In-silico ADMET profile of α-Pinene Oxide from *Rosmarinus officinalis*

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Abstract Plant Based Natural Products (PBNPs) have contributed to the development of many drugs for diverse indications. Worldwide interest in use of plants based natural products (PBNPs) has been growing, and its beneficial effects being rediscovered for the development of new drugs. Literature survey on indigenous traditional knowledge bestows ethnopharmacological potentials of PBNPs, which has inspired current research in drug discovery; PBNPs provide baseline for the development of novel drug leads against various pharmacological targets. Studies report that rosemary essential oil (REO) extracts in particular show biological bioactivities such as hepatoprotective, antifungal, insecticide, antioxidant and antibacterial. It is well known that the biological properties in rosemary are mainly due to phenolic compounds. However, their application is limited because of their odor, color and taste. Owing to the widespread applications of phyto-compounds in REO - GCMS was performed. GCMS analysis detected 22 compounds of which 6 compounds were in abundant. Their ADMET properties were evaluated to ponder its application.

KEY WORDS: *Rosmarinus officinalis*; Rosemary Essential Oils (REO); Pharmacological Activity; ADMET; Bioactive Compounds; GCMS

I INTRODUCTION

Rosmarinus officinalis L. (Rosemary) is a medicinal plant native to the Mediterranean region and cultivated around the world (De Oliveira *et al.,* 2019). Besides, therapeutic application, it is commonly used as a condiment and food preservative. *R. officinalis* is contains many bioactive molecules, phyto-compounds, endowed with pharmacological activities, such as anti-aging, anti-inflammatory, antioxidant, antimicrobial, anti-proliferative, antitumor, tumor-protective, tumor-inhibitory and attenuating activities (Stevanović *et al.,* 2018). Essential oils (EOs) a major group of phytogenic bioactive compounds (PBAC) have been used for 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 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).

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 due to fact that 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, antitoxigenic and antibacterial. Among the most effective antioxidant constituents of REO, cyclic diterpene diphenols, carnosolic acid and carnosol have been identified. In addition, REO extract contains carnosic acid, epirosmanol, rosmanol, methylcarnosate and isorosmanol (Bosin *et al.,* 2007). However, validating and using plants as phyto-pharmaceutical chemistry requires a great deal of basic and applied research, in order to set this resource at the same level of importance of conventional pharmaceutical products (Atanasov et al., 2015).

Rosmarinus officinalis L., commonly known as rosemary, belongs to the Lamiaceae family. The genus *Rosmarinus* has been merged into the genus *Salvia* in a recent phylogenetic analysis. Botanical Description: Plants to 2 m tall. Bark dark grey, irregularly fissured, exfoliating, young branches densely white stellate-tomentulose. Leaves tufted on branches, sessile to short petiolate; leaf blade 1-2.5 cm × 1-2 mm, leathery, adaxially somewhat shiny, sub-glabrous, abaxially densely white stellate-tomentose, base attenuate, margin entire, revolute, apex obtuse. Calyx ca. 4 mm, densely white stellate tomentose and glandular outside, upper lip sub-circular, teeth of lower lip ovate-triangular. Corolla blue-purple, less than 1 cm, sparsely pubescent outside, tube slightly exserted, apex of upper lip 2-lobed, lobes ovate, middle lobe of lower lip constricted at base into claw, lateral lobes oblong. Fl. Nov (Gamble, 1935; Mathews, 1981).

Ethnobotanical perspective: Bioactive molecules have pharmacological activities, such as anti-inflammatory, antioxidant, antimicrobial, anti-proliferative, antitumor and protective, inhibitory and attenuating activities with 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 (Tai *et al.,* 2007) and antiproliferative effects, antiviral and antimicrobial actions, hepatoprotective, nephroprotective and radioprotective capacities.

R. officinalis 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. REO extracts have been used in the treatment of diseases, due to its hepatoprotective potential (Rašković et al., 2014), therapeutic potential for Alzheimer's disease (Habtemariam, 2016) and its antiangiogenic effect (Kayashima and Matsubara, 2012). On the other hand, it is used in food preservation, because they prevent oxidation and microbial contamination (Alavi et al., 2020). Therefore, rosemary extract could be useful for replacing or even decreasing synthetic antioxidants in foods. EFSA (European Food Safety Authority) recently, reviewed the safety of rosemary extracts and concluded that there are high-intake estimates ranging from 0.09 (elderly) to 0.81 (children) mg/kg per day.

Class	:	Equisetopsida
Subclass	:	Magnoliidae
Superorder	:	Asteranae
Order	:	Lamiales
Family	:	Lamiaceae
Genus	:	*Rosmarinus*
Species	:	*officinalis*

II MATERIALS AND METHODS

2.1 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. 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.,* (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 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

Rosmarinus officinalis L. (Rosemary) Essential Oil was purchased commercially from the local market in Palani, Dindigul District, Tamil Nadu, India. Phyto-components were identified using GC–MS detection system as previously described Rašković *et al.,* (2015) but with minor 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 (Zhou *et al.,* 2020).

III RESULTS AND DISCUSSION

3.1 GCMS analysis of Rosmarinus officinalis (Rosemary) essential oil

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 (Ramya *et al.,* 2012). GC-MS analysis revealed that the extract of *Rosmarinus officinalis* contained different volatile oils. Tricyclo[3.2.1.0(2,4)] octane,8-methylene (1.α.,2. α.,4.α., 5.α.)- (C_9H_{12}), 3.237, 2 hits; Benzene, 1-ethyl-2,3-dimethyl- ($C_{10}H_{14}$), 4.318 min, 10 hits; Cyclohexanemethanol, 4-hydroxy-.α.,α.,4-trimethyl- ($C_{10}H_{20}O_2$), 4.436 min, 10 hits; Cyclohexanol, 5-methyl-2-(1-methylethenyl)- ($C_{10}H_{18}O$), 0.508 min, 10 hits; Eucalyptol ($C_{10}H_{18}O$), 4.566, 6 hits; 1,8-Cineole; 470-82-6; 1,8-Cineol; ($C_{10}H_{18}O$), 4.655 min, 10 hits; Geranyl tiglate ($C_{15}H_{24}O_2$), 4.811, 2 hits; 3-Oxatricyclo[4.1.1.0(2,4)]octane, 2,7,7-trimethyl- ($C_{10}H_{16}O$), 4.885 min, 10 hits; -Naphthalenol, decahydro- ($C_{10}H_{18}O$), 4.959 min, 10 hits; 4-Cyclooctene-1-methanol ($C_9H_{16}O$), 5.02 min, 10 hits; 1,2,4,5-Tetrazine ($C_2H_2N_4$), 5.243 min, 10 hits; 1-Cyclopentene-1-methanol, .α.,α.,4,5- tetramethyl-, trans- ($C_{10}H_{18}O$), 6.045 min, 10 hits; Tricyclo[4.2.2.0(1,5)]dec-7-ene ($C_{10}H_{14}$), 6.159 min, 10 hits; (1S-(1A,2α,β))-1-isopropenyl-4- methyl-1,2-cyclohexanediol ($C_{10}H_{18}O_2$), 6.208 min, 10 hits; Bicyclo[3.1.1]hept-3-en-2-one, 4,6,6-trimethyl-,(1S)- ($C_{10}H_{14}O$), 6.244 min, 10 hits; Linalyl isobutyrate ($C_{14}H_{24}O_2$), 6.454 min, 10 hits; Bicyclo[2.2.2]oct-2-ene, 1-methylamino- ($C_9H_{15}N$), 7.084 min, 10 hits; Benzenemethanol, 4-ethyl- ($C_9H_{12}O$), 7.092 min, 10 hits; Dicyclopentadiene diepoxide ($C_{10}H_{12}O_2$), 7.344 min, 10 hits; 1,8-Nonadiyne (C_9H_{12}), 7.5 min, 10 hits; 2,6,11,15-Tetramethyl-hexadeca-2,6,8,10,14- pentaene ($C_{20}H_{32}$), 20.122, 2 hits; Phthalic acid, di(6-methylhept-2-yl) ester ($C_{24}H_{38}O_4$), 35.075 min, 10 hits respectively **(Table 1; Fig. 1).**

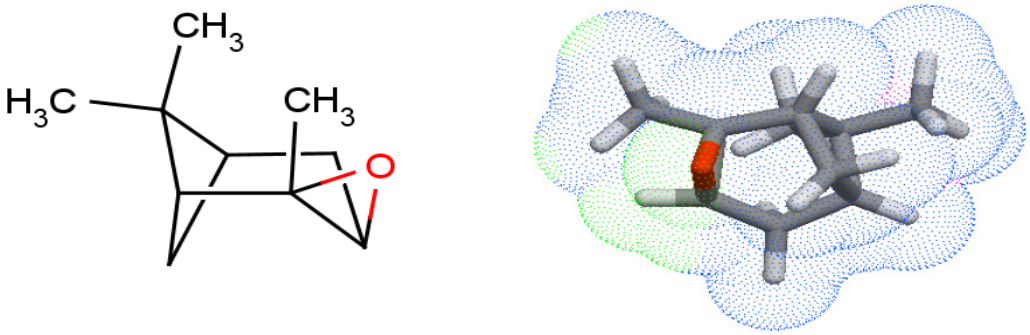

Figure 1 2D and 3D Structure of α-Pinene oxide from *Rosmarinus officinalis*

Table 1 GC-MS based list of bioactive compounds in *Rosmarinus officinalis*

RT	NAME OF THE COMPOUND	MF	HITS
3.237	Tricyclo[3.2.1.0(2,4)]octane, 8-methylene(1.α.,2.α.,4.α.,5.α.)-	C_9H_{12}	2
4.318	Benzene, 1-ethyl-2,3-dimethyl-	$C_{10}H_{14}$	10
4.436	Cyclohexanemethanol, 4-hydroxy-.α.,α.,4-trimethyl-	$C_{10}H_{20}O_2$	10
0.508	Cyclohexanol, 5-methyl-2-(1-methylethenyl)-	$C_{10}H_{18}O$	10
4.566	Eucalyptol	$C_{10}H_{18}O$	6
4.655	1,8-Cineole; 470-82-6; 1,8-Cineol;	$C_{10}H_{18}O$	10
4.811	Geranyl tiglate	$C_{15}H_{24}O_2$	2

4.885	3-Oxatricyclo[4.1.1.0(2,4)]octane, 2,7,7-trimethyl-	$C_{10}H_{16}O$	10
4.959	-Naphthalenol, decahydro-	$C_{10}H_{18}O$	10
5.02	4-Cyclooctene-1-methanol	$C_9H_{16}O$	10
5.243	1,2,4,5-Tetrazine	$C_2H_2N_4$	10
6.045	1-Cyclopentene-1-methanol, .α.,α.,4,5- tetramethyl-, trans-	$C_{10}H_{18}O$	10
6.159	Tricyclo[4.2.2.0(1,5)]dec-7-ene	$C_{10}H_{14}$	10
6.208	(1S-(1A,2α,4β))-1-isopropenyl-4- methyl-1,2-cyclohexanediol	$C_{10}H_{18}O_2$	10
6.244	Bicyclo[3.1.1]hept-3-en-2-one, 4,6,6-trimethyl-,(1S)-	$C_{10}H_{14}O$	10
6.454	Linalyl isobutyrate	$C_{14}H_{24}O_2$	10
7.084	Bicyclo[2.2.2]oct-2-ene, 1-methylamino-	$C_9H_{15}N$	10
7.092	Benzenemethanol, 4-ethyl-	$C_9H_{12}O$	10
7.344	Dicyclopentadiene diepoxide	$C_{10}H_{12}O_2$	10
7.5	1,8-Nonadiyne	C_9H_{12}	10
20.122	2,6,11,15-Tetramethyl-hexadeca-2,6,8,10,14- pentaene	$C_{20}H_{32}$	2
35.075	Phthalic acid, di(6-methylhept-2-yl) ester	$C_{24}H_{38}O_4$	10

Table 2 Physiochemical, molecular and biological properties of α-Pinene oxide

COMPOUND	A-PINENE OXIDE
CID	91508
IUPAC Name	3-Oxatricyclo[4.1.1.0(2,4)]octane, 2,7,7-trimethyl-
Canonical SMILES	CC1(C2CC1C3(C(C2)O3)C)C
MF	$C_{10}H_{16}O$
miLogP	2.74
MW (g/mol)	152.23
TPSA	12.53
natoms	11
nON	1
nOHNH	0
nviolations	0
nrotb	0
volume	155.87
GPCR ligand	- 0.40
Ion channel modulator	- 0.41
Kinase inhibitor	- 1.24
Nuclear receptor ligand	- 0.17
Protease inhibitor	0.15
Enzyme inhibitor	0.34
Mutagenic	High
Tumorigenic	None
Irritant	High
Reproduction	None
Drug likeness	-1.28
Drug score	0.21

Table 3 Physiochemical, druggability and ADMET properties of α-Pinene oxide

PHYSICOCHEMICAL PROPERTIES	VALUE
Molecular weight	152.24g/mol
LogP	2.21
LogD	1.98
LogSw	-2.13
Number of stereocenters	4
Stereochemical complexity	0.400
Fsp3	1.000
Topological polar surface area	12.53 $Å^2$
Number of hydrogen bond donors	0
Number of hydrogen bond acceptors	1
Number of smallest set of smallest rings (SSSR)	1
Size of the biggest system ring	9
Number of rotatable bonds	0
Number of rigid bonds	10
Number of charged groups	0
Total charge of the compound	0
Number of carbon atoms	10
Number of heteroatoms	1
Number of heavy atoms	11
Ratio between number of non-carbon atoms and carbon atoms	0.1
DRUGGABILITY PROPERTIES	
Lipinski's rule of 5 violations	0

Veber rule		**Good**
Egan rule		**Good**
Oral PhysChem score (Traffic Lights)		**0**
GSK's 4/400 score		**Good**
Pfizer's 3/75 score		**Warning**
Weighted quantitative estimate of drug-likeness (QEDw) score		**0.483**
Solubility		**18168.11**
Solubility Forecast Index		**Good**
ADMET PROPERTIES		
Property	**Value**	**Probability**
Human Intestinal Absorption	**HIA+**	**0.993**
Blood Brain Barrier	**BBB+**	**0.954**
Caco-2 permeable	**Caco2+**	**0.632**
P-glycoprotein substrate	**Non-substrate**	**0.527**
P-glycoprotein inhibitor I	**Non-inhibitor**	**0.623**
P-glycoprotein inhibitor II	**Non-inhibitor**	**0.871**
CYP450 2C9 substrate	**Non-substrate**	**0.775**
CYP450 2D6 substrate	**Non-substrate**	**0.818**
CYP450 3A4 substrate	**Substrate**	**0.576**
CYP450 1A2 inhibitor	**Non-inhibitor**	**0.638**
CYP450 2C9 inhibitor	**Non-inhibitor**	**0.579**
CYP450 2D6 inhibitor	**Non-inhibitor**	**0.929**
CYP450 2C19 inhibitor	**Inhibitor**	**0.509**
CYP450 3A4 inhibitor	**Non-inhibitor**	**0.957**
CYP450 inhibitory promiscuity	**Low CYP Inhibitory Promiscuity**	**0.865**
Ames test	**Non AMES toxic**	**0.913**
Carcinogenicity	**Non-carcinogens**	**0.675**
Biodegradation	**Not ready biodegradable**	**0.877**
Rat acute toxicity	**1.837 LD50, mol/kg**	**Not applicable**
hERG inhibition (predictor I)	**Weak inhibitor**	**0.983**
hERG inhibition (predictor II)	**Non-inhibitor**	**0.801**

Note: Physicochemical properties were computed using FAF-Drugs4 (28961788) RDKit open-source cheminformatics platform. Druggabiity scoring schemes were computed using FAF-Drugs4 (28961788) and FAF-QED (28961788) open-source cheminformatics platform. ADMET features were predicted using admetSAR (23092397) open-source tool.

Sienkiewicz et al. (2013) reported that rosemary essential oil contains mainly 1,8-cineole (46.4%), camphor (11.4%) and α-pinene (11.0%). The composition of the rosemary essential oil used by Jiang et al. (2011), was composed mainly by 1,8-cineole (26.54%) and α-pinene (20.14%). Bendeddouche et al. (2011), observed that the main constituents of the tested essential oil were camphor (37.6%), 1,8-cineole (10.0%), p-cymene-7-ol (7.8%) and borneol (5.4%). Biological activities of these secondary metabolites of *R. officinalis* 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 ascardiac remodeling after myocardial infarction, body weight changes, dyslipidemia, cerebral ischemia, hepato-nephrotoxicity, stress, and anxiety. Anti-inflammatory activity of rosemary has been attributed to the presence and synergistic activity of carnosol and carnosic, rosmarinic, ursolic, oleanolic, and micromeric acids (Alavi et al., 2020). Specifically, anti-inflammatory activity has been attributed to synergic effects of ursolic and micromeric acids present in REO.

Physiochemical, molecular and biological properties of α-Pinene oxide - CID (91508); IUPAC Name (3-Oxatricyclo[4.1.1.0(2,4)]octane, 2,7,7-trimethyl-); Canonical SMILES (CC1(C2CC1C3(C(C2)O3)C)C); MF (C10H16O); miLogP(2.74); MW (g/mol) (152.23); TPSA(12.53); natoms (11); nON (1); nOHNH (0); nviolations (0); nrotb (0); volume(155.87); GPCR ligand (- 0.40); Ion channel modulator (- 0.41); Kinase inhibitor (- 1.24); Nuclear receptor ligand (- 0.17); Protease inhibitor (0.15); Enzyme inhibitor (0.34); Mutagenic (High); Tumorigenic (None); Irritant (High); Reproduction (None); Drug likeness (-1.28); Drug score (0.21) (Table 2).

Physicochemical and druggability properties - Molecular weight (152.24g/mol); LogP (2.21); LogD (1.98); LogSw (-2.13); Number of stereocenters (4); Stereochemical complexity (0.400); Fsp3 (1.000); Topological polar surface area (12.53 Å2); Number of hydrogen bond donors (0); Number of hydrogen bond acceptors (1); Number of smallest set of smallest rings (SSSR) (1); Size of the biggest system ring (9); Number of rotatable bonds (0); Number of rigid bonds (10); Number of charged groups (0); Total charge of the compound (0); Number of carbon atoms (10); Number of heteroatoms (1); Number of heavy atoms (11); Ratio between number of non-carbon atoms and carbon atoms (0.1); Lipinski's rule of 5 violations (0); Veber rule (Good); Egan rule (Good); Oral PhysChem score (Traffic Lights) (0); GSK's 4/400 score (Good); Pfizer's 3/75 score (Warning); Weighted quantitative estimate of drug-likeness (QEDw) score (0.483); Solubility (18168.11); Solubility Forecast Index (Good) (Table 3).

ADMET properties - Human Intestinal Absorption (HIA+ - 0.993); Blood Brain Barrier (BBB+ - 0.954); Caco-2 permeable (Caco2+ - 0.632); P-glycoprotein substrate (Non-substrate - 0.527); P-glycoprotein inhibitor I (Non-inhibitor - 0.623); P-glycoprotein inhibitor II (Non-inhibitor - 0.871); CYP450 2C9 substrate (Non-substrate - 0.775); CYP450 2D6 substrate (Non-substrate - 0.818); CYP450 3A4 substrate (Substrate - 0.576); CYP450 1A2 inhibitor (Non-inhibitor - 0.638); CYP450 2C9 inhibitor (Non-inhibitor - 0.579); CYP450 2D6 inhibitor (Non-inhibitor - 0.929); CYP450 2C19 inhibitor (Inhibitor - 0.509); CYP450 3A4 inhibitor (Non-

inhibitor - 0.957); CYP450 inhibitory promiscuity (Low CYP Inhibitory Promiscuity - 0.865); Ames test (Non AMES toxic - 0.913); Carcinogenicity (Non-carcinogens - 0.675); Biodegradation (Not ready biodegradable - 0.877); Rat acute toxicity (1.837 LD50, mol/kg - Not applicable); hERG inhibition (predictor I) (Weak inhibitor - 0.983); hERG inhibition (predictor II) (Non-inhibitor - 0.801) (Table 3). These natural drugs can be proposed for preclinical and clinical studies in different diseases and pathological conditions.

IV CONCLUSION

Rosemary contains a large variety of bioactive molecules with great therapeutic potential such as triterpenes (e.g., ursolic and oleanolic acid), tricyclic diterpenes (e.g., carnosic acid and carnosol), phenolic acids (e.g., caffeic acid and rosmarinic acid), and essential oils. These secondary metabolites have been formulated in topical dosages. REO has anti-inflammatory, antimicrobial, and antioxidant properties, which have been extensively reported in oral formulations. However, development of new formulations containing other less common REO extracts is warranted through trials to evaluate and establish the potentials of pharmacologically active phyto-compounds towards safety and efficacy, in treating various pathological conditions.

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