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MANUKA HONEY AND ITS FLAVONOID COMPONENTS - AN AFFORDABLE THERAPEUTIC OPTION TO FIGHT SARS-COV-2 INFECTIONS: IN SILICO EVALUATION

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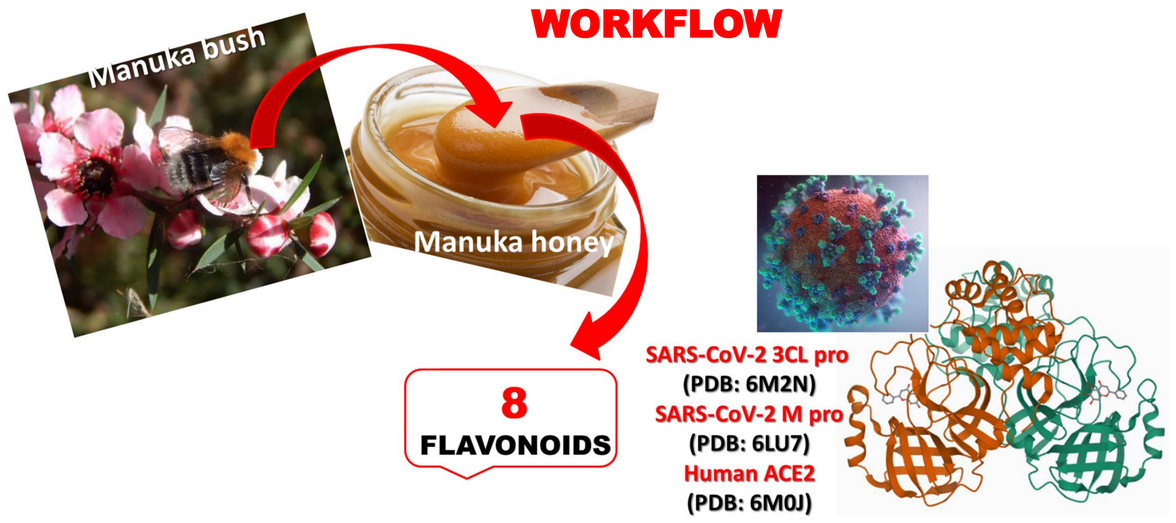
OVERVIEW

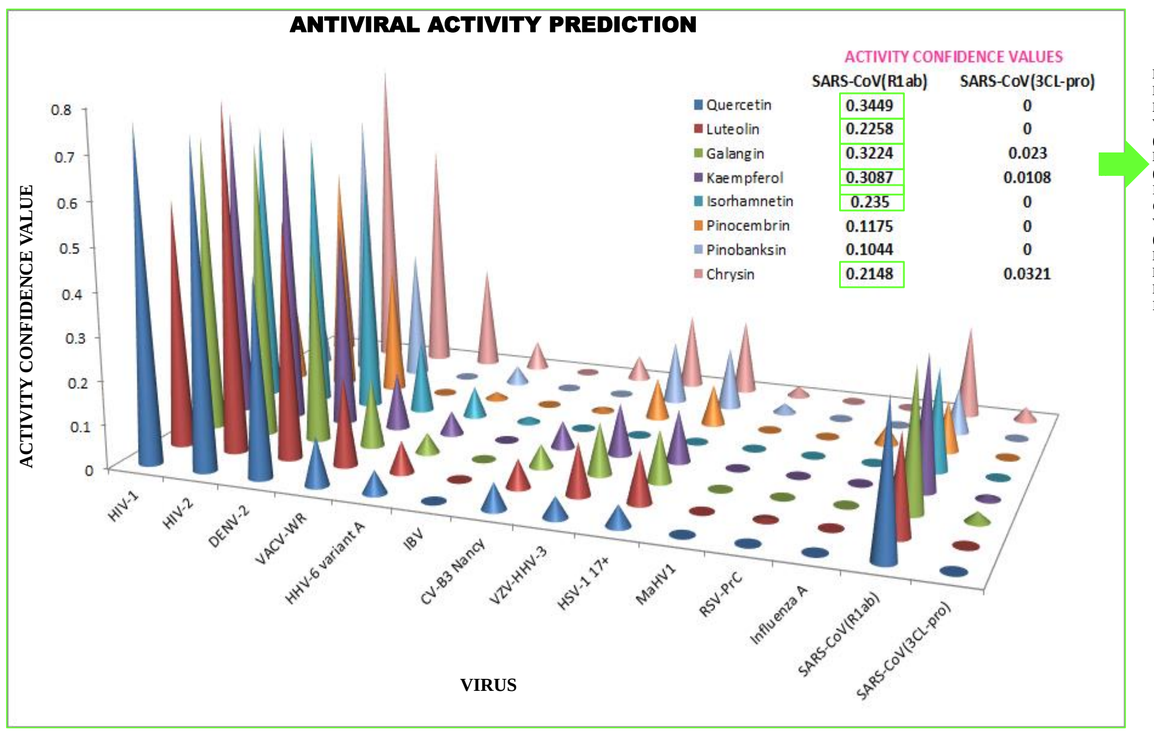
Coronaviruses (COVs) are a group of RNA viruses, involving SARS, MERS, and COVID-19, which provoke mild to severe respiratory illness. Coronavirus disease 2019 (COVID-19), a severe acute respiratory syndrome induced by coronavirus 2 exposure (SARS-CoV-2), has spread rapidly and caused a global pandemic, resulting in a large number of confirmed cases and deaths (e.g. global situation at 24 September 2021, 230418451 confirmed cases and 4,724,876 deaths, https://covid19.who.int/). To date, remdesivir is the only FDA-approved drug to manage COVID-19 infection.

Manuka honey (the product of the New Zealand bush, *Leptospermum scoparium*) is very popular due to its antibacterial, antimicrobial, and anti-inflammatory properties. Moreover, it can be applied topically for skin-healing benefits, and in acute cough caused by upper respiratory tract infection, which is the main symptom of COVID-19. *Due to its demonstrated antiviral efficacy, Manuka Honey and its components can be safely evaluated as an alternative option for patients with COVID-19. So far, there are no published theoretical studies evaluating the effects of honey on SARS-CoV-2, except for four registered clinical trials.*

Aim: The present study aims to report the potential of eight natural flavonoids components of Manuka Honey as anti-SARS-CoV-2 through their binding on 3C-like protease (3CLpro), main protease (Mpro) and viral target angiotensin-converting enzyme 2 (ACE2). Molecular docking study was selected as an appropriate tool to evaluate the interaction of natural flavonoids, *quercetin, luteolin, galangin, kaempferol, isorhamnetin, pinocembrin, pinobanksin and chrysin*, with the SARS-CoV-2 proteases and ACE2 and to rank the conformations through a scoring function to predict their binding affinity. Additionally, drug-likeness and toxicity related parameters were evaluated.

WORKFLOW





SARS-CoV(R1ab)= SARS coronavirus with Replicase polyprotein 1ab protein target; SARS-CoV(3CL-pro)= SARS coronavirus with SARS coronavirus 3C-like proteinase target

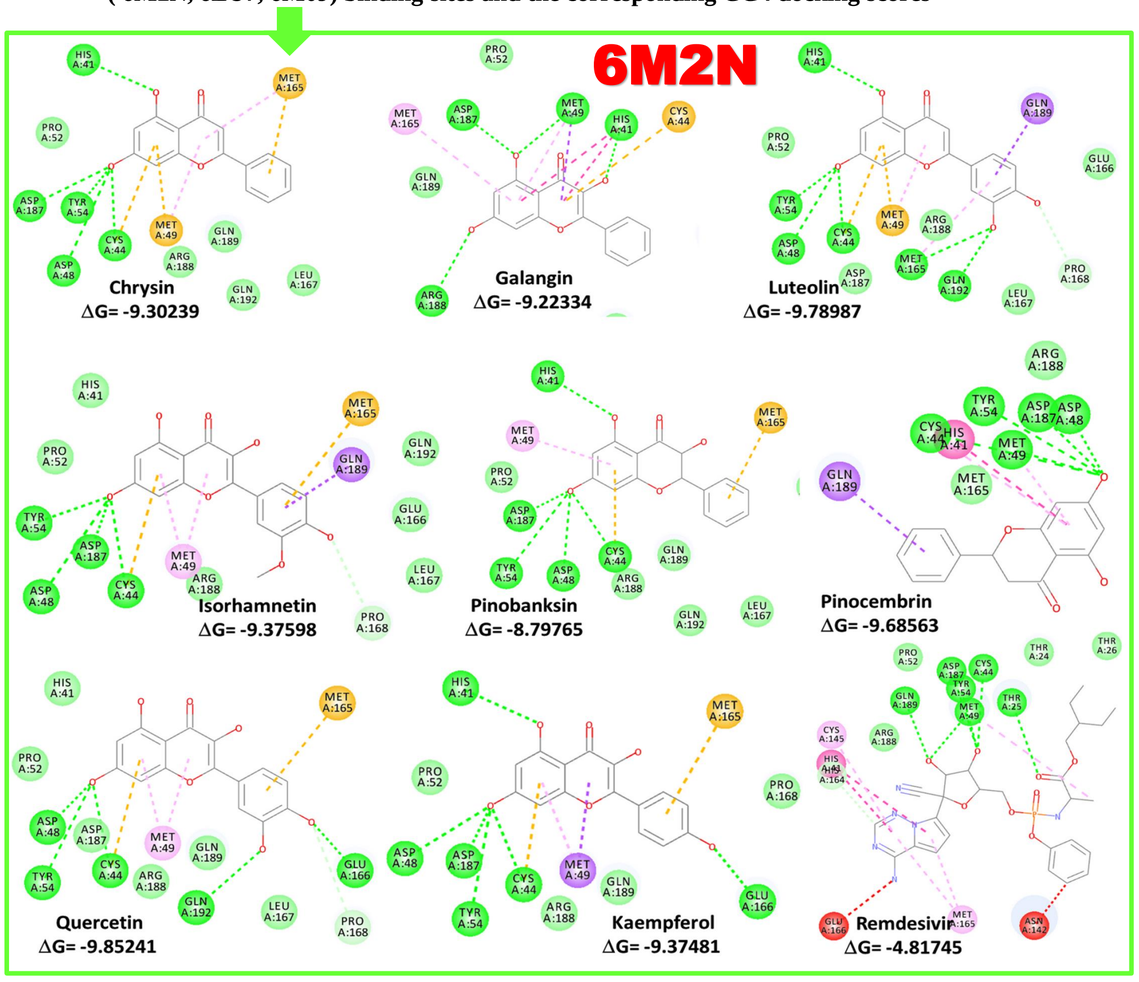
HIV-1 = Human immunodeficiency virus 1;
HIV-2 = Human immunodeficiency virus 2;
DENV-2 = Dengue virus type 2;
VACV-WR = Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR));
HHV-6 variant A = Human herpesvirus 6A (strain Uganda-1102) (HHV-6 variant A) (Human Blymphotropic virus);
IBV=Infectious bronchitis virus;
CV-B3 Nancy = Coxsackievirus B3 (strain Nancy);
VZV-HHV-3 = Varicella-zoster virus (strain Dumas) (HHV-3) (Human herpesvirus 3);
HSV-1 17+ = Herpes simplex virus (type 1 / strain 17);
MaHV1= Macacine herpesvirus 1;
RSV-PrC = Rous sarcoma virus-strain Prague C;
Influenza A = Influenza A virus.

●: indicates drug-like conform behavior; ●: designates properties with high risks of undesired effects; MW: Molecular weight; RBN: Number of rotatable bonds; TPSA: Topological Polar Surface Area; HBA/HBD: hydrogen bond acceptor/donor; Consensus logP o/w: average of all five partition coefficients (ILOGP, WLOGP, MLOGP, SILICOS-IT); BBB: Blood-Brain Barrier permeate; CYPs: cytochromes

Parameters	Molecule	Quercetin	Pinocembrin	Pinobanksin	Luteolin	Kaempferol	Galangin	Chrysin	Isorhamnetin	Remdesivir
ADME	MW	302.24	302.24	272.25	286.24	286.24	270.24	254.24	316.26	602.58
	RB	1	1	1	1	1	1	1	2	14
	HBA	7	7	5	6	6	5	4	7	12
	HBD	5	5	3	4	4	3	2	4	4
	TPSA	131.36	131.36	86.99	111.13	111.13	90.9	70.67	120.36	213.36
	Consensus logPo/w	1.23	1.23	1.39	1.73	1.58	1.99	2.55	1.65	1.5
	BBB permeat	No	No	No	No	No	No	Yes	No	No
	CYP1A2	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
	CYP2C19	No	No	No	No	No	No	No	No	No
	CYP2C9	No	No	No	No	No	No	No	No	No
	CYP2D6	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
	CYP3A4	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Toxicity risk	Mutagenic	●	●	●	●	●	●	●	●	●
	Tumorigenic	●	●	●	●	●	●	●	●	●
	Irritant	●	●	●	●	●	●	●	●	●
	Reproductive effective	●	●	●	●	●	●	●	●	●

RESULTS

2D interaction diagrams of 8 flavonoids and remdesivir in targets (6M2N, 6LU7, 6M0J) binding sites and the corresponding CG4 docking scores



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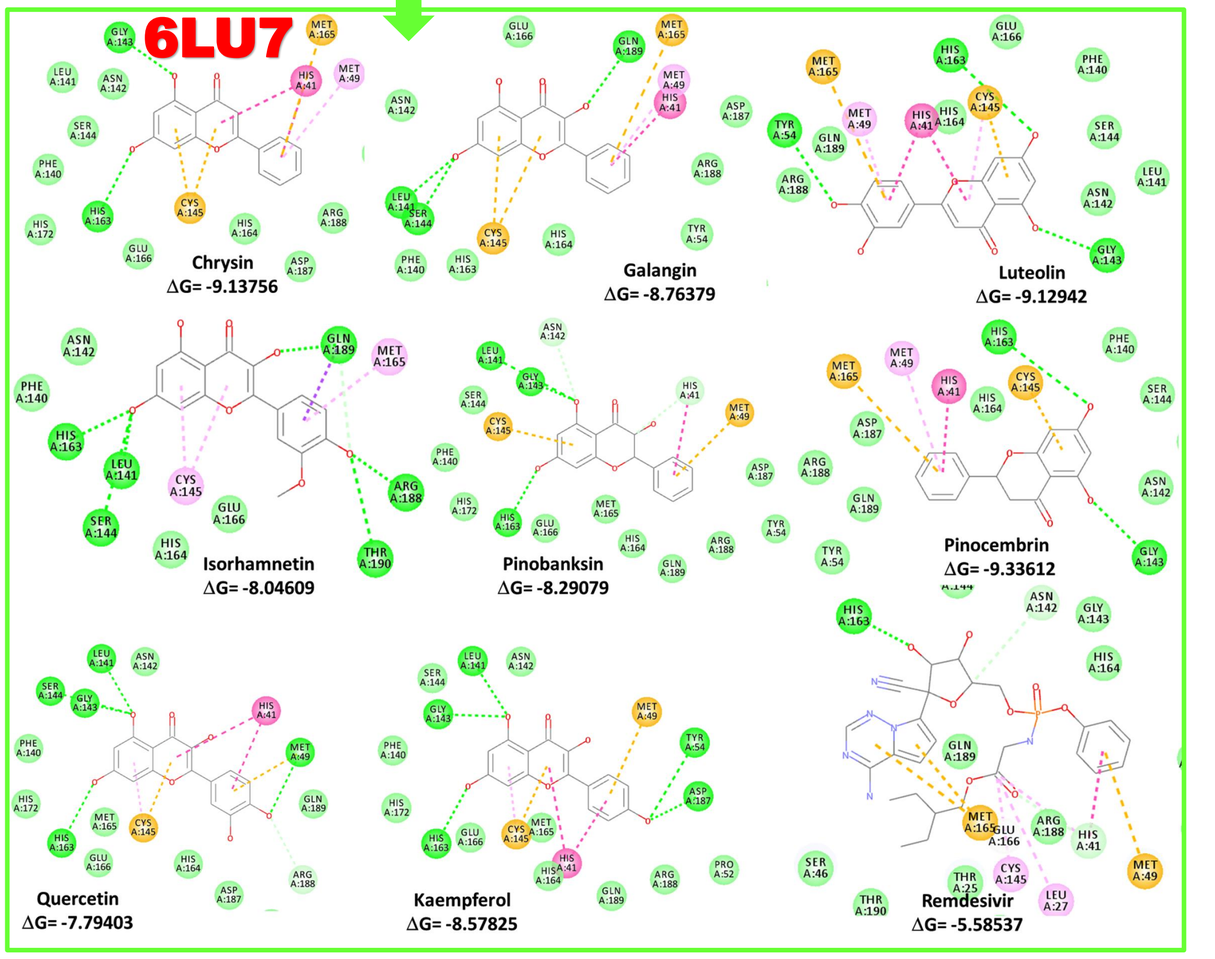

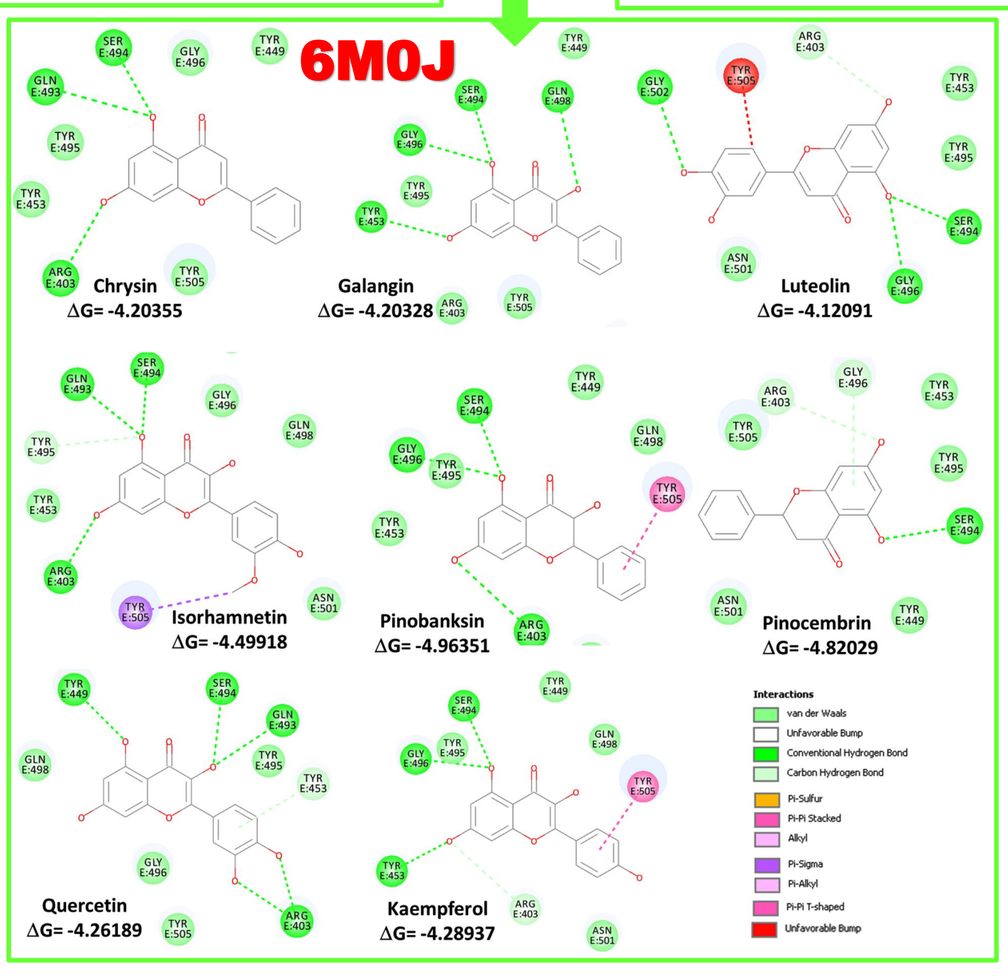

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CONCLUSIONS

- **Molecular docking, ADME, toxicity risk and antiviral activity prediction simulations were performed within 8 flavonoids components of Manuka honey and viral and human target proteins to identify their potential use as complementary solution to fight SARS-Cov-2 infections.**
- **Most of the investigated flavonoids showed a potent inhibition of viral entry by forming hydrogen bonds with significant amino acid residues in viral (Gln169, His163, Cys145, Gly143, Leu141, Glu166, Thr190, His41, Met49, Tyr54, Asp187, Asp48, and Cys44) and human target proteins (Gly496, Tyr505, Gly502, Gln493), interaction that contributes to antiviral activity.**
- **All eight flavonoids fall into the accepted values range of ADME and toxicity-related parameters except galagin, kaempferol, isorhamnetin, and quercetin which possess high risks of undesired mutagenic effects; quercetin also has a high risk of mutagenic effects.**
- **Concerning the antiviral activity evaluated by Way2drugAntiVir-Pred tool, 6 out of 8 flavonoids showed activity against SARS-CoV(R1ab) and only 3 against SARS-CoV(3CL-pro).**
- **Future studies will explore this potential antiviral activity against SARS-CoV(R1ab) of all 8 flavonoids of Manuka Honey.**
- **Overall, our preliminary results suggest the potential use of Manuka honey as a safe preventive chemotherapeutic agent, as well as a complementary solution to conventional drugs indicated in the COVID-19 treatment.**
- ***Future work* - these preliminary results encourage us to improve the applied protocol using flexible docking, molecular dynamic and MM-GBSA simulation, in order to obtain more reliable and soundness results.**