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IN-SILICO ADMET PREDICTION ON PHYTOCHEMICAL COMPONENTS OF CITRUS SINENSIS

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Keywords:

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ABSTRACT: *Citrus sinensis* are treasuries to deliver novel drugs and a significant aromatic medicinal plant reported to possess a broad spectrum of medicinal uses. The compounds present in these plants can deliver the potential therapeutic drug. A free web tool, SWISS ADME predictor, was used to evaluate the pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of phytoconstituents under investigation. The *in-silico* study has been deployed to screen the phytochemical components D-limonene, α-pinene, and β-pinene in *Citrus sinensis.* Against the protein target of RNA-dependent RNA-polymerase and Spike receptor binding domain with the aid of AutoDockVina software. All calculations for protein-fixed ligand-flexible docking were done using the Lamarckian Genetic Algorithm (LGA) method and analyzed using BIOVIA Discovery Studio 2016.13. The Phytoconstituents also showed good hydrophilic-lipophilic balance, good bioavailability, and decent GI absorption. The results obtained after docking showed a good binding affinity and implicated the active phytoconstituents for drug discovery and development.

INTRODUCTION: The *Citrus* species are an inherent source of valuable essential oil that might possess various pharmacological actions. One such species, Sweet Orange (Citrus sinensis), is an important source of phytochemicals such as phenolics, vitamin C and carotenoids rich in vitamin C and a hesperidium, belongs to the Rutaceae family [1]. These compounds, also known as nutraceuticals, provide health benefits due to a risk reduction of chronic illnesses such as cancer and cardiovascular disease [2, 3]. The essential oil from the leaves and fruits consists of various phytoconstituents, including D-limonene, α-pinene, β-pinene, β-Myrcene, *etc*. [6, 7, 8].

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These constituents are reported to possess Antioxidant, Anticancer, Antibacterial, and Antiviral properties [9, 10, 11]. The current study is aimed to explore the antiviral potential of components, namely D-limonene, α-pinene, and β-pinene, with target protein RNA-dependent RNA-polymerase (RdRp) by adopting computational (*in-silico*) approaches [4, 5]. Further evaluation of dug-likeness involves predicting ADMET (Absorption, Distribution, Metabolism, Excretion, toxicity) properties. *In-silico* HIA (Human Intestinal Absorption) model and skin permeability model can predict potential drugs for oral delivery and transdermal delivery.

MATERIALS AND METHODS:

Drug Likeness Properties and ADME Screening of Phytoconstituents: Since most herbal medicines are taken orally, an *in-silico* combining a model of absorption, distribution, metabolism, and excretion (ADME) was used to screen the phytoconstituents that are biologically active by oral administration.

A free web tool, SWISS ADME predictor was used to evaluating the pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of phytoconstituents under investigation.

Drug Likeness Property: molecular weight <500g/mol, hydrogen bond donors<5 Acceptor< 10 rotatable bonds <10 were chosen as criteria to satisfy.

Lipophilicity and Hydrophilicity: Log P and S prediction programs (ILOGP, XLOGP3, WLOGP, ESOL, and SILICOS-IT).

Further, the chemical compound with anticancer and antiviral activity of *Citrus sinensis* 34 compounds was screened from Dr. Duke's Phytochemical and ethnobotanical data (http://ars-grin.gov/duke/). The mol formats collected from Chemspider (http:// Chemspider.com). The ADMET properties, which evaluate drug-likeness and toxicity for all compounds, were predicted using TOPKAT (Toxicity Prediction by Komputer Assisted Technology) to check the mutagenicity and probability values of the compounds.

Retrieval and Preparation of Protein Structures: The three-dimensional/crystal structures of protein targets RNA-dependent RNA-polymerase (RdRp) (PDB ID: 6M71) and Spike receptor binding domain (PDB ID: 6M0J) were obtained from Protein Data Bank. The water molecules, cofactors, and other ligands were removed through Molegro molecular viewer and used for molecular docking studies.

Preparation of Ligands for Docking: The 3D structures of chemical constituents from *Citrus sinensis*viz., D-limonene, α-pinene, β-pinene, were retrieved from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format and converted into PDB format using BOVIA Discovery studio Visualiser 2016. Energy minimization was done using Open babel version 2.4.1.

FIG. 1: FRUITS, LEAVES AND WHOLE PLANT OF *C. SINENSIS*

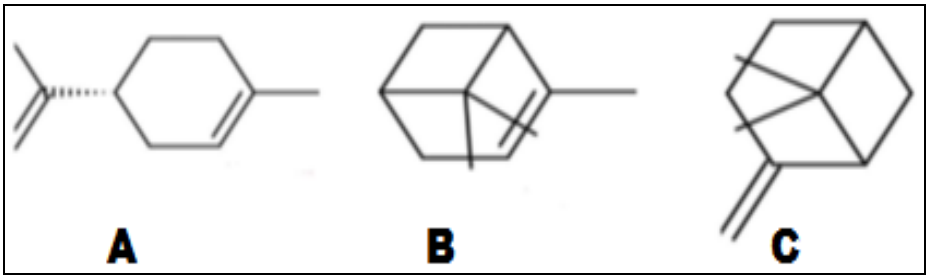


FIG. 2: (A) D- LIMONENE (B) A-PINENE (C) B-PINENE

Detection of Binding site and Validation: The interaction between the amino acids and ligands is considered the active binding sites in the main protease.

TABLE 1: AMINO ACID RESIDUES IN THE BINDING SITE

Target protein	Binding site residues
RNA-dependent RNA-polymerase	TRP509, LEU371, PHE368, ALA375, LEU372, TYR515, PHE506
Spike receptor binding domain	GLU435, GLU430, THR434, PHE428, ASN290, ILE291, PRO289, PRO415, THR414, LYS541, HIS540, PHE438

Molecular docking Analysis: Binding mode and interaction of individual bioactive constituents of *Citrus sinensis* was performed using AutoDockVina software. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. The protein was loaded in PyRx software, creating a PDBQT file that contains a protein structure with

hydrogens in all polar residues. All bonds of ligands were set to be rotatable. All calculations for protein-fixed ligand-flexible docking were done using the Lamarckian Genetic Algorithm (LGA) method and analyzed using BIOVIA Discovery Studio 2016.13.

RESULTS AND DISCUSSION: The results obtained from the SWISS ADME predictor indicated that the value of Log P, molar refractivity, and the total polar surface area in these phytoconstituents was in excellent agreement with Lipinski's rule of drug-likeness.

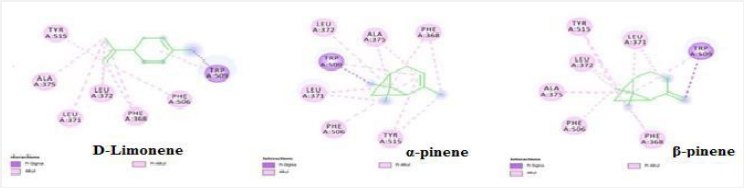
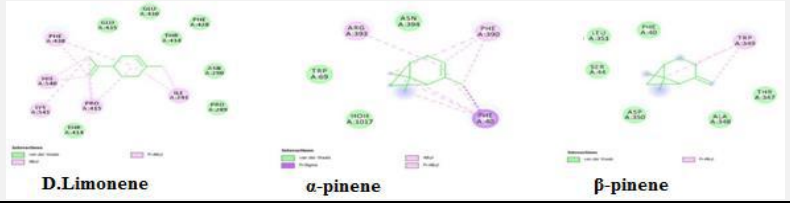
The Phytoconstituents also showed good hydrophilic-lipophilic balance, good bio-availability and decent GI absorption. Molecular docking of target proteins, namely main protease, spike protein, and RNA-dependent RNA polymerase, was carried out with phytoconstituents using Autodock Vina software.

TABLE 2: CHARACTERISTIC FEATURES OF LIGANDS

Compound	Log P (iLOGP)	Log S (ESOL)
D-limonene	2.63	-3.51
α-pinene	2.59	-3.31
β-pinene	2.58	-3.34
Molecular weight (g/mol) : 136, No. of hydrogen bond donors, acceptors and rotatable bonds: 0, Total Polar Surface Area (A°) : 0		

Analysis of molecular docking revealed D-Limonene, a major phytoconstituents from *Citrus sinensis.* To be the most promising inhibitor of targets. The results also implicated that other phytoconstituents α-pinene, β-pinene, and Camphene also showed significant interaction with RNA-dependent RNA-polymerase (-5.4,-5.4 and -5.5 kcal/mol, respectively) and with Spike protein (-5.0,-4.8 and -4.8 kcal/mol). Also, bioactive compounds' binding energies were nearly similar to that of standard drugs. The above results implicate the antiviral activity of medicinal plants.

TABLE 3: PHYTOCONSTITUENTS OF *CITRUS SINENSIS* (BINDING ENERGY AND LIGAND INTERACTION)

Target Protein	Name of the ligand		
	D-limonene	α-pinene	β-pinene
RNA-dependent RNA-polymerase (6M71)			
Binding energy (kcal/mol)	-5.4	-5.4	-5.4
Ligand interactions			
Spike receptor binding domain (6MOJ)			
Binding energy (kcal/mol)	-7.1	-5.0	-4.8
Ligand interactions			

For ADMET prediction of phytochemicals in *Citrus sinensis*, 13 and 21 were screened for anticancer and antiviral activity, respectively **Table 4**. The screened compounds from Dr. Duke's Phytochemical and Ethnobotanical database were energy minimized and studied for Lipinski's rule of five **Table 4.**

TABLE 4: SCREENING OF COMPOUNDS FROM DATABASE PLANT

Citrus sinensis	ANTICANCER ACTIVITY	ANTIVIRAL ACTIVITY
	Alpha-Carotene, Alpha-Terpineol, Alpha-Tocopherol, Beta-Carotene, Butyric-Acid, Caffeic-Acid, Chlorogenic Acid, Diosmin, Ferulic acid, Limonene, Naringenin, Neohesperidin, Rutin	Alpha-Pinene, Ascorbic acid, Beta-sitosterol, Caffeic acid, Caffeine, Chlorine, , Geranial, Hesperidin, Limonene, Linalool, Lithium, Myricetin, Naringenin, Naringin, Neryl-acetate, P-cymene, Quercetin, Rutin, Scutellarein, Stigmasterol, Subaphyllin

CONCLUSION: *Citrus sinensis* are treasuries to deliver novel drugs and a significant aromatic medicinal plant reported to possess a broad spectrum of medicinal uses, including antitumor, antioxidant, antibacterial, antiviral activities, *etc*. The antiviral property of *C. sinensis* has been reported in many articles. This *in-silico* study helps to screen the compounds and lead to the development of various diseases; the present study attempted to prove that phytocompound D-Limonene from *Citrus sinensis* acts as a promising adjunct for drug designing. D-Limonene possesses excellent drug-likeness parameters with zero violations of Lipinski's Rule and very good ADME pharmacokinetic properties. This implies that the active phytoconstituents, especially D- Limonene of *Citrus sinensis.* would serve as a supportive measure for the management of this pandemic disease upon further investigation.

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