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Research Article

Profile of bioactive compounds in *Rosmarinus officinalis*

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Abstract

Plant Based Natural Products (PBNPs) have contributed to the development of drugs for diverse indications. Worldwide interest in use of PBNPs has been growing, and its beneficial effects being rediscovered for the development of drug leads. Literature survey on indigenous traditional knowledge bestows ethnopharmacological potentials of PBNPs, has inspired research in drug design and discovery; PBNPs provide a baseline for the development of novel drug leads against various pharmacological targets. Reports indicate that rosemary essential oil (ROEO) extracts show biological bioactivities such as hepatoprotective, antifungal, insecticide, antioxidant and antibacterial. However, their application is limited because of their odor, color and taste. Phytochemical screening indicates the presence of phenol, flavonoids, tannins, alkaloids, carbohydrates, proteins, glycosides, saponins, coumarins, terpenoids, quinones, steroids. Owing to widespread applications of phyto-compounds in ROEO - GCMS was performed. GCMS analysis detected the presence of 22 compounds (α-Pinene, Camphene, β-Myrcene, α-Terpinine, p-Cymene, trans-3-Caren-2-ol, 1,8-Cineole, γ-Terpinene, α-Terpinolene, Linalool, Isopulegol, Eucalyptol, Terpinen-4-ol, 2-Naphthalenol, (-)-Myrtenol, Verbenone, Terpine, α-Copaene, β-Caryophyllene, γ-Cadinene, Caryophyllene oxide) of which 6 compounds (α-Pinene, p-Cymene, Isopulegol, Eucalyptol, 2-Naphthalenol, Terpine) were in abundant. These compounds have been prospected for their molecular and biological properties in the present study.

Keywords: *Rosmarinus officinalis*; Rosemary Essential Oils (ROEO); GCMS; Bioprospecting; PBNPs

INTRODUCTION

Rosemary (*Rosmarinus officinalis* L.), belongs to family Lamiaceae, is aromatic, evergreen, usually erect, bushy shrub up to 2m tall and wide. Stem indistinctly quadrangular finely grey pubescent. Leaves opposite, tufted on the branches, sessile to short, petiolate, blade linear, 1-5cm×1-2mm, base attenuate, margin entire but revolute, apex obtuse, leathery, dark glossy, sea green and sub glabrous above, white felted tomentose beneath, aromatically fragrant when crushed. Inflorescence Racemose, axillary 5-10 flowered, 0.5-2.5 cm long, terminating short lateral branches, pedicle 2-5mm long, calyx campanulate, 2-lipped, 5-6mm long, densely stellate tomentose, upper lip small and 3 dentate, lower lip 2–lobed, corolla tabular, 2 lipped, 10- 13 mm long, pale blue or white, upper lip or curved , 2-lobed, ovate, about 4mm long, lower lip 3-lobed above 7mm long, with large concave middle lobe; 2 anterior stamens perfect, 7-8 mm long, ascending under the base of the upper lip, two posterior stamens reduced to hardly visible staminodes, pistil with deeply 4-parite ovary style incurved, 1.5 cm long ending into 2 short, unequal branches with stigma. Fruit composed of 4sub-globose to obovoid nutlets, above 2mm long, glabrous and smooth; Flowering – Nov - Jan[1,2].

Since antiquity foliage is used as a common household culinary spice for flavouring. Rosemary extracts, derived from leaves, are used as flavouring and antioxidant agents in food processing and cosmetics. Rosemary has been used in traditional and complementary alternative medicine for its digestive, tonic, astringent, diuretic, and diaphoretic properties. It has been linked to a broad range of beneficial health benefits[3].

Main constituents of ROEO are camphor (5.0–21%), 1,8-cineole (15–55%), α-pinene (9.0–26%), borneol (1.5–5.0%), camphene (2.5–12%), β-pinene (2.0–9.0%) and limonene (1.5–5.0%) in proportions that vary according to the vegetative stage and bioclimatic conditions[4]. Rosemary has long been used in traditional medicine to cure a variety of ailments[5]. Phytochemicals in R. officinalis include rosmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid, carnosic acid and carnosol[6]. ROEO composed of phenolic compounds, di and triterpenes and essential oils. In traditional medicine ROEO is used to treat wounds, rashes, headache, dyspepsia,

circulation problems, and as expectorant, diuretic and anti-spasmodic in treatment of renal colic[7] which is attributed to the class of chemical compounds. Polyphenols are antioxidants primarily responsible for fruit colouring, and are classified as phenolic acids, flavonoids and non-flavonoids. Epidemiology evidence indicates that a diet rich in antioxidant fruits and vegetables significantly reduces the risk of many oxidative stress related diseases viz. cancers, diabetes and cardiovascular diseases (CVD). In addition to their antioxidant properties, ROEO play a very important role in plant defences against herbivores, pathogens and predators; therefore, used to control infectious agents in humans. Polyphenols in ROEO are apigenin, diosmin, luteolin, genkwanin and phenolic acids (>3%), especially rosmarinic acid, chlorogenic acid and caffeic acid. furthermore, biological activities exhibited by phenolic acids in There are numerous epidemiological and experimental evidences present describing the protective role of phenolic acids in degenerative diseases such as cardiovascular, cancer, diabetes, inflammation and many more[9]. The ability of plant secondary metabolites depends on the bioavailability which accounts for the proportion of their absorption, digestion, and metabolism after entering in the circulation system[10-28].

MATERIALS AND METHODS

Collection of Plant material: *Rosmarinus officinalis* L. (Rosemary) leaves were collected from Palani Hills, Western Ghats (2000 m above the mean sea level), and identity of the plant was confirmed by Botanical Survey of India, Southern circle, Coimbatore, Tamil Nadu. The collected leaves samples were rinsed with tap water dried and powdered and then stored at 4 °C. Plant extracts preparation 5g of each sample of *R. officinalis* was extracted with 100 ml of methanol using Soxhlet apparatus. The extract was filtered and methanol was evaporated by rotary evaporator and then stored at 4°C for future use.

Phytochemical Screening

The methanolic extracts were subjected to chemical tests for the detection of different phytoconstituents using standard procedures[21,27].

Test for Phenols

To 1 ml of the extract, 3 ml of distilled water followed by few drops of 10%aqueous Ferric chloride solution was added. Formation of blue or green colour indicates the presence of phenols.

Test for Flavonoids

To 2 ml of the extract, 1 ml of 1% ammonia solution was added. Appearance of yellow colour indicates the presence of flavonoids.

Test for Tannins

To 1 ml of the extract, 1 ml of 0.008 M Potassium ferricyanide was added and then add 1ml of 0.02 M Ferric chloride containing 0.1 N HCl. Appearance of blue-black colour indicates the presence of Tannins.

Test for Alkaloids

Approximately, 1 ml of crude extract was mixed with 2 ml of Wagner's reagent. Reddish brown colour precipitate indicates the presence of alkaloids.

Test for carbohydrates

Fehling's test Equal volume of Fehling A and Fehling B reagents were mixed together and then add 2ml of crude extract in it and gently boiled. A brick red precipitate appeared at the bottom of the test-tube indicates the presence of reducing sugars.

Benedict's test1 ml of crude extract was mixed with 2ml of Benedict's reagent and boiled. A reddish brown precipitate was formed which indicates the presence of the carbohydrates.

Test for proteins

Millon's test1 ml of crude extract was mixed with 2ml of Millon's reagent, white precipitate appeared which turned red upon gentle heating that confirmed the presence of protein.

Ninhydrin test1 ml of crude extract was mixed with 2ml of 0.2% solution of Ninhydrin and boiled. A violet colour precipitate was appeared suggesting the presence of amino acids and proteins.

Test for Cardiac glycosides (Keller-Kiliani test)

5 ml of extract was treated with 2 ml of glacial acetic acid containing one drop of ferricchloride solution. This was underlayed with 1 ml of concentrated sulphuric acid. A browning of the interface indicates a deoxy sugar characteristic of cardenolides. A violet ring may appear below the brown ring, while in the acetic acid layer, a greenish ring may form just gradually throughout thin layer.

Test for Saponins

2 ml of crude extract was mixed with 5 ml of distilled water in a test tube and it was shaken vigorously. Add some drops of olive oil. The formation of stable foam was taken as an indication for the presence of saponins.

Test for Coumarin

10 % Sodium hydroxide was added to the extract and chloroform was added. Formation of yellow color shows the presence of Coumarin.

Test for Terpenoids (Salkowski test)

5 ml of extract was mixed with 2 ml of chloroform and 3 ml of concentrated sulphuric acid was carefully added to form a layer. A reddish brown colouration of the inter face was formed which indicates the presence of terpenoids.

Test for Steroids

2 ml of acetic anhydride was added to 0.5 ml of crude extract containing 2 ml of sulphuric acid. The colour changed from violet to blue or green in samples indicates the presence of steroids.

Test for Quinones

Diluted sodium hydroxide was added to the 1 ml of crude extract. Blue green or red coloration indicates the presence of quinones.

Test for anthraquinones (Borntragers test)

0.5 g of each extract was boiled with 10% hydrochloric acid for few minutes in water bath. It was filtered and allowed to cool. Equal volume of $CHCl_3$ was added to the filtrate. Few drops of 10% ammonia was added to the mixture and heated. Formation of rose – pink color indicates of n-hexane, chloroform, ethyl acetate and methanol of the presence of the anthroquinones.

Preparation and extraction of sample

Protocol for preparation of sample was according to the methods previously described[27], 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[24]. 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 and subjected to GC-MS analysis.

GC-MS Analysis

Phyto-components were identified using GCMS detection system as previously with minor modification, whereby portion of the extract was analysed directly by headspace sampling. GCMS 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.

RESULTS AND DISCUSSION

Chemical Properties and Identifier

Chemical kingdom	Organic compounds
Superclass	Lipids and lipid-like molecules
Class	Prenol lipids
Subclass	Monoterpenoids
PubChem Identifier	170833
Synonyms	ISOPULEGOL; ALPHA-TERPINEOL;
Canonical SMILES	C[C@@H]1CC[C@H]([C@@H](C1)O)C(=C)C
InChI Key	ZYTMANIQRDEHIO-KXUCPTDWSA-N

GCMS analysis of *Rosmarinus officinalis* (Rosemary)

The chemical composition of ROEO 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).**

Secondary metabolites of ROEO 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[3,6]. Structure and molecular biological properties of selected compounds in R. officinalis has been the determinant of the biological activity as depicted in Fig. 2a-f. Similarly, Sienkiewicz et al.[26] reported that ROEO contains 1,8-cineole (46.4%), camphor (11.4%) and α-pinene (11.0%) and precursors of other significant bioactive molecules used for therapeutic, cosmetics, and food industries. ROEO used by Jiang et al[18] had 1,8-cineole (26.54%) and α-pinene (20.14%) present significant antimicrobial activity. Bendeddouche et al.[13] reported that camphor (37.6%), 1,8-cineole (10.0%), p-cymene-7-ol (7.8%) and borneol (5.4%) were the main bioactive metabolites. Anti-inflammatory activity of rosemary has been attributed to the synergistic activity of carnosol and carnosic, rosmarinic, ursolic, oleanolic, and micromeric acids[7]. Specifically, anti-inflammatory activity has been attributed to synergic effects of ursolic and micromeric acids present in ROEO. These natural drugs can be proposed for preclinical and clinical studies in different diseases and pathological conditions[29-31].

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. ROEO has anti-inflammatory, antimicrobial, and antioxidant properties, which have been extensively reported in oral formulations. However, development of new formulations containing other less common ROEO extracts is warranted through ADMET to evaluate and establish the potentials of pharmacologically active phyto-compounds towards safety and efficacy, in treating various pathological conditions.

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Table 1 Qualitative phytochemical analysis of methanolic extract of *R. officinalis*

PHYTOCONSTITUENTS	TEST	PRESENT/ ABSENT
Phenol	FeCl3 Test	**+++**
Flavonoids	Shinoda Test	**++**
Tannins	FeCl3 Test	**++**
Alkaloids	Wagner's reagent Test	**+**
Carbohydrates	Fehling's test, Benedict's test	**++**
Proteins	Millon's Test, Ninhydrin Test	**++**
Glycosides	Keller-Kiliani Test	**+**
Saponins	Foam Test	**+**
Coumarins	Coumarins Test	**+**
Terpenoids	Salkowski Test	**++**
Quinones	Quinone Test	**+**
Steroids	Salkowski Test	**+**
Anthraquinones	Borntragers Test	**-**

+++ = Copiously present; ++ = moderately present; + = slightly present; - = absent

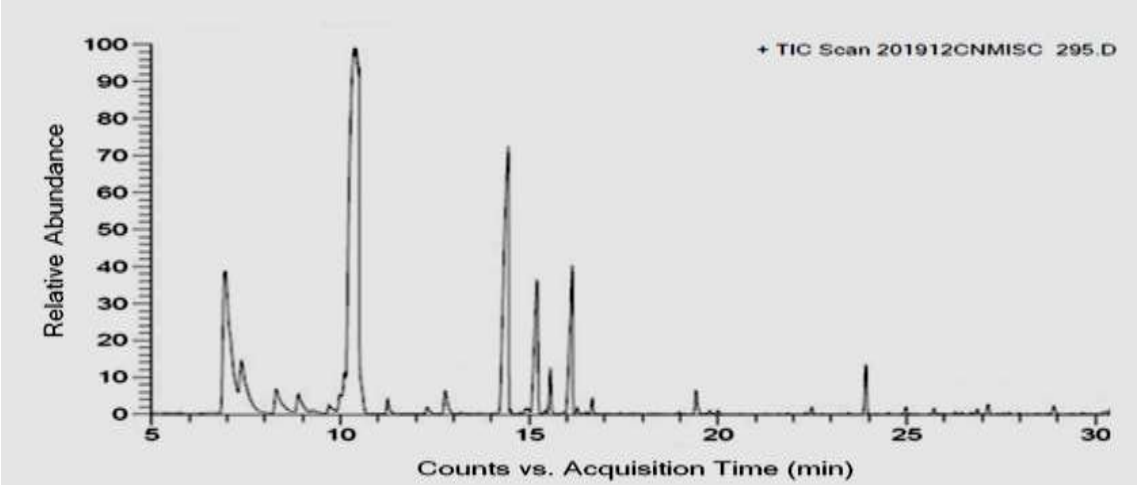


Figure 1: GCMS analysis of *Rosmarinus officinalis* (Rosemary) essential oil

Table 2: GCMS profile of *Rosmarinus officinalis* (Rosemary) essential oil

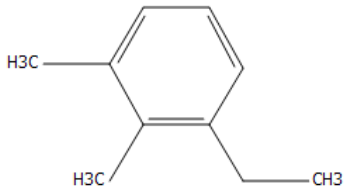
S.No	Compound	Molecular Formula	Retention Time (min)	Percentage (%)
1.	**α-Pinene**	$C_{10}H_{16}O$	6.94	13.64
2.	Camphene	$C_{10}H_{16}$	7.38	2.42
3.	β-Myrcene	$C_{10}H_{16}$	8.88	1.19
4.	α-Terpinine	$C_{10}H_{16}$	9.70	0.41
5.	**p-Cymene**	$C_{10}H_{14}$	9.98	6.23
6.	trans-3-Caren-2-ol	$C_{10}H_{16}O$	10.10	0.20
7.	1,8-Cineole	$C_{10}H_{18}O$	10.38	41.75
8.	γ-Terpinene	$C_{10}H_{16}$	11.25	0.59
9.	α-Terpinolene	$C_{10}H_{16}$	12.30	0.35
10.	Linalool	$C_{10}H_{18}O$	12.78	1.19

11.	**Isopulegol**	$C_{10}H_{16}O$	14.44	13.66
12.	**Eucalyptol**	$C_{10}H_{18}O$	15.21	6.71
13.	Terpinen-4-ol	$C_{10}H_{18}O$	15.56	1.24
14.	**2-Naphthalenol**	$C_{10}H_{18}O$	16.14	6.35
15.	(-)-Myrtenol	$C_{10}H_{16}O$	16.27	0.16
16.	Verbenone	$C_{10}H_{14}O$	16.67	0.42
17.	**Terpine**	$C_{12}H_{20}O_2$	19.42	2.80
18.	α-Copaene	$C_{15}H_{24}$	22.49	0.20
19.	β-Caryophyllene	$C_{15}H_{24}$	23.92	1.40
20.	γ-Cadinene	$C_{15}H_{24}$	27.16	0.34
21.	Caryophyllene oxide	$C_{15}H_{24}O$	28.90	0.32

a)

p-Cymene

CCC1=CC=CC(=C1C)C



MF	**$C_{10}H_{14}$**
Molecular Properties	**Calculated Values**
miLogP	3.65
TPSA	0.00
natoms	10
MW	134.22
nON	0
nOHNH	0
nviolations	0
nrotb	1
volume	150.53

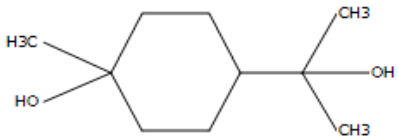
Biological Properties	**Bioactivity Scores**
GPCR ligand	- 1.11
Ion channel modulator	- 0.81
Kinase inhibitor	- 1.41
Nuclear receptor ligand	- 1.23
Protease inhibitor	- 1.47
Enzyme inhibitor	- 0.77

b)

Terpin

(Cyclohexanemethanol, 4-hydroxy-.alpha.,.alpha.,4-trimethyl-)

CC1(CCC(CC1)C(C)(C)O)O



MF	**$C_{10}H_{20}O_2$**
Molecular Properties	**Calculated Values**
miLogP	1.61
TPSA	40.46
natoms	12
MW	172.27
nON	2
nOHNH	2
nviolations	0
nrotb	1
volume	184.55

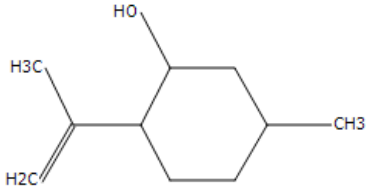
Biological Properties	**Bioactivity Scores**
GPCR ligand	- 0.39
Ion channel modulator	**0.35**
Kinase inhibitor	- 1.12
Nuclear receptor ligand	- 0.35
Protease inhibitor	- 0.55
Enzyme inhibitor	- 0.02

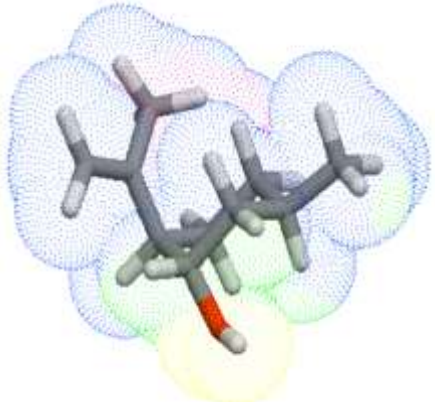
c)

Isopulegol

(Cyclohexanol, 5-methyl-2-(1-methylethenyl)-)

CC1CCC(C(C1)O)C(=C)C





MF	**$C_{10}H_{18}O$**
Molecular Properties	**Calculated Values**
miLogP	2.65
TPSA	20.23
natoms	11
MW	154.25
nON	1
nOHNH	1
nviolations	0
nrotb	1
volume	171.55

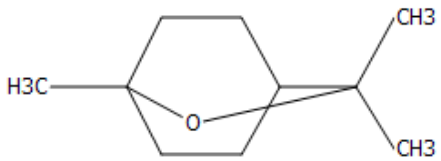
Biological Properties	**Bioactivity Scores**
GPCR ligand	- 0.78
Ion channel modulator	- 0.16
Kinase inhibitor	- 1.59
Nuclear receptor ligand	- 0.22
Protease inhibitor	- 0.71
Enzyme inhibitor	- 0.14

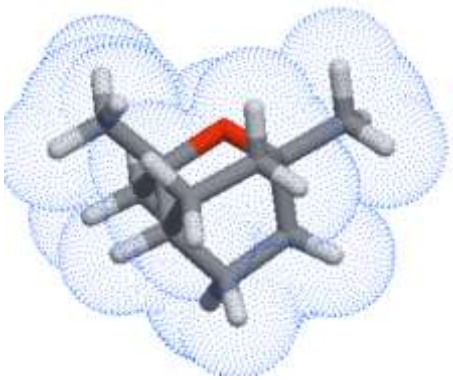
d)

Eucalyptol

(1,8-Cineole; 470-82-6; 1,8-Cineol)

CC1(C2CCC(O1)(CC2)C)C





MF	**$C_{10}H_{18}O$**
Molecular Properties	**Calculated Values**
miLogP	2.72
TPSA	9.23
natoms	11
MW	154.25
nON	1
nOHNH	0
nviolations	0
nrotb	0
volume	166.66

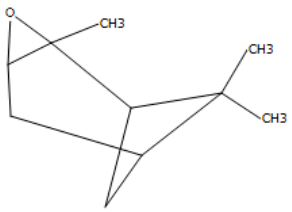
Biological Properties	**Bioactivity Scores**
GPCR ligand	- 0.93
Ion channel modulator	- 0.01
Kinase inhibitor	- 1.60
Nuclear receptor ligand	- 1.07
Protease inhibitor	- 0.90
Enzyme inhibitor	- 0.15

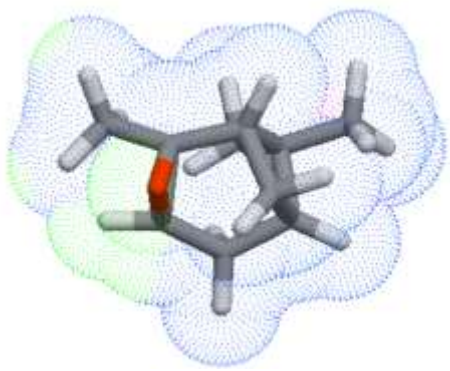
e)

alpha-Pinene oxide

(3-Oxatricyclo[4.1.1.0(2,4)]octane, 2,7,7-trimethyl-)

CC1(C2CC1C3(C(C2)O3)C)C





MF	**$C_{10}H_{16}O$**
Molecular Properties	**Calculated Values**
miLogP	2.74
TPSA	12.53
natoms	11
MW	152.24
nON	1
nOHNH	0
nviolations	0
nrotb	0
volume	155.87

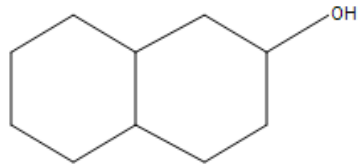
Biological Properties	**Bioactivity Scores**
GPCR ligand	- 0.40
Ion channel modulator	- 0.41
Kinase inhibitor	- 1.24
Nuclear receptor ligand	- 0.17
Protease inhibitor	**0.15**
Enzyme inhibitor	**0.34**

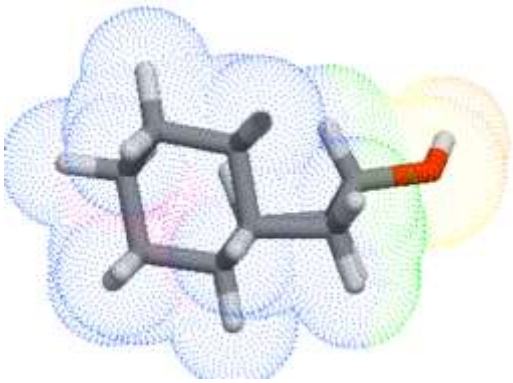
f)

2-Naphthalenol, decahydro-

(-Naphthalenol, decahydro-)

C1CCC2CC(CCC2C1)O





MF	**$C_{10}H_{18}O$**
Molecular Properties	**Calculated Values**
miLogP	2.50
TPSA	20.23
natoms	11
MW	154.25
nON	1
nOHNH	1
nviolations	0
nrotb	0
volume	167.06

Biological Properties	**Bioactivity Scores**
GPCR ligand	- 0.49
Ion channel modulator	- 0.09
Kinase inhibitor	- 0.98
Nuclear receptor ligand	- 0.48
Protease inhibitor	- 0.40
Enzyme inhibitor	- 0.02

Figure 2a-f Structure (2D, 3D), molecular biological properties of compounds in *R. officinalis*