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Review Article

Anti-viral herbal phytoconstituents of tulsi (*Ocimum sanctum*) against Covid-19

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ABSTRACT

A novel corona virus originated from Wuhan, China in 2019. Millions of people were affected due to this virus outbreak and quarantined for almost 2 years resulting in great loss in millions of lives in the world. This also resulted in a great impact in economy and health sector globally. After the outbreak the development of cure against SARS-CoV-2 is in full motion, less efforts have been spent on the prevention of rapidly spreading respiratory infectious agents. At present there is no effective treatment that could mitigate SARS-CoV-2. Available clinical intervention for covid-19 is only limited to support. Due to dreadful situation caused by COVID-19, there is an immediate need to discover potent therapeutic agents and targeted deliveries which can inhibit COVID-19 entry, progression and spread in human beings. Comprehensive understanding on the life cycle of SARS-CoV-2viruses and their interaction with hosts is important in the fight against these viruses. Thus, there is an urgent need for effective treatment. Intensive research on synthetic, semi synthetic, herbal, ayurvedic, siddha and unani drugs is necessary for this cause. In this review we focus on literature investigated on herbal drugs which might help in inhibition of COVID-19 via inhibition of angiotensinogen converting enzyme (ACE) and RNA dependent RNA polymerase (RdRp) through computational studies using AutoDockVina followed by their formulation development.

1. Indian Herbs Against COVID-19

The ministry of Ayurvedic, Yoga and Naturopathy, Unani,Sidha and Homeopathy has suggested a possible Ayurvedic treatment for COVID-19.[1] The traditional system of herbal medicine focused on cure of the disease and promptly implementing infection control. Potential selected Indian herbs are *Ocimum sanctum* (Tulsi), Glycyrrhiza glabra (Liquorice), Curcuma domesticaVahl (Turmeric), Tinospora cordifolia (Giloy), Withania somnifera (Ashwagandha), Cinnamon (Dalchini), Shoot of Triticumaestivum Linn. (Wheatgrass), with their antiviral properties to prevent infection and fight against COVID-19 (Table 1).[2]

2. Tulsi

A recent study in India reported that *Ocimum sanctum* (Tulsi) may be effective in the prevention and management of COVID19. Keeping in view the tremendous pharmacological application of *Ocimum sanctum* may be utilized to alleviate the symptoms of a variety of diseases.[10] Basil leaves of O*ocimum sanctum* contains chicoric acid (chicoric acid; also known as dicaffeoyltartaric acid, which is a caffeic acid derivatized with tartaric acid). Rosmarinic acid, chicoric acid and caftaric acid (derivatives of caffeic acid) were identified in fresh basil leaves. Rosmarinic acid was the main phenolic compound found in both leaves and stems. Chicoric acid was not detected in sweet basil stems, although a small amount was present in Thai basil stems. Other cinnamic acid monomers, dimers and trimers were also found in minor quantities in both stems and leaves.[11]

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Table 1: Medicinal propertiesof Indian herbs

S. No.	Botanical name	Active Constituents	Property	Medicinal uses
1.	Tinospora cordifolia	Berberine, choline, magnoflorine, tinosporin, tinosporic acid	Anti-bacterial, antioxidant, anti-cancer, anti-viral. Antimalarial	Chronic fever , anti-HIV, diabetes, immunity enhancer, arthritis etc.[3]
2.	Withania somnifera	Withanolides, withaferin A, alkaloids, steroidal lactones, tropine	Anti-inflammatory, anti-tumor, antistress	Arthritis, anxiety, insomnia, tumors[4]
3.	*Ocimum sanctum*	Oleanolic acid, ursolic acid, rosmarinic acid, eugenol, Caffeic acid linalool, β-caryophyllene	Anti-fertility, anticancer, antidiabetic, anti-fungal, antimicrobial	Bronchitis, bronchial asthma, malaria, diarrhea, skin diseases, etc.[5]
4.	Shoot of Triticum aestivum Linn	Potassium, dietary fiber, vitamin A, vitamin C, vitamin E, vitamin K, thiamin, riboflavin, niacin	Anti-cancer, antiulcer, green blood,	Cancer prevention, blood purifier, liver disease etc.[6]
5.	Cinnamon	Cinnamaldehyde, cinnamate, cinnamic acid, and eugenol	Anti-inflammatory, antimicrobial, antioxidant,	Parkinson disease, colon cancer, oral microbiota, etc.[7]
6.	Curcuma longa domestica Vahl	Diarylheptanoids, curcuminoids, turmerone, germacrone, atlantone, and zingiberene	Anti-inflammatory, anti-tumor, antistress, anti-oxidant,	Body pain, antiseptic, fever, AIDs, cancer etc.[8]
7.	Glycyrrhiza Glabra	Glycyrrhizin, isoflaveneglabrene, isoflavaneglabridin	Anti-inflammatory	Throat infection, cough infection[9]

3. Computational Studies and Analysis of Viral Protein Structure

Computer assisted drug design (CADD) has been preferred over several years for determining various ligands binding affinity with respect to particular protein.[12] It provides significant interactions of identified hits against their biological targets to understand their mode of action.[13] Recently, we have performed in silico screening of significant phytochemicals against RNA-dependent RNA Polymerase (RdRp), main protease (Mpro) and membrane protein using molecular docking in search of effective SARS CoV-2 inhibitors motivated by the potential of computational chemistry and in search of potent inhibitors of SARS CoV-2, herein we have performed the virtual screening of total 3 ligands from 2020-01 AsinexEiteSynergy (91,473) and BioDesign (175,851) libraries using AutoDockVina against RdRp and membrane protein using molecular docking followed by their further assessment by formulation development with its evaluation parameter.[14]

3.1. Analysis of protein structure

RNA dependent RNA polymerase (RdRp) co-crystallized with remdesivir having resolution 2.8 Å (PDB ID: 7BV2). This complex contain double-stranded RNA template which was implanted into the central channel of the RdRp where remdesivir was fused into the primer strand covalently. The core component of the viral replication complex is the non-structural proteins (nsp 12) of the RdRp. Second protein selected from protein data bank is Membrane protein (PDB ID: 6M0J) of SARS-CoV-2.[15]

4. Experimental Section

4.1. Computational studies for analysis of membrane protein and RNA dependent RNA polymerase

The molecular docking has been performed against selected protein (PDB ID: 7BV2 and 6M0J) using AutoDockVina to evaluate binding affinity of ligand and interactions in the active site. The required three ligands chicoric acid, caftaric acid, rosmarinic acid have been obtained from PubChem database consist of small molecule, which can be easily synthesized in organic chemistry labs.[16] This proteins and ligands in PDBQT format have been used for docking process. The binding energy of ligands with protein 7BV2 (RNA and 6M0J have been shown in Figures 2 and 3 respectively.

5. Collection and Preparation of Data

The 3-dimentonal structure of the SARS-CoV-2 RdRp evaluated through cryo electron microscopy (resolution: 2.8 Å) having antiviral remdesivir as a co-crystallised inhibitor (PDB ID: 7BV2) was obtained from RCSB protein data bank.[18] The protein was prepared for further molecular modeling using AutodockVina. All water molecules were

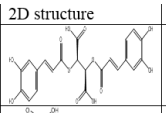
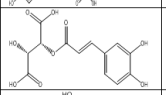
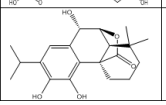
Compound No.	Dataset Name	2D structure	Binding Energy (Kcal/mol)
1.	Chicoric acid(A)		-8.6
2.	Caftaric acid(B)		-7.1
3.	Rosmarinic acid(C)		-8.2

Fig. 1: Binding Energy of ligands with 7BV2 protein

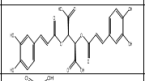
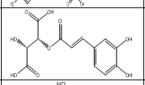
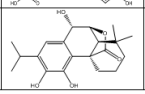
Compound No.	Dataset Name	2D structure	Binding Energy (Kcal/mol)
1.	Chicoric acid(A)		-7.6
2.	Caftaric acid(B)		-5.8
3.	Rosmarinic acid(C)		-6.0

Fig. 2: Binding Energy of ligand with 6M0J (Membrane protein)

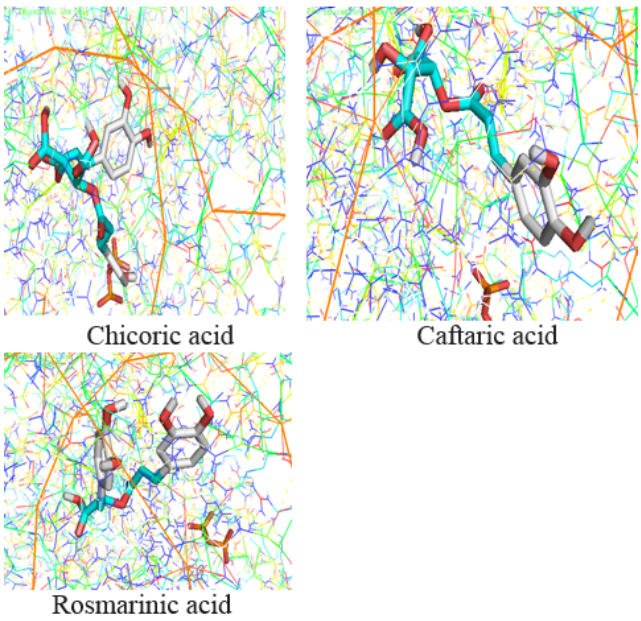


Fig. 3: 3D interaction of ligands A, B, C with 7BV2 (RdRp). Poses have been generated using Biovia Discovery studio 2020.[17]

deleted along with addition of polar hydrogen atoms and kollman charges to complete the proteins in terms of polarity and charges, respectively. The generation of the receptor grid box around the macromolecule of co-crystallised ligand remdesivir was achieved with the size of 90.768 × 99.896 × 99.788 Å (x,y and z) and the coordinates of centres 70 × 70 ×70 Å (x, y and z). The prepared protein has been kept in PDBQT format which has been further used

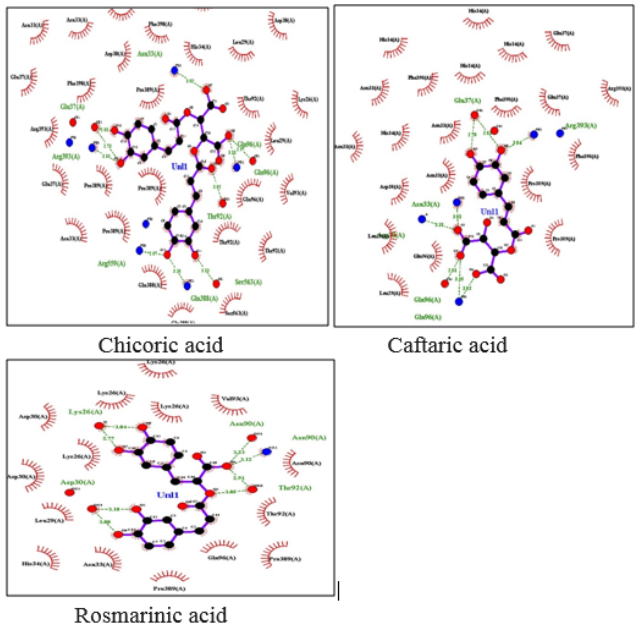


Fig. 4: 2D interaction of ligands A, B, C with Membrane protein (6M0J). Poses have been generated using Biovia Discovery studio 2020.

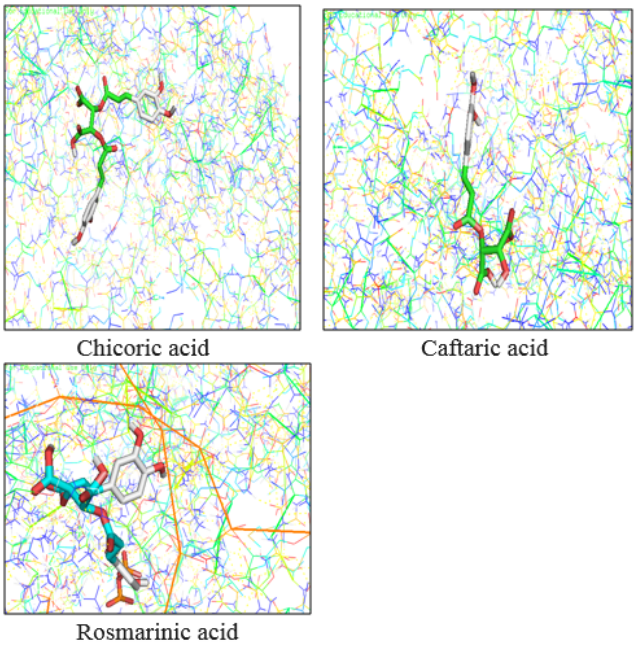


Fig. 5: 3-D interaction of ligands A, B, C with membrane protein (6M0J). Poses have been generated usingBiovia discovery studio 2020.

for the molecular docking. The present docking protocol has been validated by docking of remdesivir using the same and observed with RMSD of less than 1.[19]

The Pubchem website contains proteins and ligands. From pubchem we downloaded 3 ligands namely chicoric acid (A), caftaric acid (B) and rosmarinic acid (C). All Ligands have been optimized and converted into PDBQT format using OpenBabel and further used for molecular dockings.

6. Molecular Docking

Molecular docking with three ligands was performed using the prepared protein using Autodockvina to reveal the binding affinity and interactions of the lingands with RdRp protein (PDB ID: 7BV2) and membrane protein (6M0J).[20] All the ligands were docked on the site using optimized grid box and ten poses per ligand were generated. The docking interaction of hits have been visualized and analyzed using Biovia Discovery studio 2020.[14]

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8. Conflict of Interest

The authors declare no relevant conflicts of interest.

9. Source of Funding

None.

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