In-Silico ADMET Informatics of Geranyl Butyrate in *Cymbopogon martinii* Essential Oil

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Abstract- Worldwide interest in use of plants based natural products (PBNPs) has been growing, and its beneficial effects being rediscovered for the development of novel drugs. Literature survey on indigenous traditional knowledge bestows ethnopharmacological potentials of PBNPs that has inspired current research in drug design and discovery; PBNPs provide baseline for the development of novel drug leads against various pharmacological targets. Studies indicate that Cymbopogon martini Essential Oil (CMEO) exhibit wide range of biological activities such as hepatoprotective, antifungal, insecticide, antioxidant and antibacterial. Pharmacological properties of CMEO may be attributed to the presence of Geranyl butyrate. Therefore, physiochemical, drugable and ADMET properties have been envisaged in the present study.

Keywords – Cymbopogon martinii Essential Oil (CMEO), Pharmacological Activity, ADMET, Bioactive Compounds, Plant Based Natural Products (PBNPs)

I. INTRODUCTION

Genus *Cymbopogon* is widely distributed in the tropical and subtropical regions of the world. *CymbopogoC*omprises of more than 144 species, and is well known for its essential oils1,2. Isolation of alkaloids, volatile and non-volatile terpenoids, flavonoids, carotenoids and tannins from every part of *Cymbopogon* species has been investigated previously. *Cymbopogon martinii* (lemongrasses) is native to India, but widely cultivated in many places. Commonly known as Palmarosa, the plant has other names: Indian geranium, ginger grass, and rosha. Besides, therapeutic application, it is commonly used as a condiment and food preservative. CMEO contains bioactive molecules, phyto-compounds, endowed with pharmacological activities3. Geraniol is used as scent and in a number of traditional medicinal. CMEO is of commercial importance, being extensively used in perfumes, soaps, cosmetics, toiletry4. CMEO has effective insect repellent property5, antihelmintic5, antifungal6,7 and mosquito repellent8. It is used to treat skin problems and has immunomodulatory effect9.

Due to their physiochemical properties and bioactive nature, EOs has been used in aromatherapy10-12. Role of EOs in drug development has been well documented since antiquity nevertheless; they are directly used as therapeutic agents due to fact that they have proven record in traditional indigenous systems of medicine such as Ayurveda, Siddha, Unani and Homeopathy due to GRAS nature. Furthermore, concern about the negative effect of synthetic chemicals as food additives warrants “GO” products with no or lesser side effects. CMEO extracts have been used in the treatment of diseases, due to its phytotherapeutic potential13,14. EFSA (European Food Safety Authority) recently, reviewed the safety of CMEO extracts and concluded that there are high-intake estimates ranging from 0.09 (elderly) to 0.81 (children) mg/kg per day. CMEO bioactive compounds however, need scientific validation.

***Cymbopogon martini* (Roxb.) Will. Watson**

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 MartiCollected 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. **Habit**: *Cymbopogon martini* is Perennial (Kellogg et al., 2020). The grass is cultivated elsewhere in the tropics for its oils oCommercial scale to meet the market demand of its essential oil. **'Motia'** yields Palmerosa Essential Oil and **'Sofia'** yields Ginger-Grass Oil.**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**: The leaf decoction is given (50-60 ml) to treat intestinal worms and diarrhea; paste of leaf and stem is applied over scabies affected area to restore discoloration of skin; CMEO extract is mixed with hot water and used for hot steam inhalation during asthma and commoCold; leaf is boiled iCow milk and given as drink (40-50 ml) to improve lactation in feeding women; leaf decoction is given (50-60 ml) as blood purifier and to improve the strength of cardiac muscles; paste of leaf is applied over joints affected with pain and inflammation as part of treatment; cold infusion of leaf is given (50-60 ml) 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.

Geranyl butyrate

Chemical kingdom: Organic compounds
Super class: Lipids and lipid-like molecules
Class: Fatty Acyls
Subclass: Fatty alcohol esters
PubChem Identifier: 5355856
Synonyms: GERANYL-N-BUTYRATE
Canonical SMILES: CCCC(=O)OC/C=C(/CCC=C(C)C)C
InChI Key: ZSBOMYJPSRFZAL-JLHYYAGUSA-N

In traditional medicine both the plant and its oils are used to treat rheumatism, hair loss, arthritis, lumbago and spasms. The essential oil is a strong fungicide. In laboratory tests it was more effective than several synthetic fungicides against pathogenic fungi and yeasts, including *Aspergillus* spp., *Candida albicans*, *Monilia sitophila* and *Trichophyton tonsurae*15. In Ayurvedic medicine - Charak gave the decoction of whole plant in the treatment of abdominal disorders, the liver disorders, jaundice, fever and disorders of the spleen. In Sushruta, decoction of whole plant is prescribed in inflammation of throat, chest pain, indigestion, bronchitis, cough and asthma.

II. MATERIALS AND METHODS

2.1 Collection, Preparation and Extraction of Oil from the sample

The leaf samples were collected from wild in the Perumalmalai Region (Perumalmalai is a hillock in the Palani Hills, Dindigul District, TamilNadu) Western Ghats, INDIA during December 2020. The leaf sample were well preserved, taken to laboratory, identified by using flora[16,17] shade dried and processed as per the protocol for preparation of sample according to the methods previously described by Eleyinmi[18], 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 into powder using Thomas-Willey milling machine and sieved on a wire mesh screen (3×3 mm^2). Sample was stored at 4°C in air-tight container with screw caps. Sample was prepared according to the methods previously described by Rašković et al.[13]. 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 to be 6.06% w/w. Extract was suspended in ethyl acetate and subjected to GC-MS analysis.

2.2 GC-MS analysis

Cymbopogon martini (Palmarosa) Essential Oil was extracted, from the leaf samples collected from the Perumalmalai Region, Palani, 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, and USA). Capillary column used was DB-5MS (30 m × 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.

2.3 ADMET prediction

Selected phytocompounds were subjected to ADMET prediction using QikProp (version 4.3, Suite 2015-1; Schrödinger, LLC: New York, NY) 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[19].

III. RESULTS AND DISCUSSION

3.1 GCMS analysis

The chemical composition of EOs depends on plant genetics, growth conditions, development stage at harvest, and processes of extracting active compounds. Different parts of the plant (bark, leaf, fruit and seed) have been extensively investigated for their bioactive phytochemical constituents in various plants[20]. GC-MS analysis revealed that the extract of *Cymbopogon martini* contained different volatile oils (Jummes et al., 2020). 4-Decen-6-yne, (Z)- ($C_{10}H_{16}$), 3.568 min, 10 hits; 2-Ethylimino-4-methyl-pent-3-enenitrile ($C_8H_{12}N_2$), 3.913 min, 10 hits; Cyanogen bromide (CBrN), 4.024, 1 hits; Cyclohexanol, 2-methyl-5-(1-methylethenyl)-, (1.alphA.,2.betA. ,5.alphA.) - ($C_{10}H_{18}O$), 4.503 min, 10 hits; Cyclohexa-1,3-diene, 5,6-diethyl- ($C_{10}H_{16}$), 4.915 min, 10 hits; Benzaldehyde, 2-methyl- (C_8H_8O), 8.154 min, 10 hits; Pyrazine ($C_4H_4N_2$), 9.32, 5 hits; 2-Norbornaneacetic acid ($C_9H_{14}O_2$), 9.378, 8 hits; cis-syn-trans-Tricyclo[7.3.0.0 (2,6)]dodec-7-ene ($C_{12}H_{18}$), 9.509 min, 10 hits; 1,2,4-Metheno-1H-indene, octahydro-1,7a-dimethyl -5-(1-methylethyl)-, [1S (1.alphA. ,2.alphA. ,3A. betA. ,4.alphA. ,5.alphA. ,7A. be tA. ,8S*)]- ($C_{15}H_{24}$), 9.913 min, 10 hits; 1,4,7, Cycloun-decatriene, 1,5,9,9-tetramethyl-Z,Z,Z- ($C_{15}H_{24}$), 10.343 min, 10 hits; Naphthalene, decahydro-4a-methyl-1-methylene- 7-(1-methylethylidene)-, (4aR-trans)- ($C_{15}H_{24}$), 10.738 min, 10 hits; Butanoic acid, 3,7-dimethyl-2,6-octadienyl ester,(E)- ($C_{14}H_{24}O_2$), 11.772 min, 10 hits; Nerolidol 2 ($C_{15}H_{26}O$), 11.948 min, 10 hits; Caryophyllene oxide ($C_{15}H_{24}O$), 12.525 min, 10 hits; 2-Azidomethyl-1,3,3-trimethyl-cyclohexene ($C_{10}H_{17}N_3$), 15.152 min, 10 hits; Hexanoic acid, 3,7-dimethyl-2,6-octadienyl ester, (E)- ($C_{16}H_{28}O_2$), 15.423 min, 10 hits; Hexanoic acid, 3,7-dimethyl-2,6-octadienyl ester, (E)- ($C_{16}H_{28}O_2$), 15.701 min, 10 hits; Farnesol, acetate ($C_{17}H_{28}O_2$), 17.258 min, 10 hits; 2,6-Octadien-1-ol, 3,7-dimethyl-, propanoate, (Z)- ($C_{13}H_{22}O_2$), 20.158, 10 hits respectively (Table 1). 2D, 3D structures of Geranyl butyrate iC. *martini* essential oil is given in Fig 1

3.2 Physicochemical properties of Geranyl butyrate

Table 2 depicts the physicochemical properties of Geranyl butyrate - Molecular Weight (224.18); Volume (260.371); Density (0.861); nHA (2); nHD (0); nRot (8); nRing (0); MaxRing (0); nHet (2); fChar (0); nRig (3); Flexibility (2.667); Stereo Centers (0); TPSA (26.3); logS (-4.674); logP (4.599); logD (4.41) indicating that the properties are within the optimal range but for logS; logP; logD. QED (No.482); SA score (2.509); Fsp3 (No.643); MCE-18 (No); NP score (1.896); Lipinski Rule (Accepted); Pfizer Rule (Rejected); GSK Rule (Rejected); Golden

Triangle (Accepted); PAINS (No alerts); ALARM NMR (No alerts); BMS (No alerts); Chelator Rule (No alerts) as indicated in Table 3. Caco-2 Permeability (-4.495); MDCK Permeability (2.80E-05); Pgp-inhibitor (0.926); Pgp-substrate (0.008); HIA (0.007); F20% (0.795); F30% (0.385) (Table 4); Distribution - PPB (97.71%); VD (2.404); BBB Penetration (0.923); Fu (4.31%) (Table 5); Metabolism - CYP1A2 inhibitor (0.972); CYP1A2 substrate (0.178); CYP2C19 inhibitor (0.643); CYP2C19 substrate (0.448); CYP2C9 inhibitor (0.483); CYP2C9 substrate (0.879); CYP2D6 inhibitor (0.332); CYP2D6 substrate (0.158); CYP3A4 inhibitor (0.183); CYP3A4 substrate (0.219) (Table 6); Excretion - CL (12.104); T1/2 (0.692) (Table 7).

3.3 Toxicity Assessment of Geranyl butyrate

Toxicity - hERG Blockers (0.014); H-HT (0.649); DILI (0.04); AMES Toxicity (0.003); Rat Oral Acute Toxicity (0.013); FDAMDD (0.022); Skin Sensitization (0.948); Carcinogenicity (0.078); Eye Corrosion (0.39); Eye Irritation (0.96); Respiratory Toxicity (0.092) (Table 8); Environmental toxicity - Bioconcentration Factors (2.021); IGC_{50} (3.738); $LC_{50}FM$ (5.739); $LC_{50}DM$ (6.013) (Table 9); Tox21 pathway - NR-AR (0.007); NR-AR-LBD (0.004); NR-AhR (0.011); NR-Aromatase (0.01); NR-ER (0.082); NR-ER-LBD (0.021); NR-PPAR-gamma (0.006); SR-ARE (0.297); SR-ATAD5 (0.004); SR-HSE (0.456); SR-MMP (0.021); SR-p53 (0.011) (Table 10); Toxicophore Rules - Acute Toxicity Rule (0 alerts); Genotoxic Carcinogenicity Rule (1 alerts); Non-Genotoxic Carcinogenicity Rule (0 alerts); Skin Sensitization Rule (2 alerts); Aquatic Toxicity Rule (0 alerts); Non-Biodegradable Rule (0 alerts); Sure ChEMBL Rule (0 alerts) (Table 11). Data clearly indicate that the molecule can be used for the design of novel drug formulations.

Studies have led to the isolation of alkaloids, volatile and non-volatile terpenoids, flavonoids, carotenoids and tannins from *Cymbopogon* species. Geranyl butyrate from CMEO has been reported to be directly beneficial for colitis, osteoarthritis, diabetes, cerebral ischemia, anxiety and depression, liver fibrosis. Biological activities of these secondary metabolites have been reported for its antitumor, antioxidant, anti-infectious, anti-inflammatory, and analgesic activities and effects on the central nervous system, endocrine system, disorders such as cardiac remodeling after myocardial infarction, body weight changes, dyslipidemia, cerebral ischemia, hepato-nephrotoxicity, stress, and anxiety. Anti-inflammatory activity of CMEO has been attributed to the presence and synergistic activity of the phytocompounds. These natural drugs can be proposed for preclinical and clinical studies in different diseases and pathological conditions.

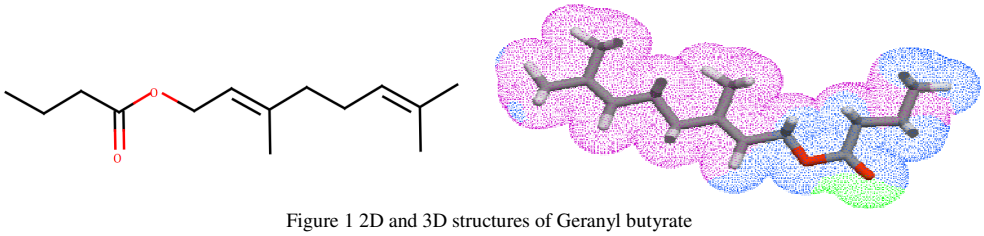

Figure 1 2D and 3D structures of Geranyl butyrate

Table 1 GC-MS profile of compounds in CMEO

RT	Name of the Compound	Molecular Formula	Hits (DB)
3.568	4-Decen-6-yne, (Z)-	$C_{10}H_{16}$	10
3.913	2-Ethylimino-4-methyl-pent-3-enenitrile	$C_8H_{12}N_2$	10
4.024	Cyanogen bromide	CBrN	1
4.503	Cyclohexanol, 2-methyl-5-(1-methylethenyl)(1.alpha.,2.beta.,5.alpha.)-	$C_{10}H_{18}O$	10
4.915	Cyclohexa-1,3-diene, 5,6-diethyl-	$C_{10}H_{16}$	10
8.154	Benzaldehyde, 2-methyl-	C_8H_8O	10
9.32	Pyrazine	$C_4H_4N_2$	5
9.378	2-Norbornaneacetic acid	$C_9H_{14}O_2$	8
9.509	cis-syn-trans-Tricyclo[7.3.0.0(2,6)]dodec-7-ene	$C_{12}H_{18}$	10
9.913	1,2,4-Metheno-1H-indene, octahydro-1,7a-dimethyl-5-(1-methylethyl)-, [1S- (1.alpha.,2.alpha.,3a.beta.,4.alpha.,5.alpha.,7a.be ta.,8S*)]-	$C_{15}H_{24}$	10
10.343	1,4,7,-Cycloundecatriene, 1,5,9,9-tetramethyl-	$C_{15}H_{24}$	10
10.738	Naphthalene, decahydro-4a-methyl-1-methylene-7-(1-methylethylidene)-, (4aR-trans)-	$C_{15}H_{24}$	10
11.772	Butanoic acid, 3,7-dimethyl-2,6-octadienyl ester,(E)-	$C_{14}H_{24}O_2$	10
11.948	Nerolidol 2	$C_{15}H_{26}O$	10
12.525	Caryophyllene oxide	$C_{15}H_{24}O$	10
15.152	2-Azidomethyl-1,3,3-trimethyl-cyclohexene	$C_{10}H_{17}N_3$	10
15.423	Hexanoic acid, 3,7-dimethyl-2,6-octadienyl ester,(E)-	$C_{16}H_{28}O_2$	10
17.258	Farnesol, acetate	$C_{16}H_{28}O_2$	10
20.158	2,6-Octadien-1-ol, 3,7-dimethyl-, propanoate, (Z)-	$C_{13}H_{22}O_2$	10

Table 2 Physicochemical Properties of Geranyl butyrate

PROPERTY	VALUE	COMMENT
Molecular Weight	224.18	Contain hydrogen atoms. Optimal:100~600
Volume	260.371	Van der Waals volume
Density	0.861	Density = MW / Volume
nHA	2	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	8	Number of rotatable bonds. Optimal:0~11
nRing	0	Number of rings. Optimal:0~6
MaxRing	0	Number of atoms in the biggest ring. Optimal:0~18
nHet	2	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	3	Number of rigid bonds. Optimal:0~30
Flexibility	2.667	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: £ 2
TPSA	26.3	Topological Polar Surface Area. Optimal:0~140
logS	-4.674	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	4.599	Log of the octanol/water partitioCoefficient. Optimal: 0~3
logD	4.41	logP at physiological pH 7.4. Optimal: 1~3

Table 3 Medicinal Chemistry Properties of Geranyl butyrate

Property	Value	Comment
QED	0.482	A measure of drug-likeness based on the concept of desirability; Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	2.509	Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules SA score ³ 6, difficult to synthesize; SA score <6, easy to synthesize
Fsp3	0.643	The number of sp3 hybridized carbons / total carbo Count, correlating with melting point and solubilityFsp3 ³0.42 is considered a suitable value.
MCE-18	0	A MCE-18 stand for medicinal chemistry evolutionMCE-18³45 is considered a suitable value.
NPscore	1.896	Natural product-likeness score This score is typically in the range from -5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	MW £ 500; logP £ 5; Hacc £ 10; Hdon £ 5 If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	MW £ 400; logP £ 4 Compounds satisfying the GSK rule may have a more favourable ADMET profile
Golden Triangle	Accepted	200 £ MW £ 50; -2 £ logD £ 5 C Compounds satisfying the Golden Triangle rule may have a more favourable ADMET profile.
PAINS	0 alerts	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	Thiol reactive compounds.
BMS	0 alerts	Undesirable, reactive compounds.
Chelator Rule	0 alerts	Chelating compounds.

Table 4 Absorption Properties of Geranyl butyrate

Property	Value	Comment
Caco-2 Permeability	-4.495	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.80E-05	low permeability: < 2 × 10-6 cm/s n medium permeability: 2–20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
Pgp-inhibitor	0.926	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.008	Category 1: substrate; Category 0: Non-substrate; The output value is the probability of being Pgp-substrate
HIA	0.007	Human Intestinal Absorption Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
F20%	0.795	20% Bioavailability Category 1: F20%+ (bioavailability < 20%); Category 0: F20%- (bioavailability ³ 20%); The output value is the probability of being F20%+
F30%	0.385	30% Bioavailability Category 1: F30%+ (bioavailability < 30%); Category 0: F30%- (bioavailability ³ 30%); The output value is the probability of being F30%+

Table 5 Distribution Properties of Geranyl butyrate

Property	Value	Comment
PPB	97.71%	n Plasma Protein Binding n Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	2.404	n Volume Distribution n Optimal: 0.04-20L/kg
BBB	0.923	n Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-; The output value is the

Penetration		probability of being BBB+
Fu	4.31%	n The fraction unbound in plasms n Low: <5%; Middle: 5~20%; High: > 20%

Table 6 Metabolism Properties of Geranyl butyrate

Property	Value	Comment
CYP1A2 inhibitor	0.972	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP1A2 substrate	0.178	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2C19 inhibitor	0.643	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C19 substrate	0.448	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2C9 inhibitor	0.483	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C9 substrate	0.879	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2D6 inhibitor	0.332	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2D6 substrate	0.158	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP3A4 inhibitor	0.183	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP3A4 substrate	0.219	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.

Table 7 Excretion Properties of Geranyl butyrate

Property	Value	Comment
CL	12.104	Clearance n High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
T1/2	0.692	Category 1: long half-life; Category 0: short half-life; long half-life: >3h; short half-life: <3h The output value is the probability of having long half-life.

Table 8 Toxicity Properties of Geranyl butyrate

Property	Value	Comment
hERG Blockers	0.014	hERG Blockers Category 1: active; Category 0: inactive; The output value is the probability of being active.
H-HT	0.649	Human Hepatotoxicity Category 1: H-HT positive(+); Category 0: H-HT negative(-); The output value is the probability of being toxic.
DILI	0.04	Drug Induced Liver Injury. Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.003	Category 1: Ames positive(+); Category 0: Ames negative(-); The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.013	Category 0: low-toxicity; Category 1: high-toxicity; The output value is the probability of being highly toxic.
FDAMDD	0.022	Maximum Recommended Daily Dose Category 1: FDAMDD (+); Category 0: FDAMDD (-) The output value is the probability of being positive.
Skin Sensitization	0.948	Category 1: Sensitizer; Category 0: Non-sensitizer; The output value is the probability of being sensitizer.
Carcinogenicity	0.078	Category 1: carcinogens; Category 0: non-carcinogens; The output value is the probability of being toxic.
Eye Corrosion	0.39	Category 1: corrosives ; Category 0: non-corrosives The output value is the probability of being corrosives.
Eye Irritation	0.96	Category 1: irritants; Category 0: non-irritants The output value is the probability of being irritants.
Respiratory Toxicity	0.092	Category 1: respiratory toxicants; Category 0: respiratory non-toxicants The output value is the probability of being toxic.

Table 9 Environmental toxicity Properties of Geranyl butyrate

Property	Value	Comment
Bioconcentration Factors	2.021	Bioconcentration factors are used for considering secondary poisoning potential assessing risks to human health via the food chain The unit is -log10[(mg/L)/(1000*MW)]
IGC50	3.738	Tetrahymena pyriformis 50 percent growth inhibition concentration The unit is -log10[(mg/L)/(1000*MW)]

LC50FM	5.739	96-h fathead minnow 50 percent lethal concentration The unit is -log10[(mg/L)/(1000*MW)]
LC50DM	6.013	48-h daphnia magna 50 percent lethal concentration The unit is -log10[(mg/L)/(1000*MW)]

Table 10 Tox21 pathway Properties of Geranyl butyrate

Property	Value	Comment
NR-AR	0.007	Androgen receptor The output value is the probability of being active.
NR-AR-LBD	0.004	Androgen receptor ligand-binding domain The output value is the probability of being active.
NR-AhR	0.011	Aryl hydrocarbon receptor The output value is the probability of being active.
NR-Aromatase	0.01	The output value is the probability of being active.
NR-ER	0.082	Estrogen receptor The output value is the probability of being active.
NR-ER-LBD	0.021	Estrogen receptor ligand-binding domain The output value is the probability of being active.
NR-PPAR-gamma	0.006	Peroxisome proliferator-activated receptor gamma The output value is the probability of being active.
SR-ARE	0.297	Antioxidant response element The output value is the probability of being active.
SR-ATAD5	0.004	ATPase family AAA domain-containing protein 5 The output value is the probability of being active.
SR-HSE	0.456	Heat shock factor response element The output value is the probability of being active.
SR-MMP	0.021	Mitochondrial membrane potential The output value is the probability of being active.
SR-p53	0.011	The output value is the probability of being active.

Table 11 Toxicophore Rules for Geranyl butyrate

Property	Value	Comment
Acute Toxicity Rule	0 alerts	20 substructures n acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	1 alerts	117 substructures Carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	23 substructures Carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	2 alerts	155 substructures n skin irritation
Aquatic Toxicity Rule	0 alerts	99 substructures n toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	19 substructures n non-biodegradable
SureChEMBL Rule	0 alerts	164 substructures n MedChem unfriendly status

IV. CONCLUSION

Cymbopogon species have been used as traditional medicine in many countries since antiquity. CMEO has been used in traditional and Conventional medicine due to the pharmacological potential of their phytochemicals. *C. martini* (Palmarosa) contains a large variety of bioactive molecules with great therapeutic potential and biological activities such as insecticidal, anti-protozoan, anticancer, anti-HIV, anti-inflammatory and anti-diabetes effects. CMEO has remarkable anti-inflammatory, antimicrobial, and antioxidant properties, which have been extensively reported in several formulations. However, development of new formulations containing other less common CMEO extracts is warranted through trials to establish the credentials of pharmacologically active phyto-compounds towards safety/ efficacy, in treating various pathological conditions including COVID-19 and other viral infections owing to the physiochemical properties and druggable nature of CMEO. In the present study Geranyl butyrate evaluated for ADMET properties shows that it could be used as novel drug lead for the development natural drugs of GRAS standards.

REFERENCES

Jummes B, Sganzerla WG, da Rosa CG, Noronha CM, Nunes MR, Bertoldi FC, Barreto PL. Antioxidant and antimicrobial poly-ε-caprolactone nanoparticles loaded with Cymbopogon martinii essential oil. *Biocatalysis and Agricultural Biotechnology*.;23:101499. 2020

Avoseh O, Oyedeji O, Rungqu P, Nkeh-Chungag B, Oyedeji A. Cymbopogon species; ethnopharmacology, phytochemistry and the pharmacological importance. *Molecules*.;20(5):7438-53. 2015

Prashar A, Hili P, Veness RG, Evans CS. Antimicrobial action of palmarosa oil (Cymbopogon martinii) on Saccharomyces cerevisiae. *Phytochemistry*.;63(5):569-75. 2003

Raina VK, Srivastava SK, Aggarwal KK, Syamasundar KV, Khanuja SP. Essential oil composition of Cymbopogon martinii from different places in India. *Flavour and Fragrance Journal*.;18(4):312-5. 2003

Kumar R, Srivastava M, Dubey NK. Evaluation of Cymbopogon martinii oil extract for control of postharvest insect deterioration in Cereals and legumes. *Journal Of Food Protection*.;70(1):172-8. 2007

Kalagatur NK, Nirmal Ghosh OS, Sundararaj N, Mudili V. Antifungal activity of chitosan nanoparticles encapsulated with Cymbopogon martinii essential oil on plant pathogenic fungi Fusarium graminearum. *Frontiers in Pharmacology*.;9:610. 2018

Mishra PK, Kedia A, Dubey NK. Chemically characterized Cymbopogon martinii (Roxb.) Wats. essential oil for shelf life enhancer of herbal raw materials based on antifungal, antiaflatoxigenic, antioxidant activity and favorable safety profile. *Plant Biosyst* 150:1313–1322. 2015

Caballero-Gallardo K, Olivero-Verbel J, Stashenko EE. Repellency and toxicity of essential oils from Cymbopogon martinii, Cymbopogon flexuosus and Lippia origanoides cultivated iColombia against Tribolium castaneum. *Journal of Stored Products Research* 50:62-5. 2012

Andrade BF, Conti BJ, Santiago KB, Fernandes A, Sforcin JM. C ymbopogon martinii essential oil and geraniol at non-cytotoxic concentrations exerted immunomodulatory/anti-inflammatory effects in human monocytes. *Journal of Pharmacy and Pharmacology*.; 66(10):1491-6. 2014

Al-Shalah LA, Hindi NK, Mohsen IH. Essential Oils. Essential Oils: Bioactive Compounds, New Perspectives and Applications.;9:29. 2020

Chávez-González ML, Rodríguez-Herrera R, Aguilar CN. Essential oils: A natural alternative to combat antibiotics resistance. Antibiotic Resistance-Mechanisms and New Antimicrobial Approaches; Kon, K., Rai, M., Eds.;227-37. 2016

Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnology advances.;*33(8):1582-614. 2015

Rašković A, Milanović I, Pavlović N, Ćebović T, Vukmirović S, Mikov M. Antioxidant activity of rosemary (Rosmarinus officinalis L.) essential oil and its hepatoprotective potential. *BMC Complementary And Alternative Medicine*.;14(1):1-9. 2014

Khan MS, Ahmad I. In vitro antifungal, anti-elastase and anti-keratinase activity of essential oils of Cinnamomum-, Syzygium- and Cymbopogon-species against Aspergillus fumigates and Trichophyto rubrum. *Phytomedicine*.;19:48–55 2011

Yoon MY, Cha B, Kim JC Recent trends in studies on botanical fungicides in agriculture. *The Plant Pathology Journal*.;29(1):1. 2013

Matthew KM. Flora of the Tamilnadu Carnatic. The Rapinat Herbarium, St. Joseph's College, Tiruchirapalli, India; 1981

Gamble JS, Fischer CE. Flora of the Presidency of Madras. London, UK: West, Newman and Adlard;1915.

Eleyinmi AF Chemical composition and antibacterial of Gongronema latifolium *J Zhejiang Univ Sci* B;8:352-3582007

Zhou Y, Wu F, Li L, Shen X, Chen G, Wang X, Liang X, Tan M, Huang Z. Computational approaches in preclinical studies on drug discovery and development. *Frontiers in Chemistry*.;8:726-31. 2020

Ramya S, Neethirajan K, Jayakumararaj R. Profile of bioactive compounds in Syzygium cumini–a review. *Journal of Pharmacy research*.;5(8):4548-53. 2012

Gaba J, Bhardwaj G, Sharma A. Lemongrass. In Antioxidants in Vegetables and Nuts-Properties and Health Benefits pp. 75-103. Springer, Singapore 2020