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Proceeding Paper

Lead Finding from Plant Cymbopogon Citratus with Immunomodulator Potentials through in Silico Methods †

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Abstract: The aim of this study was to examine the correlation between immunomodulators and the molecular properties of the *Cymbopogon citratus* derivatives in search of a lead compound through molinspiration cheminformatics software. Ten naturally occurring derivatives of *Cymbopogon citratus* were selected for bioactivity prediction and drug likeness score on the basis of Lipinski's rule. All of the compounds fulfilled Lipinski's rule as their Milog P score was below 5, suggesting these compounds show good permeability across cell membranes. All the screened compounds had minimum or no violations of the Lipinski rule. *Cymbopogon citratus* and its derivatives showed a good bioactivity score for drug targets including nuclear receptor ligand, protease inhibitor and enzyme inhibition and thus are expected to have excellent pharmacological activity in vivo. The results of this study justify their topical application as immunomodulators but some structural modifications in order to make the compound more polar would definitely improve oral bioavailability and thus the usefulness and therapeutic efficacy of *Cymbopogon citratus*. All the *Cymbopogon citratus* derivatives are predicted to be orally active and are considered as potential candidates for further research as their bioactivity score due to high affinity for various drug targets was better than the standard as well as among other tested compounds.

Keywords: *Cymbopogon citratus* derivatives; lemongrass; immunomodulators; Lipinski's rule; molinspiration

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1. Introduction: Research Background

Currently, the global public health threat of international concern is the coronavirus disease2019 (COVID-19), a viral disease of worldwide prevalence caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). At present the disease has no known cure or vaccine. Plants worldwide including Indian traditional plants of ethnopharmacological relevance are a natural source of abundant and diverse phytochemicals with bioactivity against microorganisms including viruses.

Lead compounds possess the desired pharmacological properties and play an important role in drug design and development. Natural products are a good source of lead compounds. Morphine, quinine, atropine, etc., are some of the lead compounds isolated from natural sources and in clinical use. However, most of the lead compounds require structural modification to overcome their low activity and/or unacceptable side effects. To develop an orally active compound, certain properties of the lead compound should be taken into consideration such as Lipinski's rule of five or Veber's parameters that help

pharmaceutical scientists to select the best candidates for development and to reject those with a low probability of success. Computer based (in silico) molecular modeling (bioinformatics and cheminformatics) are quite useful for this purpose, because they are extremely fast and cost efficient and can be applied even when a compound is not physically available [1–4].

2. Material and Methods

2.1. Lemon Grass

Cymbopogon, also known as lemongrass (Figure 1), barbed wire grass, silky heads, Cochin grass, Malabar grass, oily heads or fever grass, is a genus of Asian, African, Australian, and tropical island plants in the grass family. Some species (particularly *Cymbopogon citratus*) are commonly cultivated as culinary and medicinal herbs because of their scent, resembling that of lemons (Citrus limon) [5].

Figure 1. *Cymbopogon citratus*, known as lemongrass in different forms, plant and leaves.

In addition, a number of biological properties of lemongrass have been reported over the years, including but not limited to antibacterial, antifungal, antiprotozoal, anti-inflammatory, antioxidant, antitussive, antiseptic, anticarcinogenic, cardioprotective and antirheumatic activities as shown in Figure 2 (Ekpenyong et al., 2015). Such a broad variety of activities of lemongrass has made it a preferred choice for research and applications, especially in recent years.

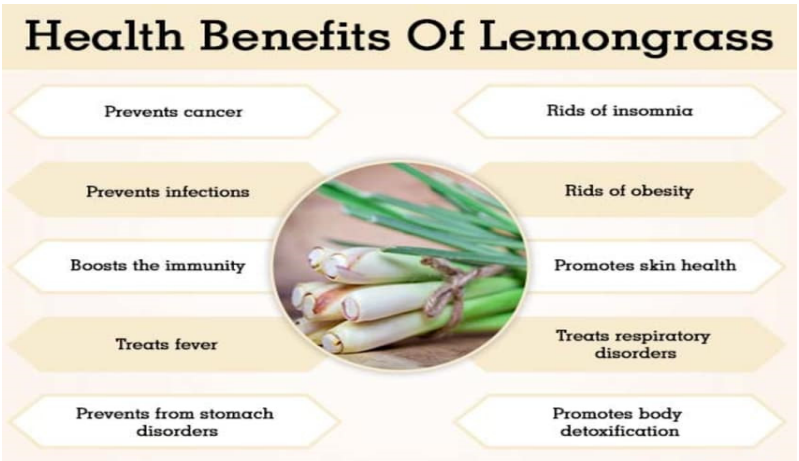

Figure 2. Health benefits of lemongrass.

2.2. Chemical Composition of Lemon Grass

Citral is comprised of mainly two stereo-isomeric mono-terpene aldehydes: geranial and neral, transcitral and cis-citral shown in Figure 3 [6,7]. In general, lemongrass oil contains more than 45% citral, but the amount can vary widely among species. The East

Indian lemongrass (C. citratus) commonly possesses around 30–94% citral [8,9]. Different hydrocarbons such as terpenes, alcohols, ketones and esters, are also reportedly found in the composition of EO [10,11]. The phytochemical composition of C. citratus also includes tannins, saponins, anthraquinones, phenols, flavonoids and alkaloids. In addition, myrcene, geraniol, borneol, citronellol, limonene, a-terpineol, elemicin, nerol, catechol, luteolin, apigenin, quercetin, kaempferol, glycosides, chlorogenic acid, caffeic acid, geranyl acetate as well as methylheptenone, isovaleric aldehyde, fumesol, L-linalool, furfurol, isopulegol, ndecyclic aldehyde, p-coumaric acid, terpinene are also evident in trace amounts in several studies [12–14]. There are also reports of the presence of isoscoparin, swertiajaponin, orientin and other phytochemicals in lemongrass [15,16]. The amount of major constituents of lemongrass EO found in studies shows a greater presence of trans-citral (geranial) and cis-citral (neral) along with more reduced amounts of nerol, geraniol, citronellol, terpinolene, geranyl acetate, myrcene, a-terpineol and other components. Different minerals are also present including potassium (54.02%), calcium (25.87%), silica (9.02%), phosphorus (1.57%). It alsopossesses vitamins A, C, and E and folate, niacin, pyridoxine, riboflavin, as well as protein, carbohydrates and fat [17].

Structures of all the selected derivatives were drawn by using ACD labs Chemsketch v 12.0 and their SMILES notations were generated. Smiles notations of the selected compounds were fed into the online molinspiration software version 2020 (www.molinspiration.com (accessed on 24/09/2020)) for calculation of molecular properties (Log P, total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds, etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors) [18].

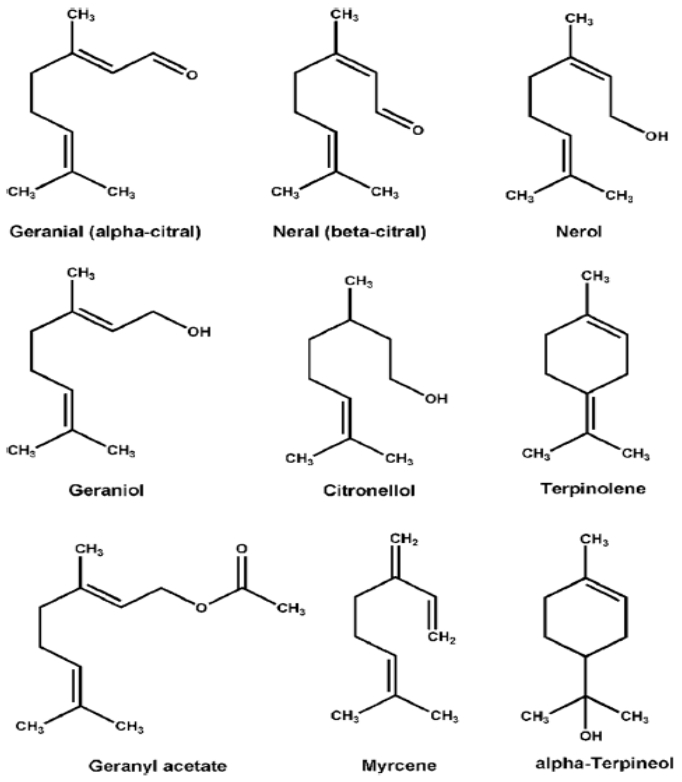

Figure 3. Chemical structure of major constituents in lemongrass essential oil.

2.3. Process

A web based software was used to obtain parameter such as Mi Log P, TPSA (Topological Polar Surface Area) and drug likeness. Mi Log P, is calculated by the methodology (Figure 4) developed by Molinspiration as a sum of fragment based contributions and correction factors. Mi Log P parameter is used to check good permeability across the cell membrane. TPSA is related to hydrogen bonding potential of compound. Calculation of volume developed at Molinspiration (Figure 5) is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailability of drugs. Through drug likeness data's of molecule, it can be checked molecular properties and structure feature in respect to known drugs.

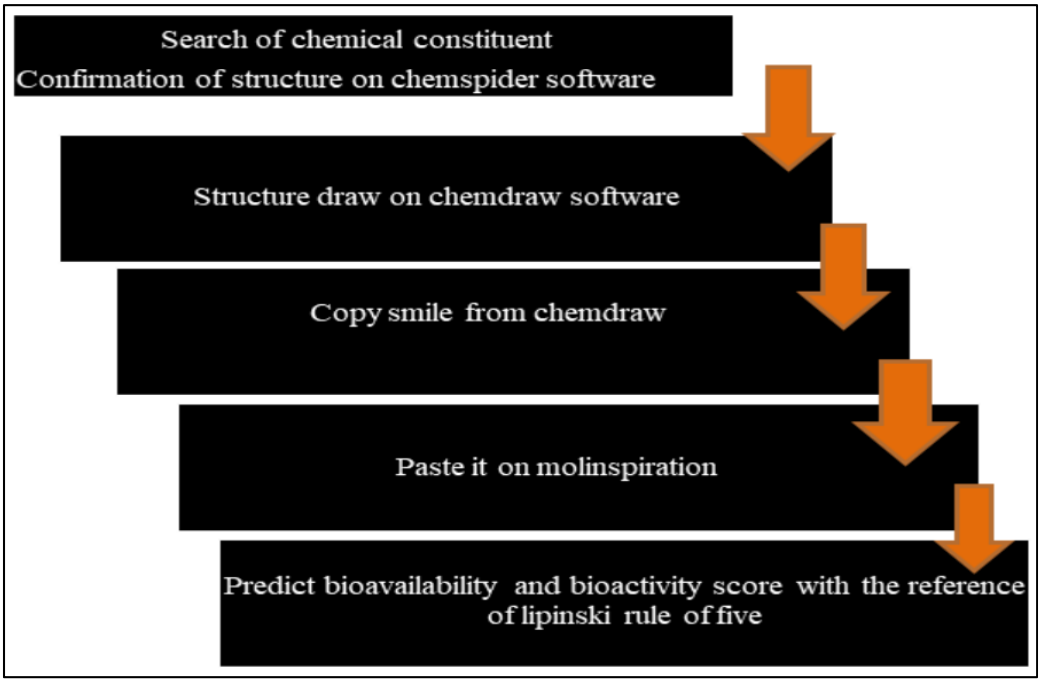

Figure 4. Process of prediction of bioavailability.

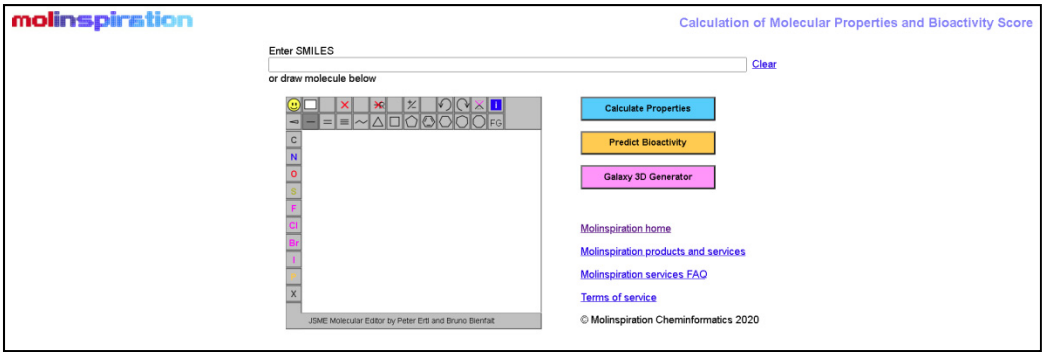

Figure 5. Molinspiration online portal for calculation of molecular properties and bioactivity score.

3. Results and Discussion

The calculated values of various parameters of the isolated compounds for drug likeness as per the process shown in (Figure 4) are presented in Table 1. Drug likeness evaluates (Figure 6) whether a particular molecule is similar to the known drug or not. It is a complex balance of various properties and structural features of a compound. Lipinski's rule is widely used to determine the molecular properties that are important for the drug's pharmacokinetics in vivo. According to Lipinski's rule of five, a candidate molecule is more likely to be orally active if: (a) the molecular weight is under 500; (b) the

calculated octanol/water partition coefficient (log P) is less than 5; (c) there are not more than 5 hydrogen bond donors (OH and NH groups); (d) there are not more than 10 hydrogen bond acceptors (notably N and O).

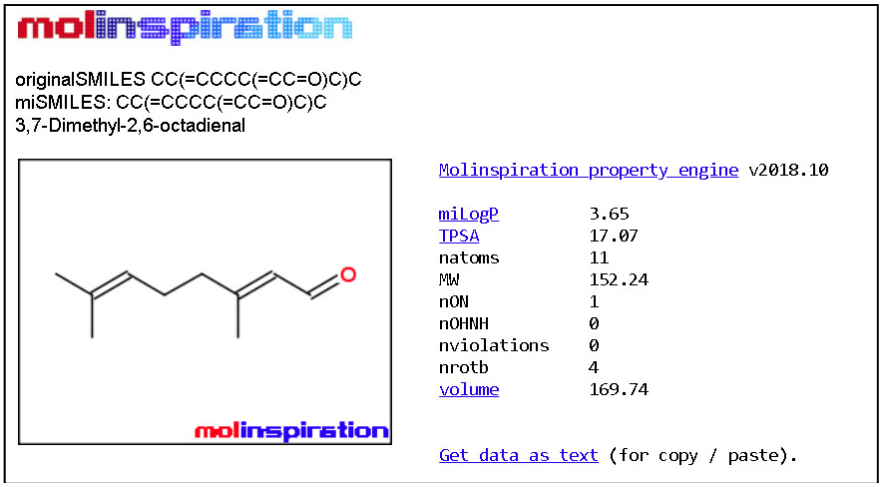

Figure 6. Molinspiration online portal shows molecular properties and bioactivity score of Citral.

Table 1. Drug likeness score for compounds.

Sr. No.	Compounds	Milog P	TPSA	N Atoms	MW	N ON	N OHNH	nViolations	N Rotb	Volume
1.	Citral	3.65	17.07	11	152.24	1	0	0	4	169.74
2.	Geranial (alpha-citral)	3.65	17.07	11	154.25	1	0	0	4	169.74
3.	Neral (beta-citral)	3.65	17.07	11	152.23	1	0	0	4	169.74
4.	Myracene	3.99	0.00	10	136.24	0	0	0	4	162.24
5.	Geraniol	3.20	20.23	11	154.25	1	1	0	4	175.57
6.	Nerol	3.20	20.23	11	153.23	1	1	0	4	175.57
7.	Citronellol	3.15	20.23	11	156.27	1	1	0	5	181.79
8.	Limonene	3.62	0.00	10	136.24	0	0	0	1	157.30
9.	Alpha-Terpinolene	2.60	20.23	11	154.25	1	1	0	1	170.65
10.	Geranyl acetate	3.91	26.30	14	196.29	2	0	0	6	212.09

3.1. Evaluation of Drug Likeness

The drug likeness was calculated and discussed (Table 2) on the basis of Lipinski's rule and its components for all prepared compounds using Molinspiration software (Figure 5).

Table 2. Biological activity of taken compounds with the reference of receptor mechanism.

Sr. No.	Compounds	GPCR Ligand	Ion channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
1.	Citral	−0.86	−0.25	−1.29	−0.42	−0.57	0.02
2.	Geranial (alpha-citral)	−0.86	−0.25	−1.29	−0.42	−0.57	0.02
3.	Neral (beta-citral)	−0.86	−0.25	−1.29	−0.42	−0.57	0.02
4.	Myracene	−1.11	−0.33	−1.51	−0.45	−1.31	−0.07
5.	Geraniol	−0.60	0.07	−1.32	−0.20	−1.03	0.28
6.	Nerol	−0.60	0.07	−1.32	−0.20	−1.03	0.28
7.	Citronellol	−0.81	−0.24	−1.16	−0.61	−0.83	−0.12
8.	Limonene	−0.91	−0.27	−2.01	−0.34	−1.38	−0.21
9.	Alpha-Terpineol	−0.51	0.15	−1.45	−0.02	−0.78	0.14
10.	Geranyl acetate	-0.50	0.04	−1.11	-0.12	-0.80	0.21

The physicochemical properties included:

An octanol-water partition coefficient (Milog P) < 5 that means these show good permeability across cell membranes;a polar surface area (TPSA) < 160 Å2 which has been shown to be a very good descriptor characterizing drug absorption; number of violation (n violations) = 1 or <0 means the compound easily binds to the receptor; a molecular weight (MW) < 500 required for characterizing drug absorption; number of rotatable bonds (n rotb) < 10 measures molecular flexibility; number of hydrogen bond donors (n OHNH) ≤ 5 (the sum of OHs and NHs); total molecular polar surface area (TPSA) > 160A^{o}2; hydrogen bond acceptors (nON) > 7.

From the results it is revealed that these compounds are orally bioactive because they possess groups which act as a substrate for transporters.

3.2. Potency of Compounds According to Obtained Data

3.2.1. Number of Violations

All 10 compounds that were most important hadthe least number or no violations observed.

3.2.2. Molecular Weight

All the constituents of the data pass the Lipinski rule of five for molecular weight.

4. Conclusions

The Phytochemical screening and Pharmacognostical evaluation parameters of *Cymbopogon citratus* were performed and it showed the presence of many pharmacological active phyto constituents. Further study into the absorption, distribution, metabolism, excretion, toxicity (ADMET) of these lead compounds in addition to in vitro and in vivo experiments are needed to validate the utilization and sourcing of various therapeutic interventions from these plants. Effective formulations could be developed using indigenous medicinal plants, with proper pharmacological experiments and clinical trials.

Institutional Review Board Statement: This study was approved by the Institutional Review Board (IRB) of, Konkan Gyanpeeth Rahul Dharkar College of Pharmacy & Research Institute, Karjat, Maharashtra, India and the protocols used in the study were approved by the Committee.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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