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Research Article

In-silico ADMET Pharmacoinformatics of Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol) - acyclic monoterpene alcohol drug from Leaf Essential Oil of *Cymbopogon martinii* from Sirumalai Hills (Eastern Ghats), INDIA

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Abstract

Cymbopogon martinii is a grass from genus *Cymbopogon* (lemongrasses) native to India, but widely cultivated in other places for its aromatic essential oil. *C. martinii* known as Palmarosa smells sweet with rose-like odor. Geraniol, a terpene alcohol present in *Cymbopogon martinii* essential oil (CMEO) is much valued for its typical aroma and medicinal uses. In addition to the pleasant odor, Geraniol is known for fungicidal, nematicidal, acaricidal, insecticidal, repellent properties hence, used as Natural Pest Control Agent (NPCA) exhibiting low toxicity. Furthermore, geraniol has been suggested to exemplify a new class of chemoprevention agents in the treatment of cancer. Biological activities such as antimicrobial, anti-oxidant, anti-inflammatory and vascular effects have been investigated. In the present study, GCMS based *in-silico* ADMET pharmacoinformatics aspects (Physicochemical, Lipophilicity, Medicinal Chemistry, Druglikeness, Absorption, Water Solubility, Distribution, Metabolism, Pharmacokinetics, Excretion, Environmental Toxicity, Tox21 Pathway and Toxicophore Rules) with PASS prediction of geraniol from CMEO has been bioprospected from human health perspective point of view.

Keywords: GCMS; ADMET; Pharmacoinformatics; Geraniol; Essential Oil; *Cymbopogon martinii*; Palmarosa; CMEO; PBNPs; Sirumalai Hills; Eastern Ghats

INTRODUCTION

Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol) is acyclic monoterpene alcohol with chemical formula $C_{10}H_{18}O$. Referred to as "***Geraniol***" is a mixture of two cis-trans isomers namely geraniol (trans) and nerol (cis). Geraniol was first isolated from *Cymbopogon martinii* essential oil while nerol was obtained from neroli[1,2]. It is a common aromatic constituent present in essential oils several medicinal plants, however, with varying concentration in leaf/ floral tissues. Maximum EO content has been reported from *Monarda fistulosa*[3] (> 95.00%), followed by ninde oil[4] (66.00%), rose oil[5] (44.40%), palmarosa oil[6] (53.50%) and citronella oil[7] (24.80%).

Geraniol[8] is clear pale-yellow oil, insoluble in water, soluble in organic solvents. It is obtained from flowers of many species. It is also present in vegetative tissues of several species of herbs; most often geranial and neral are present together as the oxidation products of geraniol[9]. Geraniol has a typical rose-like odor; taste of Geraniol at a concentration of 10 ppm is sweet[10] therefore, commonly used as a fragrance material world over. It has been reported that geraniol is the main component of deodorants (76%); domestic/ household products (41%); cosmetic formulations (33%) available in market world over. Geraniol as a plant based natural product (PBNPs) is directly used as natural ingredient in aforesaid products, to meet and feed the market demand its production exceeds 1000 mt per annum[8].

Geraniol is well documented to exhibit biochemical and pharmacological properties. It has been shown that geraniol is an effective plant-based insect repellent. CMEO is of demand in the market as natural pest control agents due to its insecticidal, repellent and/or antifeedant properties[11]. Further, its low mammalian toxicity and biodegradability favor its development as a lead drug in many pharma-industrial products. Using an impregnated fabric disc bioassay Jeon et al. demonstrated the acaricidal activities of geraniol against storage food mite and compared the activity of geraniol to benzyl benzoate (acaricide) to show that geraniol was more effective than benzyl benzoate[12].

Khallaayoune et al.[13] demonstrated that among four monoterpenes (α-pinene, geraniol, limonene and p-cymene), geraniol, in a 5% dilution displayed the strongest acaricidal activity by direct contact with the mites[14]. In a study lemongrass oil extract added to 25% geraniol oil exhibited longest protection time against mosquitoes[15]. Müller et al.[16] determined the degree of personal protection provided by commercial citronella, linalool and geraniol candles or diffusers. Indoors, the repellency rate of geraniol candles was 50%, while the diffusers provided a repellency rate of 97%. Geraniol exerts in vitro and in vivo antitumor activity against murine leukemia, hepatoma and melanoma cells.[17,18]

In-vitro study demonstrated antibiofilm activity of carvacrol, geraniol, and thymol against Candida[19]. Acne - Palmarosa essential oil showed antibacterial activity against the bacteria that can cause skin acne with geraniol as the most likely active constituent. More research is warranted[20]. Anti-Allergy - Geraniol and beta-citronellol isolated from P. graveolens was effective against house dust mites[21]. Anti-Parasite - Palmarosa and its geraniol constituent both showed potent anthelmintic activity against *Caenorhabditis elegans*[22]. Preservative - Essential oils of cilantro, coriander, cinnamon, oregano, rosemary, sage, clove, thyme, lemongrass, turmeric, mint, basil, and constituents of linalool, cinnamaldehyde, carvacrol, thymol, terpinene, cymene, alpha/beta pinene, bornyl acetate, camphor, 1,8-cineole, alpha terpeneol, geraniol, perrilaldehyde, and eugenol have demonstrated food preserving potential.[23] Anti-Cancer - Citronellol, citronellyl formate, geraniol and citronellyl acetate from geranium oil exhibited marginal anti-tumour activities.[24] Repellent - Constituents of geranium oil demonstrated safe repelling action against the mosquito associated with the West Nile virus.[25] Antioxidant - Coriander seed essential oil and its major components of geraniol (24%), d-linanol (16%), borneol (7%), α-pinene (9%) and β-pinene showed antioxidant activities in vitro.[26]

The Plant Source: *Cymbopogon martini* (Roxb.) Will. Watson[27]

Systematic Position

Class: Equisetopsida C. Agardh

Subclass: Magnoliidae Novák Ex Takht.

Superorder: Lilianae Takht.

Order: Poales Small

Family: Poaceae Barnhart

Genus: *Cymbopogon* Spreng.

Species: *C. martini* (Roxb.) Will. Watson.

Common Name: Palmarosa grass

Vernacular Name: Hindi – Rusa Ghas; Tamil – Kavathampullu; Marathi - Rohish

Citation: *Cymbopogon martini* (Roxb.) Will. Watson in Atkins., Bot. Himalayan Distr. N. W. Prov. 392. 1882; *Andropogon martini* Roxb., Fl. Ind. (Carey and Wallich ed.) 1: 280–281. 1820. Type: "A native of the high lands of Balla-ghat, General Martin collected the seeds while there with the army, during the last war with Tippoo Sultan, and has reared abundance of it at Lucknow." *Andropogon schoenanthus* L. var. martini (Roxb.) Hook. f., Fl. Brit. India (J.D. Hooker). 7(21): 204. 1896; *Cymbopogon martini* (Roxb.) Will. Watson var. sofia B.K. Gupta, Proc. Indian Acad. Sci., B 71: 97. 1970. *Andropogon pachnodes* Trin., Mém. Acad. Imp. Sci. St.-Pétersbourg, Sér. 6, Sci. Math. 2(3): 284. 1832. Type: Nepal; Wallich s.n; *Cymbopogon pachnodes* (Trin.) Will. Watson in Atkins., Bot. Himalayan Distr. N.W. Prov. 392. 1882; *Cymbopogon motia* B.K. Gupta, Proc. Indian Acad. Sci., B 71: 92. 1970. Type: India; B.K. Gupta 25 (DD); *Cymbopogon martinianus* Schult., Mant. 2 (Schultes) 459. 1824, nom. superfl. & illegit. for *Andropogon martini* Roxb.

Distribution: Native to India - Andhra Pradesh, Assam, Bihar, Chhattisgarh, Goa, Gujarat, Himachal Pradesh, Karnataka, Kerala, Maharashtra, Odisha, Punjab, Rajasthan, Telangana, Tamil Nadu; Asia: China, Srilanka, Myanmar, Nepal, Bhutan, Bangladesh, Pakistan[27].

Habit: *Cymbopogon martini* is Perennial. The grass is cultivated elsewhere in the tropics for its oils on commercial scale to meet the market demand of its essential oil. **'Motia'** yields Palmarosa Essential Oil and **'Sofia'** yields Ginger-Grass Oil[27].

Botanical Description: Perennial from a short woody rootstock. Culms tufted, up to 3 m tall, lower nodes often swollen, mealy. Leaf sheaths glabrous; leaf blades lanceolate, usually glaucous below, dark green above, up to 50 × 2–3 cm, glabrous, base cordate, often amplexicaul, apex filiform; ligule 2–4 mm. Spathate panicle narrow, dense, erect, 20–30 cm; spatheoles green becoming reddish, 2–4 cm; racemes 1.5–2 cm; rachis internodes and pedicels ciliate on margins, back sometimes pubescent; pedicel of homogamous pair swollen, barrel-shaped, shiny, fused to internode at base. Sessile spikelet oblong, 3.5–4.5 mm; lower glume flat, deeply grooved below middle (appearing as a line or keel on inside), keels winged above middle, vein-less or 2-veined between keels; upper lemma 2-lobed; awn 1.4–1.8 cm. Pedicelled spikelet 3.5–4 mm. Fl. and fr. Jul–Oct.

Ethnobotanical Narration and Medicinal Uses: *Cymbopogon martinii* Leaf decoction (CMLD) 50-60 ml is used to treat intestinal worms/ diarrhea and other gastro intestinal disorders (GID); paste of leaf and stem is applied over scabies affected area to restore discoloration of skin; PEO mixed with hot water is used for steam inhalation during asthma and common cold; leaf is boiled in cow milk (40-50 ml) and consumed orally to improve lactation in feeding mothers; CMLD 50-60 ml is used as blood purifier; CMLD improves the strength of cardiac muscles; *Cymbopogon martinii* Leaf Paste (CMLP) is applied over joints with pain and inflammation as part of treatment; cold infusion of leaf (50-60 ml) is given to treat fever and

anorexia. *C. martinii* is an Ayurvedic plant used in the treatment of joint pain, respiratory diseases, anorexia, intestinal worms, skin diseases and diarrhea.[28-30,]

MATERIALS AND METHODS

Collection, Preparation and Extraction of Oil from the leaf sample: The leaf samples were collected from wild in Sirumalai Region 10.1942° N, 77.9967° E; Elevation - 1,600 m (5,200 ft) (Part of Eastern Ghats, Dindigul District, TamilNadu, INDIA) during Feb 2021. The leaf sample were preserved, taken to laboratory, identified by using flora[31,32] shade dried and processed as per the protocol for preparation of sample according to the methods previously described by Soorya et al.[30] however, with modifications in the temperature and duration of processing of the sample. As much as 100 g leaf was weighed and dried in an oven at 60°C. Dried sample was ground to powder using Thomas Willey milling machine and sieved on a mesh screen (3×3 mm^2). Sample was stored at 4°C in air-tight container with screw caps until further use. Sample was prepared according to the methods previously described by Soorya et al.[30] 25 g of sample was suspended in 250 mL of distilled water in stoppered flasks and allowed to stand for 24 h, filtered with Whatman No 24 filter paper, concentrated in a rotary evaporator for 12 h at 50°C and dried in vacuum desiccator. Yield was calculated; extract was suspended in ethyl acetate and subjected to GC-MS analysis.

GC-MS Analysis

Cymbopogon martini Essential Oil (CMEO) was extracted, from the leaf samples collected from the Sirumalai Hills, Kodai Road Region, Dindigul District, Tamil Nadu, India. Phyto-components were identified using GC–MS detection system as described previously, however with modification, whereby portion of the extract was analysed directly by headspace sampling. GC–MS analysis was accomplished using an Agilent 7890A GC system set up with 5975C VL MSD (Agilent Technologies, CA, USA). Capillary column used was DB-5MS (30×0.25 mm, film thickness of 0.25 µm; J&W Scientific, CA, USA). Temperature program was set as follows: initial temperature 50°C held for 1 min, 5°C per min to 100°C, 9°C per min to 200°C held for 7.89 min, and the total run time was 30 min. The flow rate of helium as a carrier gas was 0.811851 mL/ min. MS system was performed in electron ionization (EI) mode with Selected Ion Monitoring (SIM). The ion source temperature and quadruple temperature were set at 230°C and 150°C, respectively. Identification of phyto-components was performed by comparison of their retention times and mass with those of authentic standards spectra using computer searches in NIST 08.L and Wiley 7n.l libraries[30].

ADMET Prediction

Selected phytocompounds were subjected to ADMET prediction (SwissADME) and toxicity prediction using TOPKAT (Accelrys, Inc., USA). QikProp develops and employs QSAR/QSPR models using partial least squares, principal component analysis and multiple linear regression to predict physic-chemically significant descriptors[33-35].

RESULTS AND DISCUSSION

The bioactivity of plant secondary metabolites including essential oils (EOs) is known for their medicinal use, flavour and fragrance since ancient times. Furthermore, it has been well established that these secondary class of compounds significant influence the physiological process in the human body (increased and/or decreased).[36-40] Therefore, a clear understanding to their physiological, biochemical and metabolic role of these compounds in human and animal system is warranted[37,38]. Accordingly, GCMS analysis has emerged as a powerful tool to analyse the composition of phytocompounds. GCMS analysis of phytocompounds in *Cymbopogon martinii* ethanolic leaf extract is given in Table 1.

Physicochemical properties of Geraniol: Molecular Weight (MW) (154.140); Volume (185.034); Density (0.833); Nha (1); Nhd (1); nRot (4); nRing (0); MaxRing (0); NHet (1); FChar (0); NRig (2); Flexibility (2.000); Stereo Centers (0); TPSA (20.230); LogS (-2.718); LogP (3.606); LogD (2.719). **Lipophilicity properties:** Log $P_{o/w}$ (iLOGP) (2.75); Log $P_{o/w}$ (XLOGP3) (3.56); Log $P_{o/w}$ (WLOGP) (2.67); Log $P_{o/w}$ (MLOGP) (2.59); Log $P_{o/w}$ (SILICOS-IT) (2.35); Consensus Log $P_{o/w}$ (2.78); Medicinal Chemistry QED (0.617); SAscore (2.681); Fsp^3 (0.600); MCE-18 (0.000); NPscore (2.905); Lipinski Rule (Accepted); Pfizer Rule (Rejected); GSK Rule (Accepted); Golden Triangle (Rejected); PAINS (0 alert(s)); ALARM NMR Rule (0 alert(s)); BMS Rule (0 alert(s)); Chelator Rule (0 alert(s)); Brenk (1 alert: isolated alkene); Leadlikeness (No; 2 violations: MW<250, XLOGP3>3.5); Synthetic accessibility (2.58). **Druglikeness properties:** 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) (Table 2a).

ADMET properties of Geraniol - Absorption: The calculated value (in parenthesis) for Caco-2 Permeability (-4.299); MDCK Permeability (1.4e-05); Pgp-inhibitor (---); Pgp-substrate (---); HIA (---); $F_{20\%}$ (+++); $F_{30\%}$ (+++). **Water Solubility:** Log *S* (ESOL) (-2.78); Solubility (2.59e-01 mg/ml ; 1.68e-03 mol/l); Class (Soluble); Log *S* (Ali) (-3.67); Solubility (3.30e-02 mg/ml ; 2.14e-04 mol/l); Class (Soluble); Log *S* (SILICOS-IT) (-1.84); Solubility (2.20e+00 mg/ml ; 1.43e-02 mol/l); Class (Soluble). **Distribution properties:** PPB (88.865%); VD (3.402); BBB Penetration (+++); Fu (9.836%), **Metabolism properties:** CYP1A2 inhibitor (+); CYP1A2 substrate (--); CYP2C19 inhibitor (---); CYP2C19 substrate (-); CYP2C9 inhibitor (---); CYP2C9 substrate (++); CYP2D6 inhibitor (---); CYP2D6 substrate (--); CYP3A4 inhibitor (---); CYP3A4 substrate (--). In a study, CYP2B6 showed high activity in geraniol metabolism before CYP1A1 and CYP3A5. CYP1B1 and CYP2E1 showed low activity. Nevertheless, CYP1A1 and CYP3A5 are responsible for the majority of geraniol metabolism in the skin because they dominate in it[40]. Furthermore, CYP2B6 a dominant isoform of CYP involved in the metabolism of xenobiotics in the liver[41-43]. However, no pharmacokinetic and bioavailability data on geraniol are currently available[42]. Systematic elucidation of the mechanism of geraniol via network pharmacology, drug design, development and therapy indicated that geraniol has superb druggability with 38 putative identified target genes. GO, KEGG, and network analyses revealed that the targets were associated with cancer, inflammatory immunoreactions related physiological processes[44].

Poor pharmacokinetics and toxicity are the most important causes of costly delays, further, they impede drug discovery and development[44]. **Pharmacokinetics properties:** GI absorption (High); BBB permeant (Yes); P-gp substrate (No). **Excretion properties:** CL (12.604); $T_{1/2}$ (0.737) (Table 2b). Comparative Toxicogenomics Database (CTD, http://ctdbase.org/), is a robust, publicly available database for toxicogenomic information. **Toxicity properties:** hERG Blockers (---); H-HT (+++); DILI (---); AMES Toxicity (---); Rat Oral Acute Toxicity (---); FDAMDD (---); Skin Sensitization (+++); Carcinogencity (+); Eye Corrosion (+); Eye Irritation

(+++); Respiratory Toxicity (---). **Environmental Toxicity properties:** Bioconcentration Factors (0.939); IGC_{50} (1.797); $LC_{50}FM$ (3.762); $LC_{50}DM$ (5.066). **Tox21 Pathway properties:** NR-AR (---); NR-AR-LBD (---) ; NR-AhR (---); NR-Aromatase (---); NR-ER (---); NR-ER-LBD (---); NR-PPAR-gamma (---); SR-ARE (---); SR-ATAD5 (---); SR-HSE (+); SR-MMP (---); SR-p53 (---). **Toxicophore Rules:** Acute Toxicity Rule (0 alert(s)); Genotoxic Carcinogenicity Rule (1 alert(s)); Non-Genotoxic Carcinogenicity Rule (0 alert(s)); Skin Sensitization Rule (1 alert(s)); Aquatic Toxicity Rule (0 alert(s)); Non-Biodegradable Rule (0 alert(s)); Sure-ChEMBL Rule (0 alert(s)); FAF-Drugs4 Rule (0 alert(s)) (Table 2c). Pharmacokinetic properties of geraniol meet the requirements, indicating that geraniol is an ideal candidate for drug development[44].

The molecular properties of geraniol including bioavailability and membrane permeability have been linked with many fundamental molecular descriptors like logP (partition coefficient), molecular weight (MW), or number of hydrogen bond acceptors and donors in a molecule. The "rule of five" has been formulated by using these molecular properties[45]. It shows that the majority molecules having fine membrane permeability have molecular weight less than or equal to 500, calculated octanol–water partition coefficient, log P ≤ 5, hydrogen bond donors less than or equal to 5, and acceptors less than or equal to 10[46]. Hence, Lipinski's Rule of Five has been used to predict and test the biological availability of properties like absorption, distribution, metabolism, and elimination (ADME) of the main compounds. Geraniol including citronellol, alpha-terpineol, o-cymene, d-limonene, eucalyptol, alpha-pinene, and 3-carene obeyed the Lipinski's rule of five, as well as the compound possess properties of drug likeliness[47].

As one of the best filters in the virtual screening of bioactive molecules, in order to be an effective drug in early preclinical development, the forecasting of ADME (absorption, distribution, metabolism and excretion) profiles of the selected compounds, including their pharmacokinetic and drug-like properties, have been investigated using Swiss ADME[48] (http://www.swissadme.ch/). The selected phytocompound geraniol correctly meet the Lipinski Rule of five, and also share topological polar surface area TPSA values less than 30 Å2, suggesting good brain penetration and good lipophilicity behaviour, which is expressed by the consensus Log Po/w in the range 2.25–4.75. Their bioavailability score of 0.55 indicates their more drug-like properties[49]. Noticeably, there is no P-glycoprotein (P–gp) substrate justifying their good intestinal absorption and bioavailability; the compounds exhibited high gastrointestinal absorption (GI) (except α-selinene), and only isocembrol and α-selinene were predicted to not cross the blood–brain barrier (BBB). However, the others easily pass the blood–brain barrier (BBB) permeant, and can bind to specific receptors. The study's components interacted at most with two isoenzymes of the Cytochrome P (CYP) family, confirming their better effectiveness with insignificant toxicity (Table 2a,b,c).

Target identification and mechanism of action in chemical biology significantly influence drug discovery.[50] PASS (Prediction of Activity Spectra for Substances) is a tool for evaluating the general biological potential of an organic drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. Thus, PASS can be used to estimate the biological activity profiles for virtual molecules, prior to their chemical synthesis and biological testing. Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds (resembles the structures of molecules, which are the most typical in a sub-set of "actives" in PASS training set). Pi (probability "to be inactive") estimates the chance that the studied compound is belonging to the sub-class of inactive compounds. PASS prediction of activity spectra of geraniol is given in Table 3a,b.

CONCLUSIONS

Medicinal plants have proven record as a source of biomolecules with therapeutic potential represent a pool for novel drug leads. In the past, pharmaceutical industry focused on libraries of synthetic compounds as drug discovery source. They are comparably easy to produce and resupply, and demonstrate good compatibility with established high throughput screening (HTS) platforms. However, a declining trend in the number of new drugs reaching the market, raising renewed scientific interest in drug discovery from natural sources, despite of its known challenges. Geraniol the main component of CMEO is a widely used as a fragrance compound in cosmetic and household products, but due to its wide array of biological activities - antimicrobial, antioxidant, anti-inflammatory, anticancer with significantly low-toxicity *vis-a-vis* proven high efficacy, it can potentially be a part of new class of therapeutic agents against several human diseases. To sum-up, geraniol is an active ingredient/ promising candidate for the development of effective multi-targeted anticancer medicament of GRAS standard. Nevertheless, its potential interactions with other biologically active substances warrant in-depth research in particular *in vitro* and animal models through clinical trials to lead the pharma-market.

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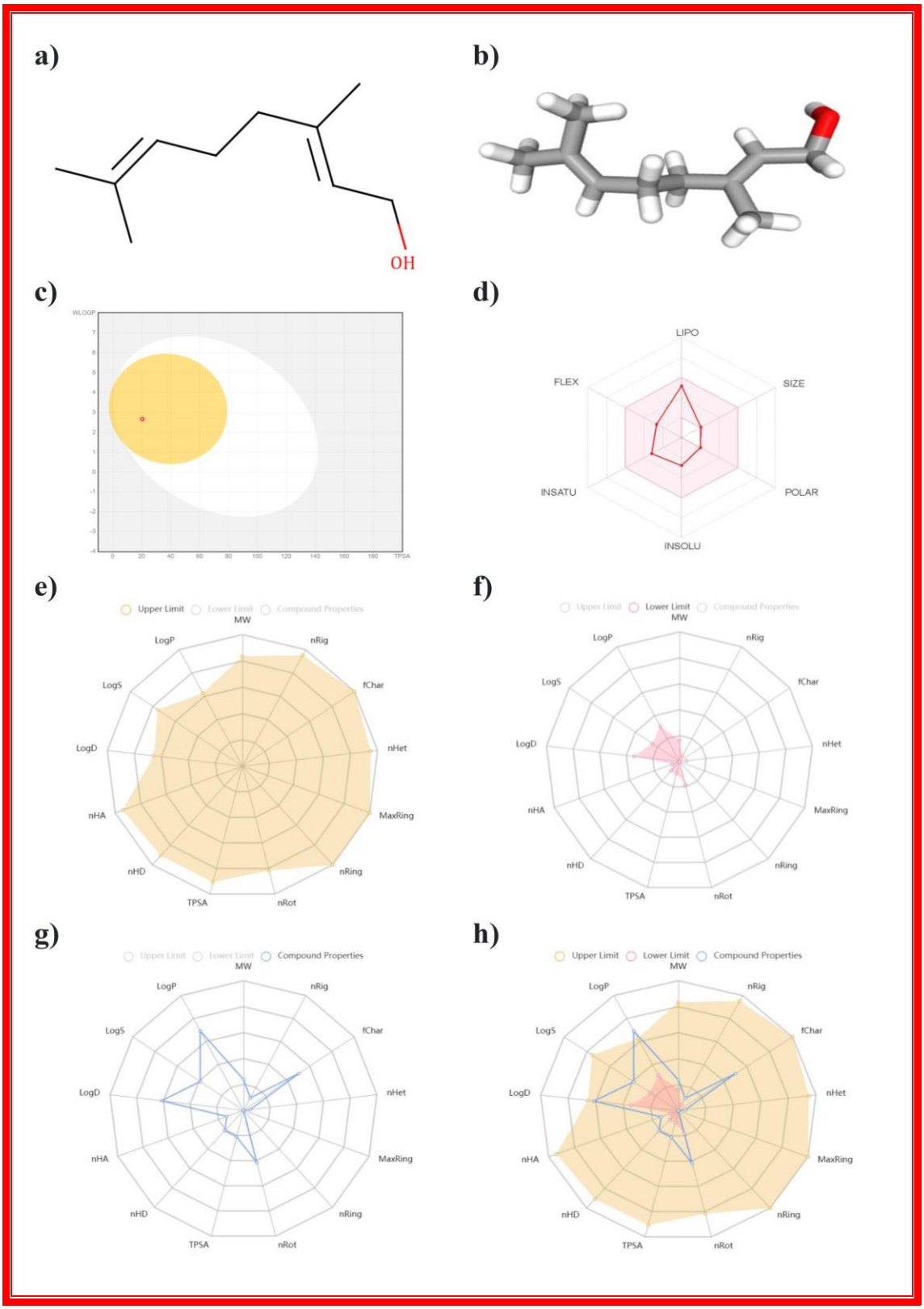

Figure 1: Phytocompound physiochemical properties of Geraniol; a) 2D, b) 3D, c) Boiled Egg Model; d) Bioavailability Radar Map, e) Upper Limit; f) Lower Limit; g) Compound Properties; h) Cumulative map.

Table 1 GCMS analysis of *Cymbopogon martinii* leaf extract

SNO	RT	COMPOUND	AREA
1.	13.2	α-Pinene	0.01
2.	18.5	β-Pinene	0.01
3.	22.3	β -Myrcene	0,24
4.	25.0	Limonene	0,17
5.	25.2	Isopentanol	0,02
6.	25.8	1,8-Cineole	0,12
7.	27.5	Cis-B-Ocimene	0,39
8.	28.8	Trans-B-Ocimene	1,63
9.	30.3	*P*-CYMENE	0,01
10.	31.2	Terpinolene	0,01
11.	35.1	6-Methyl-5-Hepten-2-One	0,03
12.	44.5	Menthone	0,06
13.	45.3	Citronellal	0,01
14.	46.5	Isomenthone	0,02
15.	49.3	Linalool	1,82
16.	50.0	1-Octanol	0,01
17.	50.2	Linalyl Acetate	0,01
18.	50.9	Menthyl Acetate	0,01
19.	52.8	β -ELEMENE	0,05
20.	53.5	β -Caryophyllene	1,07
21.	55.6	Menthol	0,63
22.	56.8	Trans-Pinocarveol	0,01
23.	57.0	Pulegone	0,01
24.	57.2	E- β -Farnesene	0,01
25.	58.2	α-Humulene	0,07
26.	58.6	Neral	0,22
27.	59.2	α-Terpineol	0,02
28.	59.4	γ-Selinene	0,01
29.	59.7	Geranyl Formate	0,09
30.	60.6	Germacrene D	0,02
31.	61.7	Geranial	0,62
32.	61.8	Piperitone	0,01
33.	63.0	Geranyl Acetate	13,45
34.	63.6	γ-Cadinene	0,01
35.	65.2	Nerol	0,13
36.	**68.2**	**Geraniol**	**76,97**
37.	70.8	Geranyl Butyrate	0,11
38.	72.2	Geranic Ester	0,04
39.	75.6	Aliphatic Ester	0,03
40.	76.3	Isocaryophyllene Oxyde	0,02
41.	76.9	Caryophyllene Oxyde	0,12
42.	78.4	Nerolidol	0,07
43.	78.7	Caprylic Acid	0,01
44.	81.3	Geranyl Caproate	0,48
45.	81.7	Aliphatic Ester	0,07
46.	83.5	Aliphatic Alcohol	0,05
47.	87.6	Sesquiterpenol	0,01
48.	90.0	Farnesyl Acetate	0,10
49.	91.2	Geranyl Caprylate	0,10
50.	92.3	Geranic Acid	0,02
51.	94.1	Farnesol	0,71
52.	97.1	Precocene Ii Mw=220	0,03
53.			**100,00**

Table 2a Physicochemical properties of Geraniol

PROPERTY	**VALUE**
Physicochemical	
Molecular Weight (MW)	154.140
Volume	185.034
Density	0.833
Nha	1
Nhd	1
nRot	4
nRing	0
MaxRing	0
NHet	1
FChar	0
NRig	2
Flexibility	2.000
Stereo Centers	0
TPSA	20.230
LogS	-2.718
LogP	3.606
LogD	2.719
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.75
Log $P_{o/w}$ (XLOGP3)	3.56
Log $P_{o/w}$ (WLOGP)	2.67
Log $P_{o/w}$ (MLOGP)	2.59
Log $P_{o/w}$ (SILICOS-IT)	2.35
Consensus Log $P_{o/w}$	2.78

Medicinal Chemistry	
QED	0.617
SAscore	2.681
Fsp^3	0.600
MCE-18	0.000
NPscore	2.905
Lipinski Rule	Accepted
Pfizer Rule	Rejected
GSK Rule	Accepted
Golden Triangle	Rejected
PAINS	0 alert(s)
ALARM NMR Rule	0 alert(s)
BMS Rule	0 alert(s)
Chelator Rule	0 alert(s)
Brenk	1 alert: isolated alkene
Leadlikeness	No; 2 violations: MW<250, XLOGP3>3.5
Synthetic accessibility	2.58
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

Table 2b ADMET properties of Geraniol

Absorption	
Caco-2 Permeability	-4.299
MDCK Permeability	1.4e-05
Pgp-inhibitor	---
Pgp-substrate	---
HIA	---
$F_{20\%}$	+++
$F_{30\%}$	+++
Water Solubility	
Log *S* (ESOL)	-2.78
Solubility	2.59e-01 mg/ml ; 1.68e-03 mol/l
Class	Soluble
Log *S* (Ali)	-3.67
Solubility	3.30e-02 mg/ml ; 2.14e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-1.84
Solubility	2.20e+00 mg/ml ; 1.43e-02 mol/l
Class	Soluble
Distribution	
PPB	88.865%
VD	3.402
BBB Penetration	+++
Fu	9.836%
Metabolism	
CYP1A2 inhibitor	+
CYP1A2 substrate	--
CYP2C19 inhibitor	---
CYP2C19 substrate	-
CYP2C9 inhibitor	---
CYP2C9 substrate	++
CYP2D6 inhibitor	---
CYP2D6 substrate	--
CYP3A4 inhibitor	---
CYP3A4 substrate	--
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
Excretion	
CL	12.604
$T_{1/2}$	0.737
Toxicity	
hERG Blockers	---
H-HT	+++
DILI	---
AMES Toxicity	---
Rat Oral Acute Toxicity	---
FDAMDD	---
Skin Sensitization	+++
Carcinogencity	+
Eye Corrosion	+
Eye Irritation	+++
Respiratory Toxicity	---

Note: For classification endpoints, the prediction probability values are transformed into six symbols:

0-0.1(---); 0.1-0.3(--); 0.3-0.5(-); 0.5-0.7(+); 0.7-0.9(++); and 0.9-1.0(+++)

Table 2c Toxicological properties of Geraniol

Environmental Toxicity	
Bioconcentration Factors	0.939
IGC_{50}	1.797
$LC_{50}FM$	3.762
$LC_{50}DM$	5.066
Tox21 Pathway	
NR-AR	---
NR-AR-LBD	---
NR-AhR	---
NR-Aromatase	---
NR-ER	---
NR-ER-LBD	---
NR-PPAR-gamma	---
SR-ARE	---
SR-ATAD5	---
SR-HSE	+
SR-MMP	---
SR-p53	---
Toxicophore Rules	
Acute Toxicity Rule	0 alert(s)
Genotoxic Carcinogenicity Rule	1 alert(s)
NonGenotoxic Carcinogenicity Rule	0 alert(s)
Skin Sensitization Rule	1 alert(s)
Aquatic Toxicity Rule	0 alert(s)
NonBiodegradable Rule	0 alert(s)
SureChEMBL Rule	0 alert(s)
FAF-Drugs4 Rule	0 alert(s)

Table 3a PASS predicted possible functional effects

Pa	*Pi*	Predicted Functional Role/ Effect
0.161	**0.052**	(N-acetylneuraminyl)-galactosylglucosylceramide N-acetylgalactosaminyltransferase inhibitor
0.467	**0.059**	(R)-6-hydroxynicotine oxidase inhibitor
0.505	**0.023**	(R)-Pantolactone dehydrogenase (flavin) inhibitor
0.185	**0.009**	(R)-aminopropanol dehydrogenase inhibitor
0.109	**0.076**	(R)-limonene 6-monooxygenase inhibitor
0.205	**0.043**	(R,R)-butanediol dehydrogenase inhibitor
0.134	**0.014**	(S)-2-Methylmalate dehydratase inhibitor
0.179	**0.031**	(S)-2-hydroxy-acid oxidase inhibitor
0.261	**0.033**	(S)-3-amino-2-methylpropionate transaminase inhibitor
0.206	**0.050**	(S)-3-hydroxyacid ester dehydrogenase inhibitor
0.370	**0.068**	(S)-6-hydroxynicotine oxidase inhibitor
0.285	**0.007**	(S)-carnitine 3-dehydrogenase inhibitor
0.254	**0.052**	1,2-alpha-L-fucosidase inhibitor
0.051	**0.033**	1,3-Beta-glucan synthase inhibitor
0.373	**0.013**	1,4-Alpha-glucan branching enzyme inhibitor
0.673	**0.012**	1,4-Lactonase inhibitor
0.239	**0.014**	1,5-Anhydro-D-fructose reductase inhibitor
0.337	**0.069**	1-Acylglycerol-3-phosphate O-acyltransferase inhibitor
0.227	**0.003**	1-Alkyl-2-acetylglycerol O-acyltransferase inhibitor
0.036	**0.010**	1-Alkyl-2-acetylglycerophosphocholine esterase inhibitor
0.513	**0.024**	1-Alkylglycerophosphocholine O-acetyltransferase inhibitor
0.274	**0.009**	1-Aminocyclopropane-1-carboxylate deaminase inhibitor
0.060	**0.027**	1-Deoxy-D-xylulose-5-phosphate reductoisomerase inhibitor
0.059	**0.038**	1-Phosphofructokinase inhibitor
0.110	**0.029**	1-Pyrroline-5-carboxylate dehydrogenase inhibitor
0.246	**0.003**	11-Cis-retinyl-palmitate hydrolase inhibitor
0.075	**0.061**	12-Lipoxygenase inhibitor
0.364	**0.018**	15-Hydroxyprostaglandin-D dehydrogenase (NADP+) inhibitor
0.096	**0.026**	15-Lipoxygenase inhibitor
0.257	**0.021**	2,2-Dialkylglycine decarboxylase (pyruvate) inhibitor
0.458	**0.015**	2,3-Dihydroxyindole 2,3-dioxygenase inhibitor
0.713	**0.001**	2,3-Oxidosqualene-lanosterol cyclase inhibitor
0.351	**0.021**	2,4-Diaminopentanoate dehydrogenase inhibitor

Table 3b PASS predicted possible adverse and toxic effects

Pa	*Pi*	Predicted possible Adverse/ Toxic Effect(s)
0.951	**0.002**	Skin irritation, moderate
0.925	**0.005**	Anemia
0.919	**0.003**	Skin irritative effect
0.895	**0.004**	Skin irritation, high
0.878	**0.004**	Hyperglycemic
0.875	**0.012**	Hepatotoxic
0.866	**0.005**	Non mutagenic, Salmonella
0.840	**0.003**	Eye irritation, weak
0.825	**0.009**	Edema
0.831	**0.016**	Ocular toxicity
0.832	**0.020**	Hematotoxic
0.814	**0.006**	Thrombocytopoiesis inhibitor
0.807	**0.003**	Lacrimal secretion stimulant
0.806	**0.005**	Eye irritation, high
0.800	**0.022**	Conjunctivitis
0.773	**0.004**	Acneiform eruption
0.792	**0.026**	Diarrhea
0.787	**0.027**	Toxic, gastrointestinal
0.761	**0.029**	Dermatitis
0.739	**0.018**	Embryotoxic
0.723	**0.007**	Irritation
0.742	**0.031**	Toxic, respiration
0.759	**0.055**	Shivering
0.717	**0.014**	Hypomagnesemia
0.703	**0.003**	Hypocalcaemic
0.711	**0.020**	Dyspnea
0.694	**0.009**	Visual acuity impairment
0.723	**0.040**	Toxic
0.710	**0.035**	Drowsiness
0.737	**0.078**	Twitching
0.700	**0.042**	Pure red cell aplasia
0.678	**0.027**	Inflammation
0.674	**0.036**	Hepatitis
0.656	**0.028**	Teratogen