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SHORT COMMUNICATION

In silico Screening of Chemical Constituents in *Rasam* as a Beneficial Supplementary Treatment for Novel Coronavirus

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Abstract

Context: The novel coronavirus named as COVID-19 (SARS-CoV-2) from its origin in Hubei spread across the continent in a short period of six months' time. Till date there is no drug to cure the novel corona virus SARS-CoV-2. Earlier studies on SARS-CoV-1 suggests that interleukin 6 (IL-6) and Interleukin 8 (IL-8) were in the higher levels indicating the key role of IL. **Aim:** Molecular simulation studies were carried out on the selected 24 chemical constituents present in *rasam* against IL-6 to identify the key interaction between the amino acid residues and their chemical structure **Materials and Methods:** A library of 24 chemical constituents was sketched using Chem Sketch programming 8.0. The 3D structures of ligands were retrieved in mol format in Maestro v 11.3 and the ligands were optimized utilizing ligprep (4.3) module (Schrödinger 2018-1). **Results:** One of the chemical constituents sinigrin a glucosinolate emerged as top scorer with a GLIDE score of -6.333. It was apparent from the examination, that the Van der Waals (ΔG bindvdW) and coulomb energy interactions were major great contributors. The structural diversity of sinigrin from the rest of other chemical constituents in *rasam* led to significantly better interaction with amino acid residues. **Conclusion:** The study identifies sinigrin, as one of the active constituents in *rasam* possessing good binding affinity against IL-6 which can be used as a dietary supplement and can be used as a control measure to fight against Covid-19.

Keywords: Functional Food, IL-6 Inhibitor, SARS-CoV-2, Sinigrin, Tartaric Acid

1. Introduction

The novel coronavirus named as COVID-19 (SARS-CoV-2) from its origin in Hubei spread across all the continent in a short period of six months' time[1]. Though a wide range of potent antiviral drugs are available, WHO concluded that none of the drugs can prevent or cure 100 % SARS-CoV-2 till date. However, discovery of newer drug molecules or drug repurposing and the development of vaccine can help us in the treatment or prevention of this viral infection. The developments of drugs or vaccines may require months or even years to prove its efficacy to control SARS-CoV-2. Hence, researchers all over the world have started *In silico* screening of a series of small molecules inhibitors either from the available chemical database or natural compounds, drug repurposing to directly inhibit the key proteins in SARS-CoV-2.

Interleukin 6 (IL-6) is a soluble mediator that acts as pro inflammatory cytokines and is made up of 212 amino acids with core protein glycosylation accounts for the size of 21–26 kDa[2]. The significant role of cytokines in various diseases including cancer is well documented[3–5].

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In recent times targeting IL-6 is considered as one of the strategies in several immune-mediated diseases. Earlier studies on SARS-CoV-1 suggests that interleukin 6 and interleukin 8 (IL 8) were in the higher levels indicating the key role of ILs in SARS-CoV-2[6]. During a SARS-CoV infection IL-6 can induce inflammatory response in the respiratory tract[7] and further the IL-6 secretion has been well correlated with viral RNA load in severely ill patients. This evidence suggests the detrimental role of IL-6 in SARS-CoV-2 infection[8,9] and hence finding an inhibitor targeting IL-6 can also lead to beneficial effects in the treatment of SARS-CoV-2.

Rasam is a spice soup, traditionally consumed in South India prepared by incorporating crushed spices such as coriander, garlic, curry leaves, tamarind, cumin, black pepper, mustard, turmeric, red chili, and asafoetida in to tamarind and tomato juice by heating. Traditionally *rasam* has been used as a home remedy for cold, cough, fever, flu and diabetes[10]. *Rasam* has been previously reported for its hypoglycaemic activity,11 in the treatment of anaemia[12], for better lactation[13,14], as antimicrobial[15], laxative[16] and for the treatment of chicken pox[17]. Each ingredient used in the preparation of *rasam* are known for various medicinal uses[18]. Recently, our research group have reported a standardization procedure[19], anti-microbial,[20] anti-platelet aggregation[21], analytical[22,23], anti-breast cancer activity[24,25] and physicochemical studies[26] on *rasam*.

In the drug discovery process for treating COVID-19, several natural products[27–30] and *Kabasurakudineer chooranam* possessing[37] chemical constituents were subjected to *in silico* screening for SARS-CoV-2[31]. Saikosaponins[32] and 48 chemical constituents from cinnamon[33] were screened against the spike glycoprotein.

The Ministry of AYUSH, Government of India have recommended *rasam* as a diet advisory for COVID-19 in their guidelines[34]. In continuation to our ongoing research on *rasam*, molecular modelling studies on various therapeutic areas[35,36] and Ministry of AYUSH recommending *rasam* as diet advisory led to screen its chemical constituents as an inhibitor of IL-6 leading to possible protection against novel coronavirus.

2. Materials and Methods

2.1 Molecular Docking

A library of 24 chemical constituents was sketched using Chem Sketch programming 8.0. The 3D structures of ligands were retrieved in mol format in Maestro v 11.3 and the ligands were optimized utilizing ligprep (4.3) module (Schrödinger 2018-1). The generated energetically minimized conformers and the chirality and ionization state was retained by Epik (4.1). By using Optimized Potentials for Liquid Simulations (OPLS-3) force field for the prepared ligands minimization was designed. This force field was designed especially for small molecule simulation. The [PDB ID: IALU] were obtained from protein data bank (www.rcsb.org) having resolution of 1.9 Å and was selected for receptor-target. The protein was prepared using the protein preparation wizard. The crystallographic inhibitor and ions (K+ and Mg+) were kept and the unwanted water molecules were deleted. The protonation at pH 7.0 ± 2.0 and assignment of the bond orders was done. The missing atoms of the side chains and the breaks present were added and repaired using prime. The hydrogen of the altered species has been minimized using PROKA at pH 7.0 and the Ramachandran plot was produced. The centroid center of the DL tartaric acid binding area of the receptor was used for 3D grid box (10Å) generation to prepare binding pocket. The van der waals radius scaling for the receptor was kept default. The scaling factor was kept at 1.0 and the partial charge cutoff was kept at 0.25. No constraints and flexibility of rotatable group was allowed during grid generation and no excluded volume was included in grid generation. The docking study was done by glide (v7.5) module using those prepared ligands. It was performed in extra-precision mode (XP) without using any constraint in ligand and receptor. Sampling of the ligand was kept flexible; sample nitrogen inversion and sample ring conformation was kept as default. Penalty for nonplanar conformation of amide group was counted and no torsional constraints for hydroxyl group were allowed. The docking model was validated by docking the co-crystal ligand tartaric acid in the same receptor binding pocket.

2.2 Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) Binding Energy Studies

The strength of these chemical constituents having high docking score (the best 6) was kept for MM-GBSA (Schrödinger 2018-1) based on free energy calculation. This module was used to determine the free binding energy of the ligands. The docked receptor-ligand complex was taken and the minimization of these complexes was done by local optimization feature in prime (v4.8) and VSGB 2.0 energy model for simulation. The simulation is a physics-based correction for hydrophobic interaction, π-π interactions, self-contact interaction, hydrogen bonding and it is also an optimized implicit solvation

model. Using the OPLS-3 force-field the energy of those complexes was carried out.

3. Results and Discussion

Rasam constitutes around 39 chemical constituents identified for various therapeutic benefits. However, the initial filtering led to identification of 24 key structures with proven therapeutic activity in *rasam* for further study. Molecular docking studies were carried out on the selected 24 chemical constituents present in *rasam* against IL-6 to identify the key interaction between the amino acid residues and their chemical structure. The molecules were docked against (PDB ID: 1ALU) using Schrodinger glide. The *in silico* docking studies and binding free energy calculations were performed by the modules Glide (v7.6 ;) and Prime (v4.9) of Schrödinger (2017-3) (Maestro v11.3) individually for the twenty-four chemical constituents as selected scaffolds towards the target. The catalytic pockets of target protein IL-6 were produced and analyzed utilizing the site map device. The protein was read utilizing protein preparation wizard and the crystallographic water atoms (water particles without H bonds) were erased. Prime was utilized for including all the missing side chain residues and to manufacture breaks present in the structure. Hydrogen bonds comparing to pH 7.0 were included considering the proper ionization states for both the acidic and fundamental amino acid residue. The approval of the docking system was performed by figuring of RMSD between the co-crystal posture of native ligand and the redocked posture of the native ligand. The redocked native ligand and co-crystallized structure were superimposed and the RMSD was seen as 0.9205 A^0. Their superimposition was likewise accurately repeated inside the binding domain of the target receptor. It splendidly coordinated the way that RMSD between the co-crystallized posture of native ligand and the redocked posture of native ligand ought not to surpass 2 angstroms as it can be obviously valued. The Ramachandran plot for IL6 was created and every one of the amino acid residues was in the favoured region. The plot was produced which uncovered that the vast majority of the amino acids and non-glycine residues (97.8%) were in most favourable region (Figure 1). The G score of DL tartaric acid (-5.078) was kept as cut off point. One of the chemical constituents sinigrin, an aliphatic glucosinolate positioned as top scorer since its GLIDE score was -6.333. However, compounds like ferulic acid, capsaicin and curcumin showed poor binding affinity (Table 1). Although, the G-Scores of the remaining compounds were less compared to the co-crystal but their Glide energies were notable. The Glide energy of sinigrin was -25.090 kcal/mol, and some of the docked chemical constituents had similar binding Glide energy. Curcumin and capsaicin had glide energy of -31.470 kcal/moland -28.549 kcal/mol respectively. Among the twenty-four chemical constituents, the top seven G-scorers were chosen for further binding energy studies. To gauge the better binding strength and binding free energy, MM-GBSA measure was additionally completed for the top seven G-scorers and the outcomes are as shown in Table 2. The Van der Waals and Coulomb energy interactions in docked complexes changed between -16.98 to -24.04 and -0.38 to -70.97 kcal/mol. This energy interaction expressed the inclination of the Van der Waals and Coulomb energy interaction components. The best binding energy ΔG -43.65 kcal/mol was found for the compound sinigrin, which additionally demonstrated a higher coulomb energy term(-70.97 kcal/mol) and a great Van der Waals force (-24.02 kcal/mol). DL-tartaric acid had binding energy ΔG -20.63 kcal/mol, which additionally demonstrated a higher coulomb energy term (--51.01 kcal/mol) and a great Van der Waals force (-18.52 kcal/mol). The 2 and 3D interactions of sinigrin and tartaric acid are shown in Figures 2 and 3. There was significant nonbonding interactions such as H bonding and salt bridge observed for compound Sinigrin when compared to the standard DL tartaric acid (Table 3).

Table 1. GLIDE Scores and binding energies of chemical constituents in *rasam*

S. No.	Pubchem id	Compound	XP GScore	Glide energy
1	44135691	Sinigrin	-6.333	-25.090
2	875	Tartaric acid	-5.078	-20.124
3	445858	Ferulic acid	-3.366	-12.048
4	1548943	Capsaicin	-2.663	-28.549
5	969516	Curcumin	-2.986	-31.470
6	5280450	Linoleic acid	-2.024	-28.590
7	637566	Geraniol	-1.724	-18.382

8	325	Cumic alcohol	-1.708	-15.630
9	160512	Ar-Turmerone	-1.582	-18.165
10	5469424	Demethoxy curcumin	-2.993	-22.434
11	6654	2-Pinene	-1.498	-11.287
12	7463	p-cymene	-1.422	-14.020
13	326	Cuminaldehyde	-1.299	-15.874
14	440917	D-limonene	-1.130	-13.359
15	5281426	Umbelliferone	-1.040	-16.650
16	445639	Oleic acid	-0.922	-22.326
17	67179	D-Linalool	-0.902	-15.104
18	985	Palmitic acid	-0.682	-25.619
19	5315472	Bisdemethoxy curcumin	-1.767	-30.865
20	96943	Girinimbine	-0.297	-19.874
21	92776	Zingiberene	-0.072	-15.337
22	14985	Alpha tocopherol	-0.056	-23.739
23	9881148	(Z)-Ajoene	0.083	-20.579
24	167963	Mahanimbine	0.466	-26.067

The structural diversity of sinigrin from the rest of other chemical constituents in *rasam* led to significantly better interaction with amino acid residues. However, no significant interactions were observed from the small other chemical constituents may be due to absence of interactive functional groups with the binding site. It was reasoned that the coulomb energy term is the main impetus for ligand binding. The outcomes have all around corresponded with the past investigation that indicated non-polar columbic interactions were the supporters for the binding efficiency into the catalytic pocket of the receptor. These binding energies and conformation analysis suggests how good the ligand fits in the macromolecule. An earlier study on SARS-CoV-1 has shown that sinigrin could be potential inhibitors of SARS-CoV-1 3CLpro[37].

Table 2. MMGBSA results of chemical constituents in *rasam*

S. No.	Pubchem id	MMGBSA dG Bind	MMGBSA dG Bind Coulomb	MMGBSA dG Bind Covalent	MMGBSA dG Bind Hbond	MMGBSA dG Bind Lipo	MMGBSA dG Bind Packing	MMGBSA dG Bind Vdw
1	44135691	-43.65	-70.97	9.95	-6.94	-11.26	0.16	-24.04
2	875	-20.63	-51.01	-2.69	-4.60	-5.02	1.88	-18.52
3	445858	-5.72	-3.67	-9.25	0.83	-7.38	0.34	-21.14
4	1548943	-43.50	-0.60	-11.83	-0.85	-13.64	-0.84	-22.49
5	969516	-36.86	-59.61	-14.63	1.34	-17.17	0.23	-20.29
6	5280450	-31.05	-0.38	-10.37	0.95	-13.42	0.79	-29.52
7	5469424	-17.91	-7.28	-1.30	0.22	-10.44	0.00	-16.98

Table 3. Non-bonding interactions of sinigrin and the co-crystal DL tartaric acid

Compound	Bond	From (Residue)	To (Compound)	Distance (Å)
DL tartaric acid	Hydrogen bond	ARG-30	OH	2.10
		ARG-182	C=O	1.91
		ARG-179	C=O	1.76
		ARG-179	OH	2.18
Sinigrin	Saltbridge	ARG-30	O-C=O	4.29
		ARG-30	O-C=O	4.25
		ARG-182	O-C=O	3.24
	Hydrogen bond	ARG-179	OH	2.44
		ARG-182	OH	2.05
		GLU-175	OH	1.75
		LEU-178	OH	1.79
	Saltbridge	ARG-30	SO_3	2.97

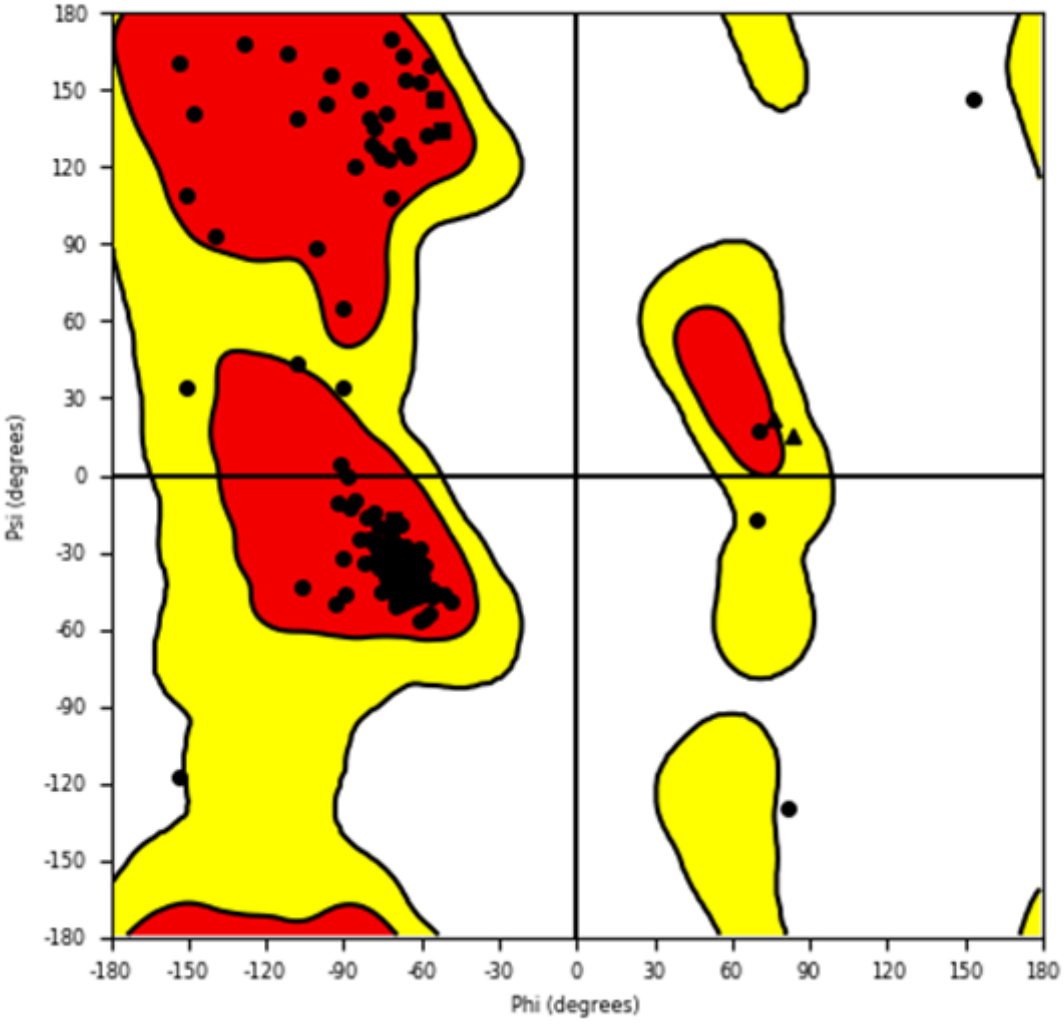
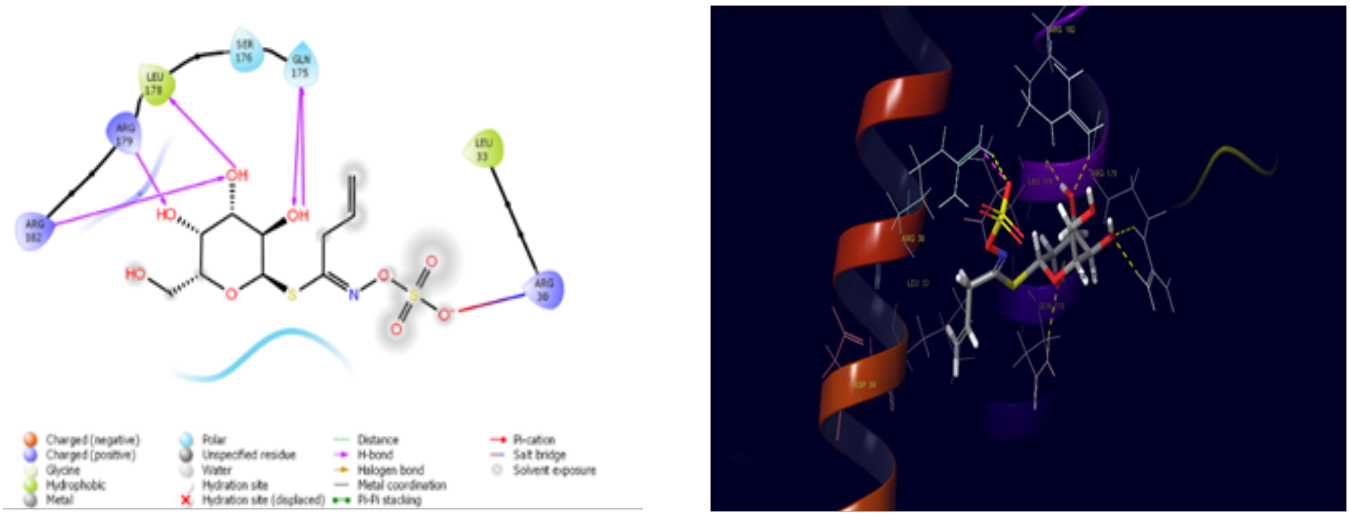
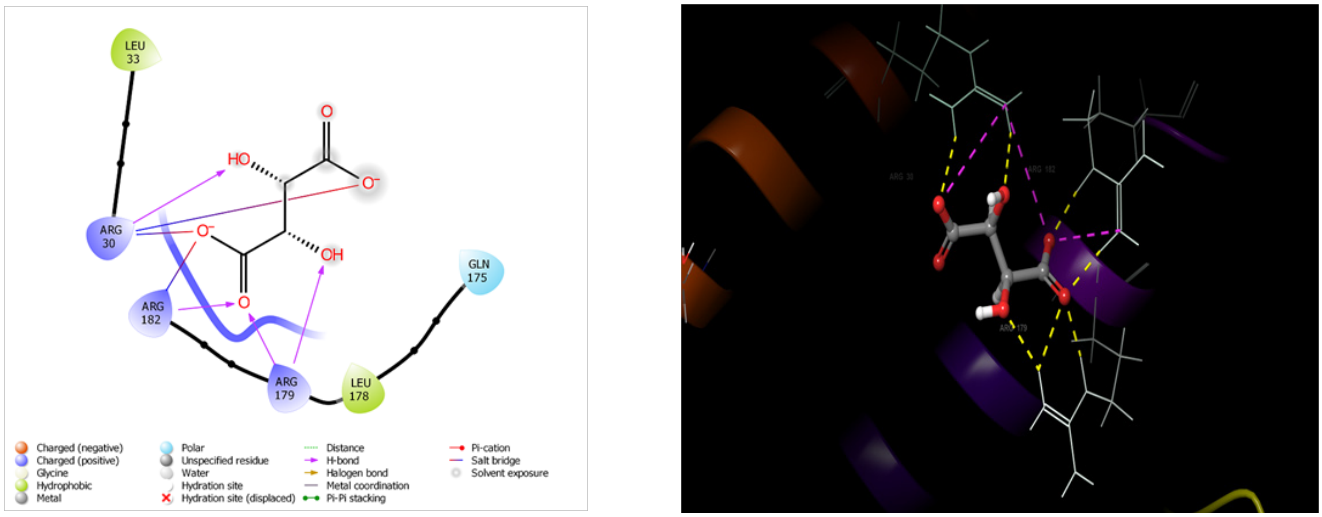


Figure 1. Ramachandran plot of 1ALU.



2a **2b**

Figure 2. 2D (2a) and 3D (2b) interactions of sinigrin.



2a **3b**

Figure 3. 2D (3a) and 3D (3b) interactions of tartaric acid.

4. Conclusion

Molecular docking studies were performed to identify the binding mode capability of IL-6 and twenty-four chemical constituents in *rasam*. The chemical constituents were docked alongside the co-crystal DL tartaric acid which filled in as reference standard also. The G-scores were utilized to look at the relative binding affinities of the structured chemical constituents against the protein NKA. The study identifies sinigrin, as one of the active constituents in *rasam* possessing good binding affinity against IL-6. The sulfonate group present in sinigrin showed salt bridge interaction with ARG-30 and showed over all good energy values when compared with standard. Hence, *rasam* can be used as a dietary supplement as a control measure to fight against COVID 19. These preliminary findings required further optimization to enhance the inhibitory activities. However, further biological studies on sinigrin needs to be carried out to further explore its beneficial effects.

5. Conflict of Interest

The authors declare no conflict of interest

6. Acknowledgement

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