GC-FID based aromatic profiling and molecular docking studies of lemon grass (*Cymbopogon citratus L.*) essential oil as novel therapeutic for SARS-Cov2 spike protein

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Abstract

SARS-CoV-2 (COVID-19) caused more than 15 % mortality worldwide. Spike (S) protein has recently been regarded as a suitable target for drug design. The present *in silico* docking study was designed to evaluate the effect of potent bioactive molecule citral present in essential oils of lemon grass plant leaves against Spike (S) protein from SARS-CoV-2. Till date there is no work is undertaken on in-silico analysis of these compounds against Spike (S) protein of SARS-CoV-2. In the present study, GC-FID (gas chromatography with flame-ionization detection) based aroma profile, molecular docking studies were conducted by using Patchdock analysis. Protein Interactions Calculator was used for protein interactions. *In-silico* absorption, distribution, metabolism, excretion and toxicity (ADMET) profile was also studied. GC-FID revealed citral as major compound in lemon grass oil. The calculated parameters such as docking score indicated effective binding of citral to COVID-19 S-protein. Interactions results indicated that, Spike (S) protein / citral complexes forms hydrophobic interactions. *In-silico* absorption, distribution, metabolism, excretion and toxicity (ADMET) studies provided guidelines and mechanistic scope for identification of potent anti-COVID 19 drug. Therefore, essential oil from lemon grass may represent potential herbal treatment to act as COVID-19 Spike (S) protein inhibitor.

Keywords: *COVID-19, Docking, lemon grass oil, citral, Herbal Drug*

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Introduction

A new corona virus, 2019-n-CoV, (SARS-CoV-2) caused a pandemic of respiratory disease (COVID-19) in Wuhan city, has since spread worldwide (Huang et al., 2020). Nevertheless, the processes that have been applied remain restricted to supportive and defensive therapies, intended to avoid additional obstacles and damage to organs. Certain primary investigations have scrutinized possible blends that comprise vaccines, anti-malarial drug hydroxychloroquine and Anti Human Immuno deficiency virus (HIV) vaccines and MERS CoV and SARS CoV neutralizing antibodies could be used for treating COVID19 infections (Liu and Wang, 2020).

Like other corona viruses, the outer membrane spike glycoprotein, is the major protein involved in interaction with specific targets of host cell (for instance adhesion factors, Ezrin, CD26, ACE2 and cyclophilins). All these targets are significant for adhesion and virulence. As far as entry of corona viruses is concerned, it is facilitated via transmembrane "S" glycoprotein that produces homo-trimer projecting from surface of virus (Lu, 2020). The SARS-Cov "S" glycoprotein comprises a conserved Receptor Binding Domain (RBD) which identifies receptors of host cell such as Ezrin, CD26, ACE2 and cyclophilins. It is 1200 amino acids long protein belongs to class1viral fusion proteins and involves in binding with cell's receptor, pathogenesis and tissue tropism [Millet et al., 2012]. In the course of infection, the trimeric"S" protein is treated via proteases of host cell at the S1 or S2 cleavage site. Subsequent cleavage, also called it as priming, the protein is separated into two terminals: one is 'S1' ectodomain (N terminal) that identifies similar surface receptor of cell and other is 'S2' membrane anchored protein (C terminal) involved in entry of virus (Sharma and Kaur, 2020). Therefore, by virtue of its key role, SARS-Cov 'S'protein is considered as an appropriate objective for developing viral inhibitor. Inhibition of SARS-Cov'S' protein activity would block replication of virus. Since in humans, not at all any proteases with comparable cleavage specific are recognized, so inhibitors are improbable to be considered as toxic. Natural sources derived bioactive molecules that can inhibit SARS-CoV-2 spike protein are measured an additional approach to combat COVID-19 (Bhardwaj et al., 2020). A computational approach based on *in silico* techniques, is the capable preliminary substantiation for drug discovery. Various molecular docking studies have recognized bioactive molecules from natural products as the potential SARS-CoV-2 spike

protein inhibitors derived from natural sources (Bhardwaj et al., 2020). The discovery of new drugs as therapeutic agents is a dreary and luxurious process. Traditional methods can take about 12-14 years with lot of expenditure to bring a drug from discovery to market. In order to overcome these challenges, multidisciplinary approaches are required in the process of drug discovery.

From ancient time, medicinal plants are beneficial in the field of drug therapeutics as they are safer alternatives being utilized by humans for centuries [Song et al., 2018]. Previously, many of the new drug formulations are derived from natural products. In addition, natural compounds are also a primary source for a huge number of modern drugs. Chloroquine and hydroxychloroquine, important natural compounds are derived from secondary metabolites of Cinchona tree that is under clinical trial and has shown potential anti SARS-CoV-2 properties (Wu et al., 2020). Our present study focuses on the *in silico* analysis of essential oil present in lemon grass plants. Various plant parts like flowers, leaves, roots and fruits have been used in various system of medicine for the past 2000 years to treat numerous diseases such as fever, skin infection, bleeding piles, asthma, cold, cough and inflammation. Hence, great attention has been paid to plant secondary metabolites as therapeutic medicines. Essential oils due to having antioxidant, antimicrobial and anti-viral bioactivities, are immensely used in cosmetic, pharmaceutical industries. Essential oils are complex mixture of volatile elements such as flavonoids, alkaloids, aromatic compounds and terpenes. Lemon grass essential oil has been empirically used as antimicrobial agents, but little is known about its antiviral potential. We hypothesize that bioactives from essential oil have the capability to prevent infection of COVID-19. Therefore the research objective of the current study was GC-FID based chemical profiling, *in-silico* analysis and comparative molecular docking studies pertain to bioactive molecules in relation with S-protein protein. The outcomes of the current study would provide researchers with prospects to recognize the accurate drug to combat COVID19. To further estimate the drug ability of this phytochemical, the present study report their ADMET profiles and potential biological activities using various *in silico* bioinformatics tools. Over the years many approaches have used to design drug and released into commercial market for use.

Among all, structure-based drug design (SBDD) is most commonly used, which based on 3-D structure protein target to propose a suitable ligand that can pose as its potential inhibitor (Singh et al., 2016). In SBDD, Molecular docking is a key technique that can be applied in designing drug making process. Molecular docking has facilitated researchers to virtually monitor a collection of bio-actives against the receptor target protein and analyze binding conformations and affinities of the compounds to the receptor (Barcellos et al., 2019). This study investigated docking of bioactive molecules from lemon grass oil as key inhibitor candidates for SARS-CoV-2 spike (S) protein. This investigation will be helpful to other scholars with more options to find out apt drug to combat SARS-CoV-2. We hypothesize that these bioactive components from lemon grass essential oil has the capability to prevent infection of SARS-CoV-2. The results of the study will provide other scholars with opportunities to identify the right drug to combat SARS-CoV-2. To further estimate the druggability of these bioactive molecules, the present study report their ADMET profiles and potential biological activities using various *in silico* bioinformatics tools.

Materials and Methods

Gas Chromatography Analysis

Lemon grass oil from leaves of *Cymbopogon citratus* was extracted by using Steam-distillation method as described by Sharma and Kaur (2022). Oil obtained was stored in dark bottles at 4°C till further use. Gas chromatography (GC-FID) analysis was performed using a Chemtron 2045 gas chromatograph coupled with FID (flame ionization detector). A 2 m long column of stainless steel filed with 10% OV-17 on 80-100% mesh Chromosorb W (HP) was used. Carrier gas was Nitrogen at flow rate of 30 ml/min. The detector and injector temperatures were kept at 210 °C and 260 °C and 0.1 µl sample was injected. Ramping conditions for oven were: 110°C (initially maintained) ramped to 200 °C at 2 °C/min. Bioactive molecules were identified by comparison of their relative retention times with either those of known standards or with published data in the literature and matching their mass GC-FID spectra with the NIST spectral libraries spectra.

Ligand modelling

Citral bioactive structure was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). SMILES (simplified molecular-input line-entry system) were retrieved for each bioactive molecules and converted to their corresponding 3D structures by using UCSF-chimera and saved in .pdb format.

Protein receptor prepration

SARS-CoV-2 spike homology modelled 3D structure in its .pdb format was retrieved from SWISS-MODEL. 3D modelled protein structure was designated as receptor. Before the docking studies, the protein structure was first prepared using the dock prep set up in chimera software. The dock preparation is an optimization part that corrects atomic and bond length, structure, charges anomalies. Original inhibitor (NAG) and water molecules were detached from the spike protein structure and any missing hydrogen atoms were added

Active sites prediction in 3D modeled receptor

CASTp (The Computed Atlas of Surface Topography of proteins) web tool was used to predict active sites residues in the spike 3D modelled protein. CASTp is an online tool used in identification and dimension of cavities on 3D protein structures. Default value of 1.4 Angstroms was used as probe radius.

Molecular Docking

The docking study of the compound over SARS-CoV-2- S-protein was studied using PatchDock (https://bioinfo3d.cs.tau.ac.il/PatchDock/) softwares. For this both ligands (biomolecules) and receptor (modeled spike protein 3D structure) molecules in pdb file formats were uploaded to PatchDock server and job was executed. The best generated docked structure was downloaded and saved as .pdb file. After docking complex structures were studied by Biovia Discovery Studio Visualizer 2020 and Chimera tools. 3D interactions were studied using PLip web tool (https://projects.biotec.tu-dresden.de/plip-web/plip/index).

In silico drug-likeness and toxicity predictions

In silico drug-likeness and toxicity predictions were studied using admetsar2 and SWISS ADMAE tool to predicting toxicity of candidate molecules (http://lmmd.ecust.edu.cn/admetsar2/). This tool estimates the carcinogenic nature, tumorigenic mutagenic, irritant and biodegradable ability. Drug-likeliness analyze a pharmalogicaly active agent and the predict its oral activeness. It is usually done by Lipinski rule of five which cite that compound likely shows poor absorption when: molecule have more than 5 H-bond donor and 10 H-bond acceptors, MW more than 500 and LogP (CLogP) greater than 5.37. Swiss ADME online tool is used to find out drug-likeness and other properties like hydrophilicity (Log kp), solubility (Log S), surface area (TPSA) and blood brain barrier penetration (BBB). It also predicts the pharmacokinetic properties such as Absorption, Distribution, Metabolism, Excretion and Toxicity. Bioactivity analysis was carried out using molinspiration tool (https://www.molinspiration.com/cgi-bin/properties)

Result and discussion

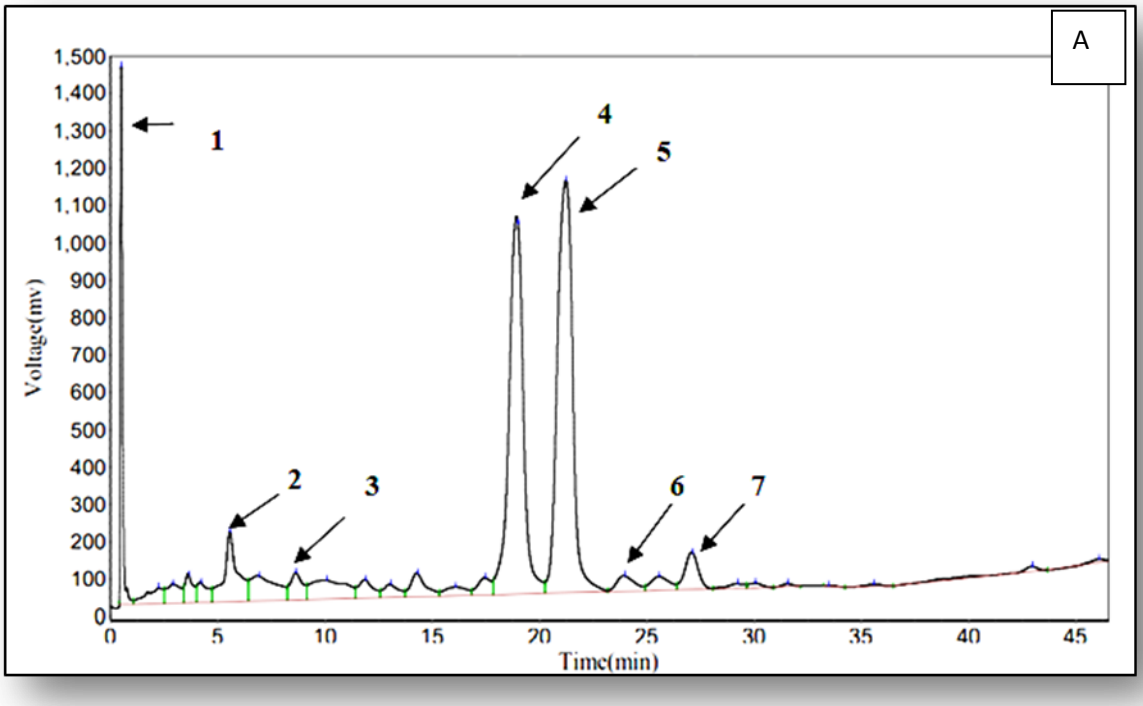
GC-FID analysis of bioactive molecules in LGO

The GC- FID chromatogram obtained was depicted in Figure 1A. The peaks observed and their respective retention time was also displayed. The GC- FID analysis of lemon grass oil obtained from *Cymbopogon citratus* revealed 26 compounds for the total of 100%. The major constituents were geraniol (27%, Citral-a), neral (31%, Citral-b). The small peaks may be ascribed to the disintegrated major bioactive compounds present in small quantities. The GC- FID analysis of lemon grass oil obtained from *Cymbopogon citratus* revealed 26 peaks for the total of 100%. In the present study, seven compounds were identified such as: micrene, limonene, linalool, geraniol, neral, undececanone and geranial acetate. GC-FID chromatogram contained major peaks along with many small peaks indicating the presence of other minor bioactive compounds**.** The major constituent was citral which comprised of a mixture of two terpenoids geometric isomers, neral (31%, Citral-a, *E*-isomer) and geranial (27%, Citral-a, *Z*-isomer) (Pihlasalo *et al*., 2007). Earlier studies also documented citral as a major constituent in the lemon grass oil from

other varieties of *Cymbopogon* (Rao *et al*., 2015). *Cymbopogon citratus* essential oils have been established to show antimicrobial, antifungal, and anti-parasitic properties (Zeng *et al*., 2015). Hence, citral was used as ligand for further molecular docking studies against SARS-Cov2 spike protein.

Molecular docking

Traditionally, the invention of recent therapeutic medicine could be a tedious and expensive method that typically takes 12-14 years with a great deal of cash to bring drug into market. With the aim of overcoming these issues a great deal several multidisciplinary approaches are accustomed discover new drug. In drug discovery processes, *in silico* coming up with of drug could be a apply of computer based mostly modeling that is extremely helpful. Within the field of drug discovery, medicative plants are advantageous as they're used as a secure seasoning different by humans for hundreds of years. The sources of many of the active constituents of medicines and novel medicine are obtained from natural product.



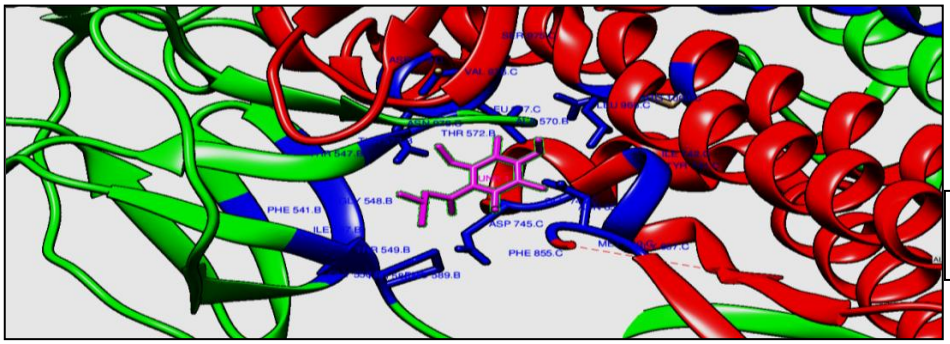
B

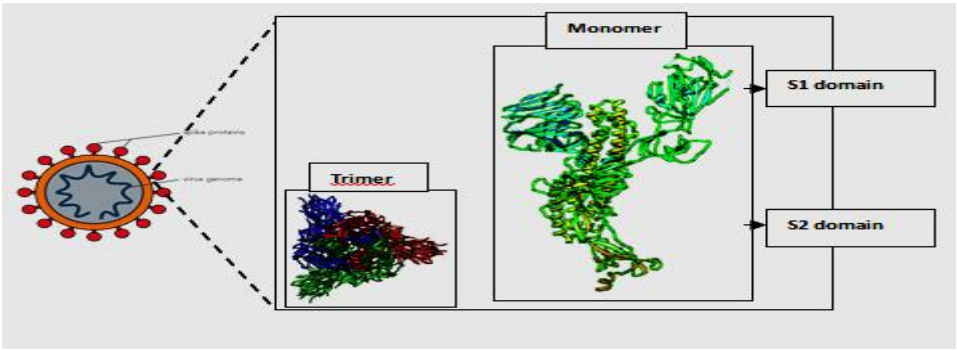
PEAK NO.	RETENTION TIME (min)	BIACTIVE COMPOUND	Conc.
1	0.498	MICRENE	6.7075
2	5.582	LIMONENE	4.9152
3	6.915	LINALOOL	3.6378
4	18.998	GERANIOL	27.0440
5	21.248	NERAL	31.5752
6	23.998	UNDECECANONE	1.5138
7	27.165	GERANIAL ACETATE	1.3755

Figure 1: GC-FID analysis (A) and chemical composition (B) of Lemongrass essential oil

Corona viruses (CoVs) are a bunch of viruses that infect animals and humans and produce symptoms like : fever, cough, cold etc. CoVs enters the host cell via fusion of spike protein encoded by the virus and embedded within the infective agent envelope (Wu et al., 2020). It's the S-protein found within the CoV related to the severe acute metabolism syndrome (SARS), which might be accessed in PDB and was instructed to be a possible drug target for 2019-nCov (Millet et al., 2012). In several viruses, S-protein play essential roles in infective agent entry into host cells; so, S-proteins are usually used as supermolecule targets throughout the event of antiviral medicine. The coronavirus spike supermolecule (S) plays apt role in virus infection, with the S1 domain liable for receptor binding and therefore the S2 domain region (aa570–aa1278), mediating membrane fusion. As cited by earlier, S-proteins represent key targets for the inhibition virus replication, and therefore the supermolecule sequences of the SARS-CoV S-protein and the 2019-nCoV S-protein are 91% identical, thence these proteins may be used as potential therapeutic targets (Song et al., 2018, Li et al., 2020, Millet et al., 2012). The invention of the spike proteolytic enzyme structure in COVID-19 provides a pleasant path to spot potential drug candidates to forestall infection. We tend to follow the structural biology aspects that specialize in the supply and retrieval of an S-protein receptor structure from PDB info. In this study, we tend to performed *in silico* analysis of lemon grass oil bioactive components against S-protein supermolecule of COVID-19.

In fashionable drug discovery method, molecular arrival could be a wide used machine technique to predict the binding mode and binding affinity of ligands with the target receptor supermolecule. The effectiveness of the docked advanced was evaluated on the idea of 2 essential criteria's: The minimum energy and therefore the interaction of the matter with the site residues. A ligand undergoes either hydrogen bonding or hydrophobic interactions or each





whereas arrival into the site. The results of arrival may be accustomed realize the most effective inhibitors for specific target proteins and so to style new medicine.

Figure 2: 3D docked structure of SARS-CoV-2 S-protein with CITRAL (A) and Molecular interactions of citral with spike protein (B). Different protomers of the trimer is shown in light blue, green and the other one in red colors. S1and S2 depicts domains.

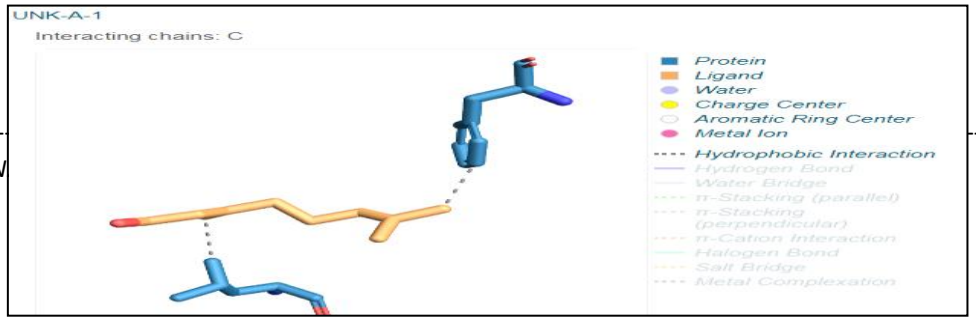


Table 1. Docking analysis of citral with spike protein

Name				Interacting residues (4 A°)	
Citral	Score	Area	ACE	H-bond interactions	Hydrophobic interactions
	3608	414.50	166.17	-	LEU 390, PHE 565

Molecular arrival exploitation patchDock dock tool that was accustomed verify interaction of substance bioactive compounds of oil with modeled 3D structure of SARS-CoV-2 S- protein disclosed twenty totally different poses supported the dock score and pose with highest score values indicated most binding affinity (data not shown). Citral exhibited highest affinity with S–protein with maximum docking score (Table 1). The high affinity of drug compounds depend on amount and the type of bonding that occur with the active site of the protein. As indicated in Figure 2, citral forms many chemical bonds with S2 domain of S protein, including hydrophobic bonds. S-protein comprises two functional subunits responsible for binding to the host cell receptor (S1 unit) and fusion of the viral and cellular membrane (S2) subunit (Song et al., 2018). According to the Plip server and Biovia studio results, the interaction of citral in the binding pocket of S2-protein domain was mediated by hydrophobic interactions via PHE565 and LEU390 with S2-protein domain at atomic distances of 3.96 and 3.18 (Figure 2). CAST-P server also revealed the presence of PHE565 and LEU390 as active site residues in the major cavity of SARS-CoV-2 S protein. With CASTp active site prediction, a major pocket was identified with Area (SA) of 138051 and Volume (SA) of 83670190 (Figure 3). The citral showed full fitness within active site amino acids of S2 domain of S-protein of SARS-CoV-2. It was postulated that these ligand-protein interactions might inhibit the formation of the S2 motif of S- protein. Coronavirus trafficking into and hijacking the host cell is primarily driven by the C-terminal S2 domain of spike conjugated protein that interacts with many host cell proteins (Liu and Wang 2019). It absolutely was postulated that COVID-19 S-protein becomes closed upon binding with eucalyptol that that in turn brings conformational changes of the S-protein and stop initiation of the fusion reaction responsible for its insertion into the host cell membrane. Earlier studies documented the role of antiviral compounds like phenolics, flavonoids, terpenoids and essential (Zakaryan et al., 2017).

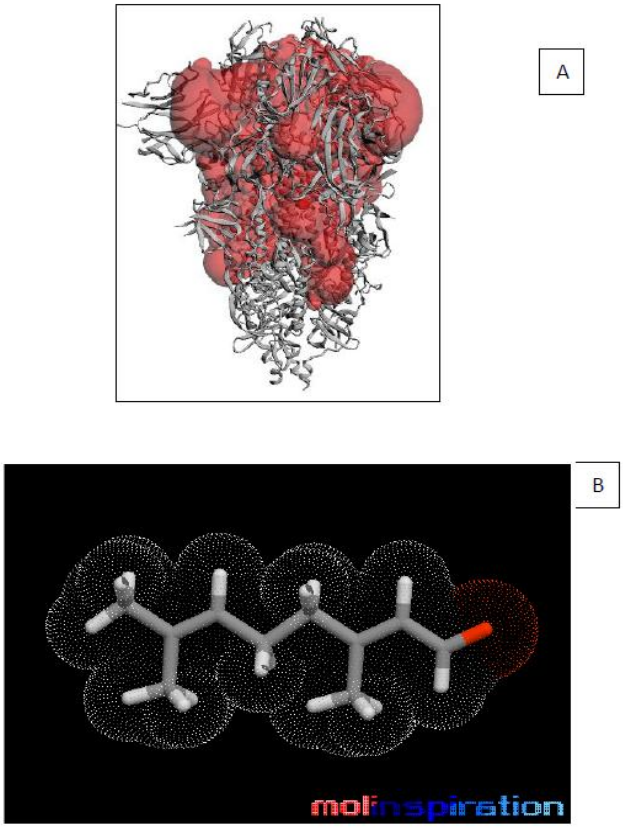


Figure 3**:** Binding pocket of SARS-Cov 2 protein (A) and Molecular lipophilicity potential (B). Hydrophobic areas: violet; hydrophilic areas: red

In-silico **Bioactivity, cell toxicity and ADMET properties**

ADMET properties (absorption, distribution, metabolism, excretion and toxicity) are very important for human therapeutic use of the compounds (Wu et al., 2020). The drug scanning results are illustrated in Table 2. All metabolites were accepted by Lipinski's rule of five. Topological polar surface area (TPSA) was very low, indicating permeating nature of metabolites across cell membranes. *In-silico* absorption of citral was high. It was observed that citral was a low molecular weight ligand. It was cited that low MWT compounds are easily diffused and transported across the biological membranes as compared to high MWT compounds (Srimai *et al*., 2013). Almost all natural metabolites were non-sensitive to efflux transporter P-glycoprotein (p-gp). Consensus Log $P_{o/w}$ (indicative of lipophilicity) was 2.71, indicating that

metabolites have optimal blood-brain-barrier penetration. Molecules were non-substrate to liver and in intestine based cytochrome P series (CYP1-3) involved in detoxific. ation. GI (Gastrointestinal tract absorption) of citral was high (Table 3). In order to exert a toxic effect, drug molecules have to be absorbed from intestinal tract in the body Molecular lipophilicity potential (MLP) and polar surface area (PSA) are also shown in Figure 2. MLP is key property to diminish various molecular ADME characteristics (like membrane penetration or plasma-protein binding). Analysis of 3-D distribution of hydrophobicity on molecular surface is particularly useful when explaining differences are observed in ADME properties of molecules with the same logP (Raies *et al*., 2016). Bioavailability score of citral was 0.55. The majority of compounds have bioavailability score of 0.55 or 0.56, which means good pharmacokinetic properties (Enrico et al., 2021). Synthetic accessibility (SAscore) score was 2.49. Synthetic accessibility evaluation is a process to assess the ease of synthesis of compounds. A rapid method for the assessment of synthetic accessibility for a vast number of chemical compounds is expected to bring about a breakthrough in the drug discovery. The development and validation of such a method that is able to characterize molecule synthetic accessibility as a score between 1 (easy to make) and 10 (very difficult to make) (Ertl and Schuffenhauer, 2009). In the case of a *de novo* designed molecule the experimental validation of its activity requires synthesis of the compound. The more difficult the synthesis of the lead candidate is, the more time and resources are needed for the exploration of this particular area of chemical space. These observations indicated that citral can easily interact with target receptors and can be further taken in the evaluation of biological activity score.

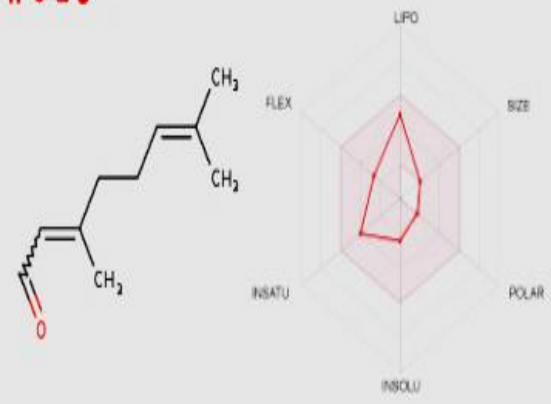
Bioactivity and toxicity of best docked bioactive molecule citral as the drug was calculated online by using Molinspiration drug-likeness score. This tool calculates bioactivity based on interaction towards various drug targets inside humans like: GPCR ligand, ion channel modulator, Kinase inhibitor, Nuclear receptor ligand. Table 3 depicts Bioactivity score of citral. Bioactivity score for GPCR ligand, ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor of citral was high (<0) while enzyme inhibitor activity was moderate (>0). All data indicated that citral can be used to calculate toxicity profile (Khan et al.,2017).

For pharmaceutical industries, proper risk assent of a chemical drug is a prerequisite to assess the safety profile of a therapeutic drug (Banerjee *et al*., 2018). In this regard, *in silico* toxicity is a

key platform to evaluate toxicity prediction of drugs that could be detrimental to humans, animals, and environments (Raies *et al*., 2016). Organ, genome and eco-toxicity was evaluated and toxicity profile revealed that citral bioactive molecule was mostly non-toxic as negative values were observed for organs, Drug-induced liver injury and human either-a-go-go-ralted gene (hERG) inhibition (Table 3). The hERG is important for cardiac repolarization that encodes rapidly activating delayed rectifier potassium channel (IKr) (Banerjee *et al*., 2018). Citral was noncancerous and eco-friendly. Thus, toxicity profile of citral was evaluated and toxicity profile revealed that citral bioactive molecule was mostly nontoxic to organs as inactive prediction was observed like hepatotoxicity (Table 4 and 5). Drug-induced hepatotoxicity is the major reason for the liver damage and main reason for the un-success of major drugs in the market (Siramshetty *et al*., 2016). Further, citral was non-carcinogenic and non-mutagenic in nature. Mutagenic nature of biomolecules is harmful to cell and is the main reason behind certain diseases, e.g., cancer (Lea *et al*, 2017). Further citral showed inactiveness towards targets based biological pathways like Nuclear receptor signaling pathways and Stress response pathways. All these targets like aryl hydrogen receptor (AhR), androgen receptor (AR), androgen receptor ligand binding domain (AR-LBD), 2/antioxidant responsive element (ARE), heat shock factor response element (HSE), mitochondrial membrane potential (MMP) are important components of biological system inside human body (Huang *et al*., 2016) . Toxicity radar chart is also shown in Figure 3, that quickly exemplify the assurance of positive toxicity outcomes compared to the average of its class. A toxicity radar plot (example below) is provided to assess the comparison between the different toxicity models active compounds average probability from the training set to that of the input compound (Banerjee et al., 2018). These prediction results are also displayed as a toxicity radar plot comparing the average confidence score of the active compounds in the training set of each model, to that of the input compound. The toxicity profile of the input compound is shown using blue lines/dots which represents the predicted probabilities of the input compound for respective ProTox-II models. The data displayed is orange dots/lines is the average probability of its active class, acquired by computing from the training set data for each model. This chart helps the user to get an understanding, how strong is the overall prediction of the input compound, considering its activity for multiple toxicity endpoints.

Table 2. ADMET properties of citral

Molecule 1



SMILES O=CC=C(CCC=C(C)C)C

Physicochemical Properties	
Formula	C10H16O
Molecular weight	152.23 g/mol
Num. heavy atoms	11
Num. arom. heavy atoms	0
Fraction Csp3	0.50
Num. rotatable bonds	4
Num. H-bond acceptors	1
Num. H-bond donors	0
Molar Refractivity	49.44
TPSA	17.07 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.47
Log $P_{o/w}$ (XLOGP3)	3.03
Log $P_{o/w}$ (WLOGP)	2.88
Log $P_{o/w}$ (MLOGP)	2.49
Log $P_{o/w}$ (SILICOS-IT)	2.65
Consensus Log $P_{o/w}$	2.71

Water Solubility	
Log S (ESOL)	-2.43
Solubility	5.67e-01 mg/ml ; 3.73e-03 mol/l
Class	Soluble
Log S (Ali)	-3.05
Solubility	1.34e-01 mg/ml ; 8.83e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-1.96
Solubility	1.66e+00 mg/ml ; 1.09e-02 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.08 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MW<160
Veber	Yes
Egan	Yes
Muegge	No; 2 violations: MW<200, Heteroatoms<2
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: aldehyde, isolated_alkene, michael_acceptor_1
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	2.49

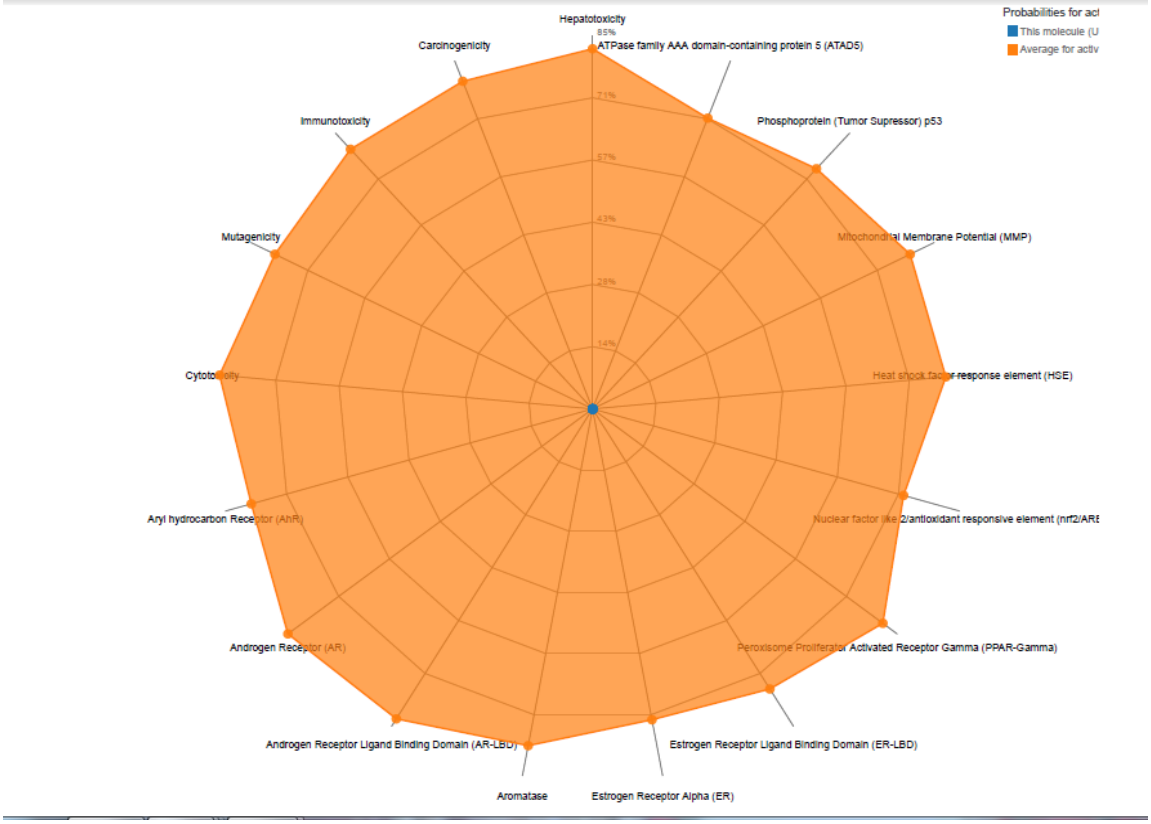


Figure 4. Toxicity radar chart of citral

Table 3. Bioactivity score of citral

Molinspiration bioactivity score	
GPCR ligand	-0.86
Ion channel modulator	-0.25
Kinase inhibitor	-1.29
Nuclear receptor ligand	-0.42
Protease inhibitor	-0.57
Enzyme inhibitor	0.02

Table 4. Toxicity profile of citral

ADMET predicted profile	Value
Carcinogenicity (binary)	-
Ames mutagenesis	-
Human Ether-a-go-go-Related Gene inhibition	-
Micronuclear	-
Hepatotoxicity	-
Respiratory toxicity	-
Reproductive toxicity	-
Mitochondrial toxicity	-
Estrogen receptor binding	-
Androgen receptor binding	-
Thyroid receptor binding	-
Glucocorticoid receptor binding	-
Aromatase binding	-
PPAR gamma	-
Honey bee toxicity	-
Biodegradation	+

Table 5. *In silico*-role of citral in biological pathways and Stress response pathways

Classification	Target	Shorthand	Prediction
Organ toxicity	Hepatotoxicity	dili	Inactive
Toxicity end points	Carcinogenicity	carcino	Inactive
Toxicity end points	Immunotoxicity	immuno	Inactive
Toxicity end points	Mutagenicity	mutagen	Inactive
Toxicity end points	Cytotoxicity	cyto	Inactive
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive

Conclusion

Due to nonapproved drugs at present Currently, SARS-CoV-2 has emerged in the human population, in China, and is a potential threat to global health, worldwide. Currently, the main target for COVID-19 treatment primarily act on the S-protein. The aim of this study was to examine bioactive molecules from lemon grass essential oil that may be used to inhibit the SARS-CoV-2 infection pathway. Therefore, we suggested that citral may represent potential treatment options, and found in medicinal plants that may act as potential inhibitors of COVID-19 S-protein. However, further studies should be conducted for the validation of these compounds using in vitro and in vivo models to pave a way for these compounds in drug discovery.

Conflict of interest: Authors declares no conflict of interest

Author contributions: ADS: designed study, IJK: interpreted study

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