IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
February 2021 Vol.:20, Issue:3

Pharmacological Perspectives of Bioactive Phyto Compounds in *Cymbopogon martinii* Essential Oil

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Submitted: 10 January 2021
Revised: 30 January 2021
Accepted: 19 February 2021

Keywords: *Cymbopogon martinii* Essential Oil (CMEO); Palmarosa Pharmacological Activity; ADMET Properties; Bioactive Compounds

ABSTRACT

Plant-Based Natural Products (PBNPs) have contributed significantly to the development of plant-based drugs for diverse indications. Worldwide interest in the use of plants based natural products (PBNPs) has been growing, and its beneficial effects being rediscovered for the development of novel drugs available in the market. Literature survey on indigenous traditional knowledge bestows ethnopharmacological potentials of PBNPs that has inspired current research in drug design and discovery; PBNPs provide a baseline for the development of novel drug leads against various pharmacological targets. Studies indicate that *Cymbopogon martini* essential oil (CMEO) extracts exhibit a wide range of biological activities such as hepatoprotective, antifungal, insecticide, antioxidant and antibacterial. It is well known that the biological properties in palmarosa essential oil may be due to the presence of compounds like 4-Decen-6-yne, (Z), 2-Ethylimino-4-methyl-pent-3-one nitrile, Dihydrocarvyl acetate, 2-Methylbenzaldehyde, Geranyl butyrate, 1,5,9,9-Tetramethyl-1,4,7-cycloundecatriene. However, its application is limited because of the odor, color, and taste.

INTRODUCTION:

The genus *Cymbopogon* is widely distributed in the tropical and subtropical regions of Africa, Asia, and America. Comprised of 144 species, this genus is famous for its high content of essential oils (Avoseh et al., 2015). Studies have led to the isolation of alkaloids, volatile and non-volatile terpenoids, flavonoids, carotenoids, and tannins from every part of *Cymbopogon* species. *Cymbopogon martinii* is a species of grass in the genus *Cymbopogon* (lemongrasses) native to India and Indochina but widely cultivated in many places for its aromatic oil. Generally known as Palmarosa, the plant has other common names include Indian geranium, ginger grass, rosha, and rosha grass. Besides, therapeutic application, it is commonly used as a condiment and food preservative. Palmarosa contains many bioactive molecules, Phyto-compounds, endowed with pharmacological activities, such as antimicrobial (Prashar et al., 2003). The essential oil of Palmarosa contains geraniol, which is valued for its scent and several traditional medicinal and household uses. Palmarosa oil is of commercial importance, being extensively used in perfumes, soaps, cosmetics, toiletry, and tobacco products (Raina et al., 2003). Palmarosa essential oil is an effective insect repellent when applied to stored grain and beans (Kumar et al., 2007) an antihelmintic against nematodes (Katiki et al., 2011), and an antifungal (Kalagatur et al., 2018) and mosquito repellent (Caballero-Gallardo et al., 2012). CMEO has been used in aromatherapy as a skin tonic due to its antimicrobial properties. It has also used in Ayurvedic medicine for skin problems and to relieve nerve pain. Immunomodulatory action CMEO (geraniol) was evaluated towards the production of pro-and anti-inflammatory cytokines (TNF-α and IL-10) by human monocytes in vitro. Data indicated that TNF-α production was not affected by CMEO and geraniol, at a concentration of 5 μg/ml of CMEO stimulated its production. On the other hand, all concentrations of CMEO and geraniol tested, increased IL-10 production by human monocytes (Murbach Teles Andrade et al., 2014).

Essential oils (EOs) a major group of photogenic bioactive compounds (PBAC) have been used for a variety of purposes over thousands of years. Due to their strong aromatic properties and bioactive nature, EOs has been used in aromatherapy, as flavor and fragrances in cosmetics, foods, and more recently as pharmaceuticals, natural preservatives, additives, and biopesticides (Al-Shalah *et al.*, 2020). EOs are a concentrated form of liquid mixtures of volatile compounds of plant origin with unique structural chemistry including terpenoid and non-terpenoid hydrocarbons and their oxygenated derivatives, with natural color, odor, and flavor, or “essence” of their source - volatile/ odoriferous oil. Essential oils are isolated from

various plant components such as leaves, fruit, bark, root, wood, heartwood, gum, balsam, berries, seeds, flowers, twigs, and buds (Chávez-González *et al.*, 2016).

The role of PBNPs in drug development has been practiced and well documented since antiquity and recently increasing, not because the bioactive compounds are directly used as therapeutic agents but because they are used as raw material for drug synthesis, or as a base model for new biologically active compounds due to its GRAS nature. As people are more concerned about the negative effect of synthetic chemicals in food, there is a need to find "GO" products with no or lesser side effects. Therefore, there is a growing interest in using natural extracts as alternatives for synthetic additives because of (a) their synergy with other preservation methods (b) generally regarded as safe, and (c) PBNPs have properties such as antioxidant, antidiabetic, antimutagenic, antioxygenic and antibacterial. Among the most effective antioxidant constituents of CMEO, cyclic diterpene diphenols, carnosolic acid and carnosol have been identified. Also, CMEO extract contains carnosic acid, epirosmanol, rosmanol, methylcarnosate, and isorosmanol (Bosin *et al.,* 2007). However, validating and using plants as phytopharmaceutical chemistry requires a great deal of basic and applied research, to set this resource at the same level of importance as conventional pharmaceutical products (Atanasov et al., 2015).

Ethnobotanical perspective: Bioactive molecules have pharmacological activities, such as anti-inflammatory, antioxidant, antimicrobial, antiproliferative, antitumor and protective, inhibitory, and attenuating activities with the ability to attenuate asthma, atherosclerosis, cataract, renal colic, hepatotoxicity, peptic ulcer, inflammatory diseases, ischemic heart disease, antioxidant and anti-inflammatory actions of rosmarinic acid, control of hypercholesterolemia myocardial blood pressure reduction with rosmarinic acid, antiulcer action, lipid peroxidation reduction in heart and brain, antiangiogenic and neuroprotective effects of carnosic acid and carnosol, prevention of problems related to atherosclerosis, anticancer and antiproliferative effects, antiviral and antimicrobial actions, hepatoprotective, nephroprotective and radioprotective capacities.

Cymbopogon martinii (Palmarosa) has been traced for its origin from the Mediterranean region. It is an aromatic plant, a unique spice commercially available for use as an antioxidant. CMEO extracts have been used in the treatment of diseases, due to their hepatoprotective potential (Rašković et al., 2014). On the other hand, it is used in food preservation, because they prevent oxidation and microbial contamination (). Therefore,

palmarosa essential oil extract could be useful for replacing or even decreasing synthetic antioxidants in foods. EFSA (European Food Safety Authority) recently, reviewed the safety of CMEO extracts and concluded that high-intake estimates are ranging from 0.09 (elderly) to 0.81 (children) mg/kg per day.

Systematic Position of *Cymbopogon martinii* (PALMAROSA)

Class	:	Equisetopsida
Subclass	:	Magnoliidae
Superorder	:	Lilianae
Order	:	Poales
Family	:	Poaceae
Genus	:	*Cymbopogon*
Species	:	*martinii*
Common	:	Palmarosa
Habit	:	Herb
Parts used	:	Leaf
Ailments	:	Arthritis, Bilious, Carminative, Lumbago, Spasm, Stimulant, Sudorific

***Cymbopogon martini* (PALMAROSA)**

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. Spathulate 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 the base. Sessile spikelet oblong, 3.5–4.5 mm; lower glume flat, deeply grooved below the middle (appearing as a line or keel on the 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. This grass is native to India but is cultivated elsewhere in the tropics for its oils.

Ethnobotanical narration: 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 9

pathogenic fungi and yeasts, including *Aspergillus* spp., *Candida albicans*, *Monilia sitophila*, and *Trichophyton tonsurae*. In Ayurvedic medicine - Charak gave the decoction of the whole plant in the treatment of abdominal disorders, liver disorders, jaundice, fever, and disorders of the spleen. In Sushruta, a decoction of the whole plant is prescribed in inflammation of the throat, chest pain, indigestion, bronchitis, cough, and asthma.

MATERIALS AND METHODS:

Preparation and extraction of sample

Protocol for preparation of sample was according to the methods previously described by Eleyinmi (2007), but with modifications wrt temperature and duration of drying the sample. A 100 g leaf was weighed and dried in an oven at 60°C. The dried sample was ground into powder using a Thomas-Willey milling machine and sieved on a wire mesh screen (3 × 3 mm^2). The sample was stored at 4°C in an air-tight container with screw caps. The sample was prepared according to the methods previously described by Rašković *et al.,* (2015). 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 a vacuum desiccator. The yield was calculated to be 6.06% w/w. The extract was suspended in ethyl acetate and subjected to analysis.

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 TOP KAT (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 (Zhou *et al.*, 2020).

RESULTS AND DISCUSSION:

2D, 3D structures of bioactive compounds in *C. martini* essential oil are given in Table 1. Molecular and biological properties (CID, MF, miLogP, TPSA, N atoms, MW (g/mol), Non, n OHNH, N violations, N rotb, volume, GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor, Enzyme inhibitor) of the bioactive compounds are provided in Table 2. Summary of toxic (mutagenic, toxicology, irritant, reproductive properties) risk assessment towards drugability/ drug score in Table 3 indicates

that the compounds were neither mutagenic nor toxic to the biological system. All the bioactive compounds studied were drugable candidates and had a good score for Druggability Properties - Lipinski's rule of 5 violations, Veber rule, Egan rule, Oral PhysChem score, GSK's 4/400 score, Pfizer's 3/75 score, QEDw score, Solubility, Solubility Index (Table 4). Similarly, ADMET properties of key molecules in CMEO (Caryophyllene oxide and Geranyl butyrate) towards Human Intestinal Absorption, Blood-Brain Barrier, Caco-2 permeable, P-glycoprotein substrate, P-glycoprotein inhibitor I, P-glycoprotein inhibitor II, CYP450 2C9 substrate, CYP450 2D6 substrate, CYP450 3A4 substrate, CYP450 1A2 inhibitor, CYP450 2C9 inhibitor, CYP450 2D6 inhibitor, CYP450 2C19 inhibitor, CYP450 3A4 inhibitor, CYP450 inhibitory promiscuity, Ames test, Carcinogenicity, Biodegradation, Rat acute toxicity, LD50 mol/kg, hERG inhibition (predictor I), hERG inhibition (predictor II) (Table 5) indicate that these molecules can be used for drug formulations.

Studies have led to the isolation of alkaloids, volatile and non-volatile terpenoids, flavonoids, carotenoids, and tannins from *Cymbopogon* species (Avoseh et al., 2015). β-Caryophyllene from CMEO has been reported to be directly beneficial for colitis (Bento et al., 2011), osteoarthritis (Rufino et al., 2015), diabetes (Basha and Sankaranarayanan, 2014), cerebral ischemia (Chang et al., 2013), anxiety and depression (Bahi et al., 2014), liver fibrosis (Calleja et al., 2013; Mahmoud et al., 2014). Biological activities of these secondary metabolites of *Cymbopogon martini* (Palmarosa) 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.

The anti-inflammatory activity of CMEO has been attributed to the presence and synergistic activity of carnosol and carnosic, rosmarinic, ursolic, oleanolic, and micrometric acids (A). Specifically, anti-inflammatory activity has been attributed to synergic effects of ursolic and micrometric acids present in CMEO. These natural drugs can be proposed for preclinical and clinical studies in different diseases and pathological conditions.

CONCLUSION:

Cymbopogon species have been used as a 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, the development of new formulations containing other less common CMEO extracts is warranted through trials to evaluate and establish the credentials of pharmacologically active Phyto-compounds towards safety and efficacy, in treating various pathological conditions.

ACKNOWLEDGMENT

The author is grateful to the Management, Arulmigu Palaniandavar College of Arts and Culture, Palani - 624601, Dindigul District, Tamil Nadu, India for their support by providing the required facilities to carry out the research work.

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Table No. 1: 2D, 3D structure of bioactive compounds in *C. martini* essential oil

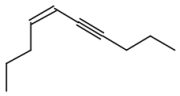
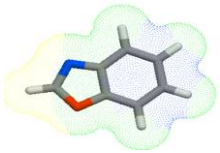
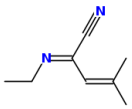
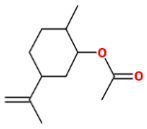
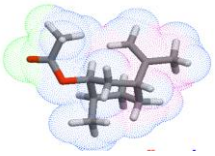
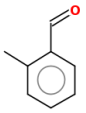
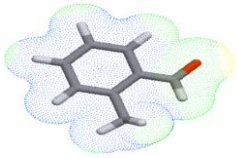
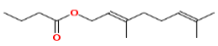
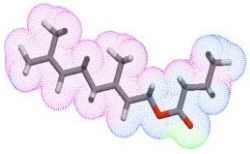
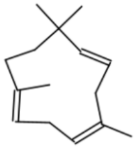
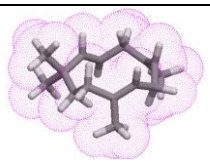
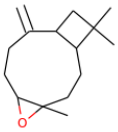
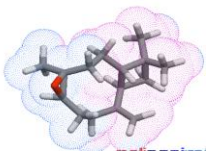
IUPAC Name/ Canonical SMILES	2D Chemical Structure	3D Interactive Chemical Structure
Cyclodecyne; 4-Decen-6-yne, (Z)		
2-Ethylimino-4-methyl-pent-3-enenitrile		
Dihydrocarvyl acetate		
2-Methylbenzaldehyde		
Geranyl butyrate		
1,5,9,9-Tetramethyl-1,4,7-cycloundecatriene		
Caryophyllene oxide		

Table No. 2: Molecular-biological properties of bioactive compounds in *C. martini*

Properties	Compounds						
CID	**137799**	**68315**	**73918**	**998**	**5282854**	**5281522**	**1742210**
MF	**$C_{10}H_{16}$**	**$C_8H_{12}N_2$**	**$C_{10}H_{18}O$**	**C_8H_8O**	**$C_{14}H_{24}O_2$**	**$C_{15}H_{24}$**	**$C_{15}H_{24}O$**
miLogP	4.54	2.09	3.35	2.13	4.83	5.07	4.14
TPSA	0.00	36.16	26.30	17.07	26.30	0.00	12.53
N atoms	10	10	4	9	16	15	16
MW (g/mol)	136.24	136.20	154.24	120.15	224.34	204.36	220.36
Non	0	2	2	1	2	0	1
n OHNH	0	0	0	0	0	0	0
N violations	0	0	0	0	0	1	0
N rotb	3	2	3	1	8	0	0
volume	162.53	146.66	208.06	119.59	245.69	234.00	234.01
GPCR ligand	-0.56	-1.64	- 0.47	- 2.33	- 0.26	**0.03**	**0.08**
Ion channel modulator	**0.57**	-1.04	**0.23**	- 1.80	**0.05**	**0.132**	**0.14**
Kinase inhibitor	-1.05	- 2.08	- 1.25	- 2.40	- 0.86	- 0.95	-0.86
Nuclear receptor ligand	-0.18	- 2.06	- 0.17	- 2.20	**0.03**	**0.40**	**0.62**
Protease inhibitor	-0.76	- 1.92	- 0.44	- 2.91	- 0.56	- 0.63	0.00
Enzyme inhibitor	**0.43**	- 0.84	- 0.12	- 1.91	**0.30**	**0.41**	**0.57**

Table No. 3: Summary of toxic (mutagenic, toxicology, irritant, reproductive properties) risk assessment towards drugability/ drug score

Compound	MP	TP	IP	RE	DL	DS
Cyclodecyne; 4-Decen-6-yne, (Z)-	None	None	High	None	-10.80	0.21
2-Ethylimino-4-methyl-pent-3-enenitrile	None	None	None	None	-4.87	0.48
Dihydrocarvyl acetate	None	None	High	None	-19.56	0.26
2-Methylbenzaldehyde	None	None	Medium	High	-5.59	0.23
Geranyl butyrate	None	None	High	None	-5.84	0.21
1,5,9,9-Tetramethyl-1,4,7-cycloundecatriene	None	None	None	None	-5.08	0.28
Caryophyllene oxide	None	Medium	None	Medium	-4.77	0.25

Table No. 4: Druggability Properties of bioactive compounds in *C. martinii*

Druggability Property	Bioactive Compounds					
	$C_{10}H_{16}$	$C_8H_{12}N_2$	$C_{10}H_{18}O$	C_8H_8O	$C_{14}H_{24}O_2$	$C_{15}H_{24}$
Lipinski's rule of 5 violations	0	0	0	0	0	0
Veber rule	Good	Good	Good	Good	Good	Good
Egan rule	Good	Good	Good	Good	Good	Good
Oral PhysChem score	0	1	2	2	1	2
GSK's 4/400 score	Good	Good	Good	Good	Good	Good
Pfizer's 3/75 score	Warning	Bad	Bad	Bad	Bad	Bad
QEDw score	0.521	0.506	0.493	0.434	0.433	0.434
Solubility	12379.28	8150.46	4750.64	5166.30	4350.64	5166.30
Solubility Index	Good	Good	Good	Good	Good	Good

Druggability scoring schemes were computed using FAF-Drugs4 (28961788) and FAF-QED (28961788) open-source chem-informatics platform.