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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 correlation between immunomodulators and molecular properties of the *Cymbopogon citratus* derivatives in search of a lead compound through molinspiration cheminformatics software. Ten naturally occurring and 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 are means these shows good permeability across cell membrane. All the screened compounds had minimum and no violations of Lipinski rule. *Cymbopogon citratus* and its derivatives showed good bioactivity score for drug targets including nuclear receptor ligand, protease inhibitor and enzyme inhibition and thus expected to have excellent pharmacological activity in vivo. The results of this study justify their topical application as immunomodulators action but some structural modifications in order to make the compound more polar will 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 is considered as a potential candidate for the further research as its 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

1. Introduction: Research Background

Presently, the global public health threat of international concern is the coronavirus disease-2019 (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 desired pharmacological properties and plays an important role in drug design and development. Natural products are good source of lead compounds. Morphine, quinine, atropine etc are some of lead compounds isolated from natural sources and are in clinical use. But 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, 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 citrates known as lemongrass in different forms plant, leaves.

In addition, a number of biological properties of lemongrass are reported over the years, including but not limited to antibacterial, antifungal, antiprotozoal, anti-inflammatory, antioxidant, antitussive, antiseptic, anti-carcinogenic, cardio-protective and anti-rheumatic activities (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 [6,7]. In general, lemongrass oil contains greater than 45% of citral, but the amount can vary widely among species. The East Indian lemongrass (C. citratus) commonly possesses around 30–94% of 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 amount in several studies [12–14]. There are also reports on the presence of isoscoparin, swertiajaponin, orientin and other phytochemicals in lemongrass [15,16]. The amount of major constituents of lemongrass EO found in studies which 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 in the online molinspiration software version 2020 (www.molinspiration.com) 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].

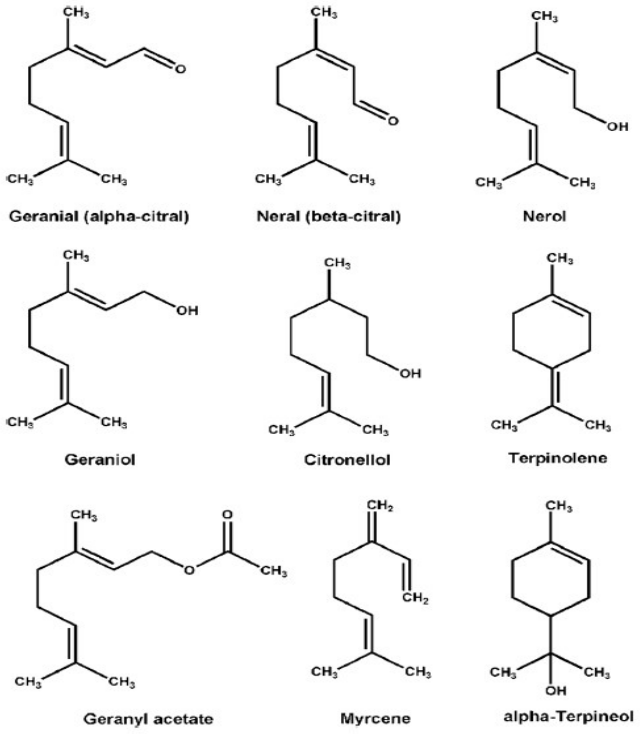

Figure 3. Chemical structure of major constituents in lemongrass essential oil.

2.3. Process

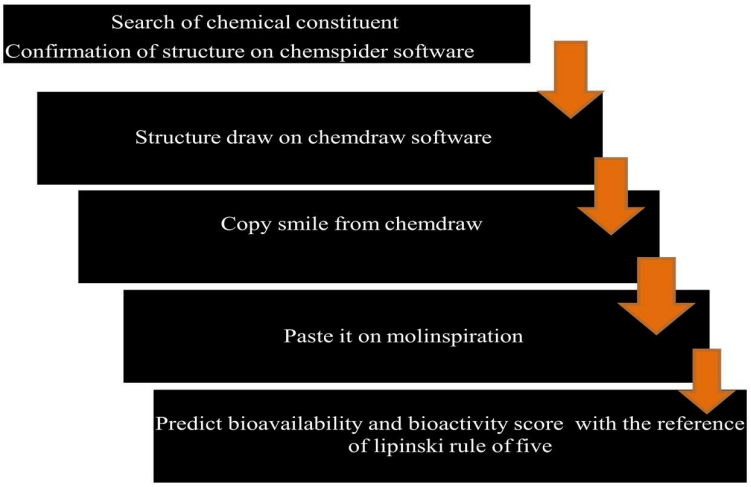

Figure 4. process of prediction of bioavailability.

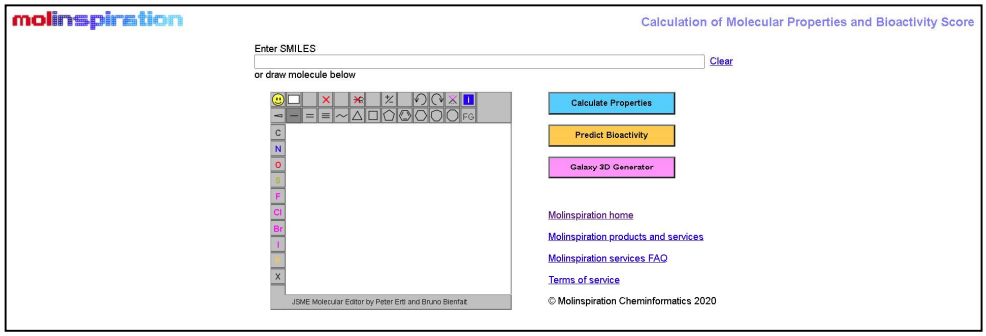

Figure 5. Molinspiration online portal for Calculation of Molecular Properties and Bioactivity Score.

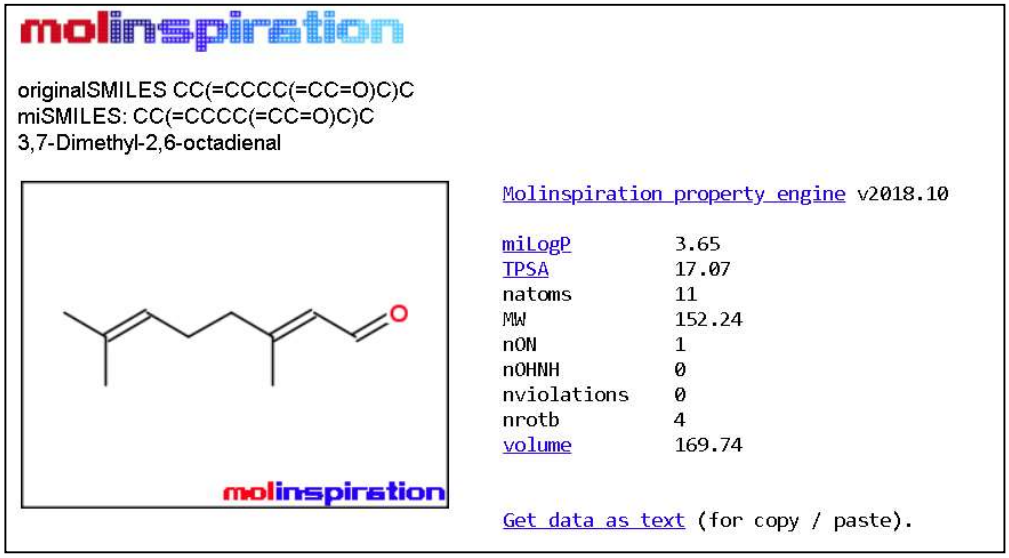

Figure 5. Molinspiration online portal shows Molecular Properties and Bioactivity Score of Citral.

3. Results and Discussion

The calculated values of various parameters of the isolated compounds for drug likeness are presented in the Table 1. Drug likeness evaluates 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 molecular properties that are important for drug's pharmacokinetic in vivo. According to Lipinski's rule of five1, 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).

Table 1. Drug likeness score for compounds.

Sr. No.	Compounds	Milog P	TPSA	N Atoms	MW	N ON	N OHNH	n Violations	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

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

3.1. Evaluation of Drug Likeliness

The drug likeness was calculated and discussed on the basis of Lipinski's rule and its component for all prepared compounds using Molinspiration software.

The physicochemical properties including:

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

From the results reveal that these compounds are orally bioactive because they possess groups which act as substrate for transporter.

3.2. Potency of Compounds According to Obtained Data

3.2.1. Number of Violations

In all the 10 compounds that are more important which have least number or no violations observed.

3.2.2. Molecular Weight

All constituents of data passes 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 utilization and sourcing of various therapeutic interventions from these plants. Effective formulations to be developed using indigenous medicinal plants, With proper pharmacological experiments and clinical trials.

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