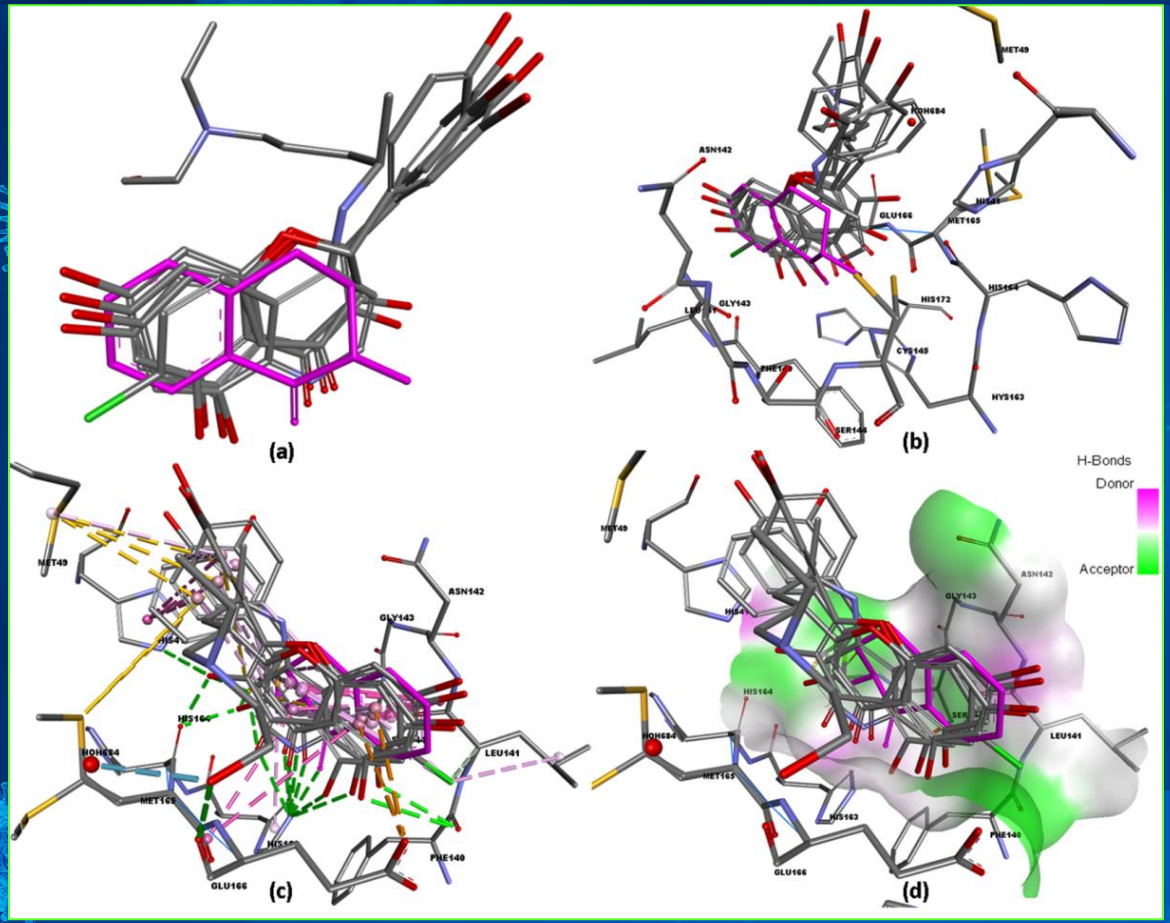
→ **QikProp** (Schrödinger; https://www.schrodinger.com)

Toxicity properties

→ **pkCSM** (http://biosig.unimelb.edu.au/pkcsm/prediction)

RESULTS AND DISSCUSSIONS

Molecular docking analysis

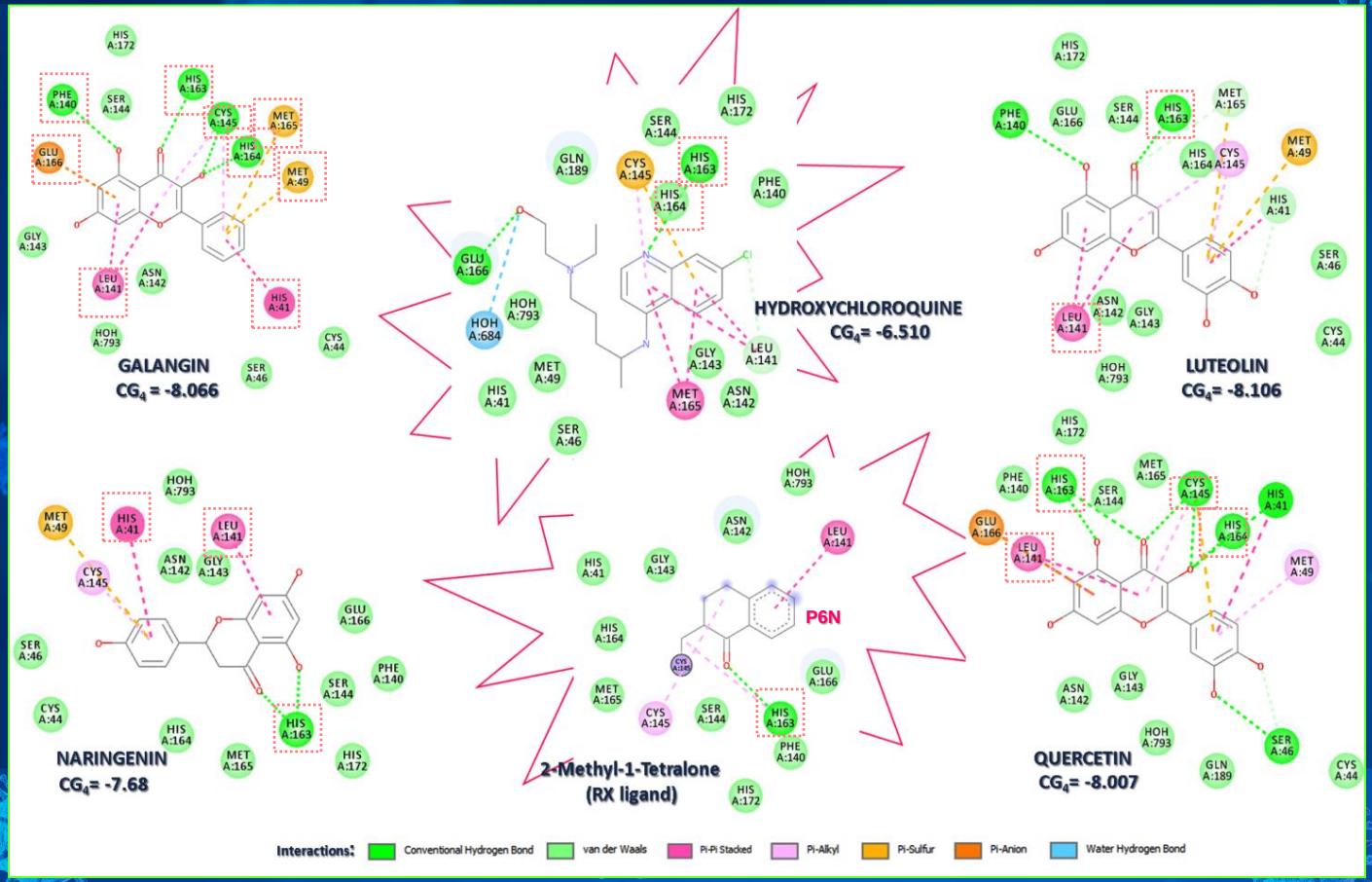


Different perspectives of the docked protein-ligand complex.

a) the hydroxychloroquine, flavonoids, and co-crystallized ligand structures superposition
b) the binding orientation of the structures of the ligands in the 6YNQ active site
c) the significant hydrogen-bond and hydrophobic interactions established by the ligands with the key residues of the 6NYQ active site
d) the donor and acceptor surfaces around ligands

RESULTS AND DISSCUSSIONS

Molecular docking analysis

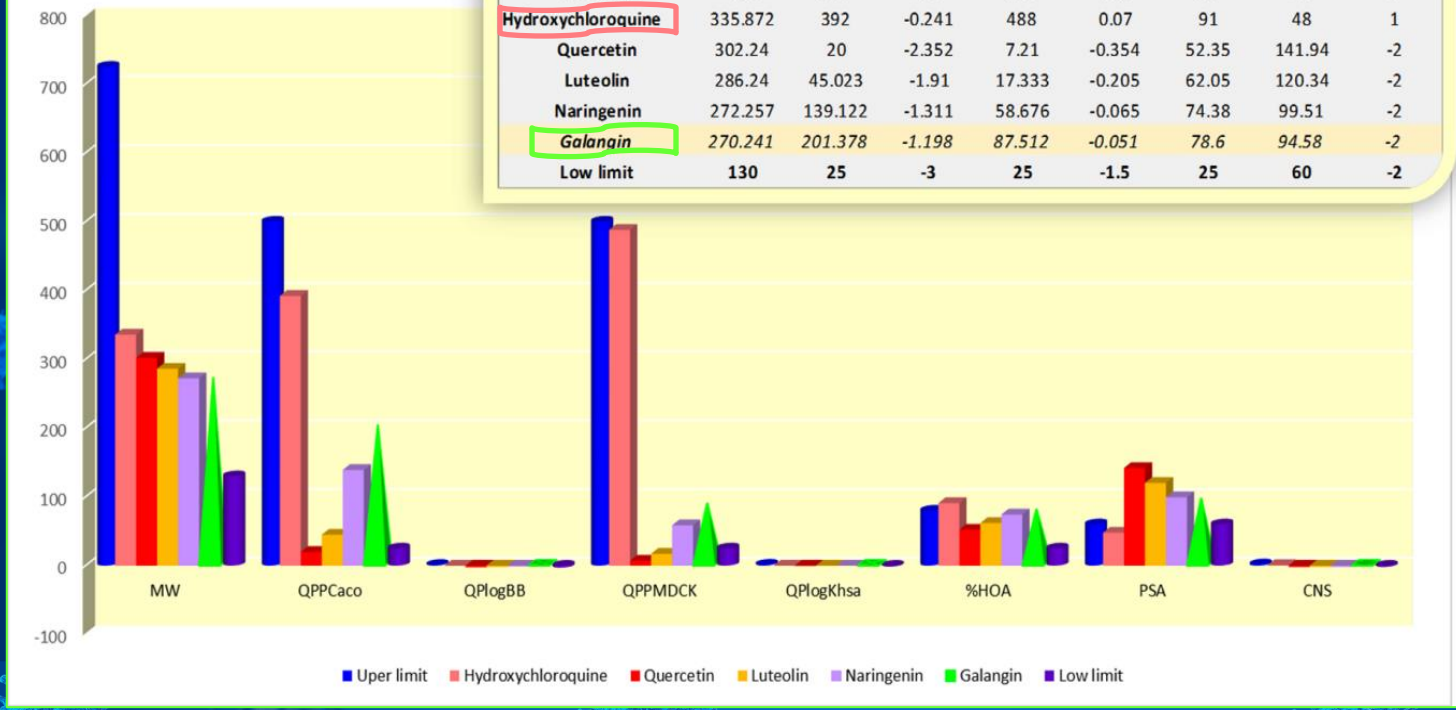


2D-representation of key interactions between hydroxychloroquine, natural flavonoids, co-crystallized P6N ligand, and the 6YNQ binding site the CG4 docking score

RESULTS AND DISSCUSSIONS

Pharmacokinetic and toxicological properties analysis

Compounds	MW	QPPCaco	QPlogBB	QPPMDCK	QPlogKhsa	%HOA	PSA	CNS
Uper limit	725	500	1.2	500	1.5	80	60	2
Hydroxychloroquine	335.872	392	-0.241	488	0.07	91	48	1
Quercetin	302.24	20	-2.352	7.21	-0.354	52.35	141.94	-2
Luteolin	286.24	45.023	-1.91	17.333	-0.205	62.05	120.34	-2
Naringenin	272.257	139.122	-1.311	58.676	-0.065	74.38	99.51	-2
Galangin	*270.241*	*201.378*	*-1.198*	*87.512*	*-0.051*	*78.6*	*94.58*	*-2*
Low limit	130	25	-3	25	-1.5	25	60	-2



Numerical values and graphical representation of the QikProp properties

Excepting quercetin with possible mutagenic and tumorigenic toxicity risks, galangin, luteolin and naringenin did not show any human toxicity alerts

Hydroxychloroquine exhibit possible hepatotoxicity likely due to quinoline unit, inhibition of HERG II channels, and risks of mutagenicity, demonstrating high degree of toxicity

QPPCaco -Predicted apparent Caco-2 cell permeability in nm/sec: >500 (great) and <25 (poor); QlogBB - Predicted brain/blood partition coefficient: -3.0 to 1.2; QPPMDCK -Predicted apparent MDCK cell permeability in nm/sec: >500 (great) and <25 (poor); CNS -Predicted central nervous system activity: –2 (low) to +2 (high); QPlogKhsa - Prediction of binding to human serum albumin): -1.5 (low)to 1.5 (high); %HOA - Predicted human oral absorption on 0 to 100% scale: >80% (high), 25-80% (medium) and <25% (poor); PSA -Van der Waals surface area of polar nitrogen and oxygen atoms: >60 does not cross the blood/brain barrier; <60 to cross the blood/brain barrier

CONCLUSIONS

- We have carried out molecular docking and pharmacokinetic studies of four natural flavonoids and hydroxychloroquine with SARS-CoV–2 main protease receptor.
- The docking results (binding energy and key interactions) and pharmacokinetic profiles were compared with hydroxychloroquine, a repurposed drug with potential benefits against COVID–19.
- Our results revealed that all flavonoids exhibited higher docking scores than hydroxychloroquine against the SARS-CoV–2 protease.
- One out of four flavonoids, GALANGIN, showed pharmacological properties similar to hydroxychloroquine, with particular improvement in its potential of not permeates the CNS. Also, GALANGIN displayed the highest number of interactions with the largest number of amino acid residues including (i) hydrogen bonds – 4 with HIS163, HIS164, CYS145, PHE140 (ii) π-π stacked – 3 with LEU141, HIS41, (iii) π-alkyl – 1 with CYS145, (iv) π-sulfur – 2 with MET49, MET165 and (v) π-anion – 1 with GLU166
- Therefore, based on the promising docking and pharmacokinetic outcomes and the medicinal relevance of GALANGIN, we suggest being further evaluated as a possible repurposed drug to combat COVID-19.

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