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RESEARCH COMMUNICATION

GC-MS analysis and *in silico* activity prediction of phytocompounds in the roots of *Chrysopogon zizanioides* (L.) Roberty

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ABSTRACT

Chrysopogon zizanioides (L.) Roberty (Poaceae) commonly known as R*amacham*is an aromatic, vigorous growing perennial grass with medicinal properties. The plant is tolerant to extreme soil and climatic conditions and is known for its cooling properties. Roots of the plant are widely used as body scrubber and is suggested for skin diseases in Ayurveda. The present work aims to identify the components in the crude methanolic root extract of *C. zizanioides* using GC-MS and also to predict the pharmacokinetic behaviour of selected compounds *in silico* using Swiss ADME online server . 41 compounds were identified of which sesquiterpenes formed the major group. Sesquiterpene Vetivenic acid was the compound with a maximum peak area of 38.9%. Components identified is reported to possess a range of biological activities like anti oxidant, antibacterial, anti cancer, anti inflammatory, anti ulcer, analgesic and insecticidal activities. Compounds with higher peak area like Vetivenic acid, beta vatirenene, beta.-Cedren-9-.alpha.-ol, D Viridiflorol, Gamma muurolene, (Z,E)-alpha-farnesene, Nootkatone, Aromadendrene oxide-(2), 7-Acetyl-2-hydroxy-2methyl-5isopropylbicyclo[4.3.0] nonane, Rosifoliol, 9,10-dehydro isolongifolene, Ylangenol, 4,7,10,13,16,19-Docosahexaenoic acid methyl ester, Carbonic acid, propargyl 2,2,2-tri chloroethyl ester, Oxacyclotetradeca-4,11-diyne, beta eudesmol and longifolene were evaluated *in silico*. All these compounds proved to obey Lipinski's rule-of-five and were water soluble. Vetivenic acid showed a good bioavailability score of 85% while the others showed 55%. None of the compounds were substrates to P glycoprotein. The values predicted may be used for preliminary evaluation of pharmacological properties of *C. zizanioides* and also as monographs for the development of potential semisynthetic or synthetic drugs.

Introduction

Chrysopogon zizanioides (L.) Roberty is a medicinally useful plant known since ancient times. It is a perennial grass belonging to family Gramineae. Oil from the root of the plant have been used by the people for centuries. The plant is tolerant to extreme soil and climatic conditions and is known for its cooling properties (1). Roots of the plant are useful for hyperdipsia, burning sensation, skin diseases, nausea, vomiting, dyspepsia, flatulence, flatulence, bilious fever, gout, lumbago, sprains, halitosis, cephalalgia, amentia, amenorrhoea, helminthiasis and general debility (2).

Few Ayurvedic preparations from the roots of *khus* (*C. zizanioides*) are particularly used in relieving sense of heat and thus alleviating the symptoms of dermatoses (3). Volatile oils from different plant parts are known to improve flexibility of skin, have skin permeability, emollience, anti-inflammatory property and are effective against various skin ailments (4, 5).

GC-MS technique has been commonly used in *C. zizanioides* to identify the components in the volatile oil of roots. The present study attempt to use crude root extract obtained by maceration method for GC-MS analysis. Maceration method is simple, cheap and less time consuming than the oil isolation methods.

Medicinal plants play a significant part in drug discovery, for the creation of novel bioactive compounds. The majority of the drugs endorsed for clinical trials are either natural Products or their analogs (6). The fact that increasing number of drugs don't reach the market because of their low

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pharmacokinetic profiles has necessitated the study of pharmacokinetic properties at early stages of drug development programmes (7).

An ideal drug needs to satisfy properties like easy oral absorption, easy transportation to the desired site of action, inability to form toxic products before reaching the targeted site of action and easy elimination from the body. All these properties are often referred to as ADME (absorption, distribution, metabolism and elimination) properties or ADMET (when toxicity assessment is included).

Use of computer-based strategies in the prediction of ADMET properties of drug leads at beginning stages of drug discovery are becoming increasingly popular being less expensive and less time consuming. Now a days various computational tools are widely used for predicting these pharmacokinetic properties. Of the several computational tools available for the prediction of pharmacokinetic properties, Swiss ADME online tool provides free access to different predictive models for pharmacokinetics, physicochemical properties, medicinal chemistry friendliness and drug-likeness of compounds (8).

The present study was aimed to evaluate the volatile components in the crude methanolic root extract of *C. zizanioides* using GC-MS and also to predict the pharmacokinetic behaviour of selected compounds *in silico* using Swiss ADME online server.

Materials and Methods

Plant collection and extraction

The root sample of *C. zizanioides* were obtained from Aromatic and Medicinal Plant Research Station (AMPRS), Odakkali (Ernakulam district), Kerala, India. The sample was identified, authenticated and submitted (voucher specimen - Accession No: 16687 in the Herbarium of Kerala Forest Research Institute, Thrissur, Kerala. The sample was washed thoroughly, dried under shade and ground to a fine powder in an electrical blender. The crude extract of *C. zizanioides* root was prepared using maceration technique by extracting 10gm of powdered sample in 50 ml methanol in stoppered glass containers kept on a rotary shaker for 48 hrs (9).

GC-MS analysis

The methanolic extract obtained from roots of *C. zizanioides* were analysed by GC-MS (Agilent, USA) using a High Performance-5MS 5% Phenyl Methyl Silox capillary column (30m length x 250 µm I.d. x 0.25 µm film thickness). Electron impact system had an ionization energy of 70 eV with a source temperature of 280 ^{0}C. High purity helium gas was used at a constant flow rate of 1ml/min. The temperature of the oven was initially kept at 40 ^{0}C for 5 min then ramped at 5 ^{0}C/min to 280 ^{0}C and finally increased to 325 ^{0}C. Injection volume of 2µl was employed (split ratio 1:25). Injector temperature was maintained at 220 °C. The MS specifications were as follows: Ion source temperature: 230 ^{0}C, interface temp: 300 °C scan range: 40-800 m/z, event time: 0.5s, solvent delay: 3 min. Positive electron impact ionization (EI) modes were used and data were collected using single ion monitoring (SIM). The mass spectra of the volatile components obtained through analysis were identified by comparing their mass spectra with the MS data library of National Institute of the Standards and Technology for The mass spectra of the volatile components obtained through analysis were identified by comparing their mass spectra with the MS data library of National Institute of Standards and Technology for identification of bioactive compounds (NIST 08.L) attached to the GC-MS instrument and the results were obtained. Identified compounds were tabulated. Based on the reported biological activity of the phytocomponents analysed, compounds showing common pharmacological action were tabulated Fig 1.

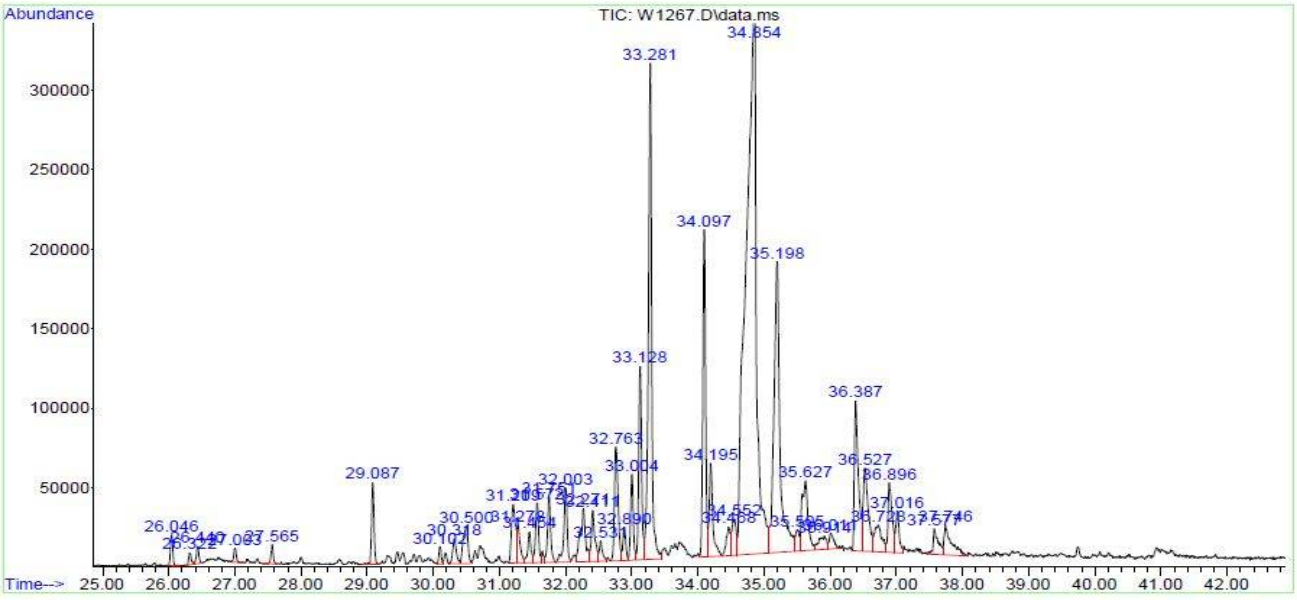

Fig. 1. GC-MS Chromatogram of *C. zizanioides* root methanolic extract.

ADME prediction

Compounds with higher peak area were evaluated *in silico*. The molecular structure of the compounds were retrieved in ".sdf" format from PubChem and were used for ADME prediction using Swiss ADME online server (http://www.swissadme.ch) of Swiss institute of bioinformatics. Computational analyses were performed to predict the core pharmacokinetics parameters such as molecular weight, lipophilicity, water solubility, gastrointestinal absorption, Blood Brain Barrier permeability, P-glycoprotein substrate and skin permeability, drug likeliness and bioavailability score. After all analyses were completed, the graphical output was obtained in the form of "BOILED – Egg" model.

Results

Chemical composition of extract by GC-MS analysis

GC-MS chromatogram of the phytocomponents detected in the methanolic and root extract of *C. zizanioides* are shown in Table 1. The GC-MS analysis of methanolic root extract of *C. zizanioides* indicated the presence of forty-onecompounds. The active principles with their retention time, peak area (%) and uses are presented in Table 2. Among the compounds identified, twenty-four compounds were sesquiterpenoids, two were monoterpenoids, two were esters, three were hydrocarbons and one was fatty acid. Cyclopentane acetaldehyde2-formyl-3-methyl-.alpha.-methylene- (dolichodial) and ocimene were the monoterpenes identified. Sesquiterpene, 1H-3a, 6-Methanoazulene-3carboxylic acid, octahydro-7, 7-dimethyl-8-methylene-[3S-(3.alpha., 3a.alpha., 8a.alpha.)]-(Vetivenic acid / Khusenic acid) was the major compound identified in the extract with a peak area of 38.9% followed by beta.-Ethylphenethyl alcohol (12.73%), beta.-Vatirenene (7.24%), beta.-Cedren-9-.alpha.-ol (4.45%), 1H-Cycloprop[e] azulen-7-ol decahydro-1,1,7- trimethyl-4-methylene [1ar-1a.alpha.,4a.alpha.,7.beta., 7b.alpha.)]- (Spthulenol / espatulenol) (3.31%), alpha.-Farnesene (2.61 %), 2(3H)-Naphthalenone, 4.4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-,[4R-(4,alpha.,4a.alpha.,6.beta.)]-(Nootkatone) (2.47%) etc.

In silico ADME evaluation

Compounds with higher peak area like Vetivenic acid, beta vatirenene, beta.-Cedren-9-.alpha.-ol, D Viridiflorol, Gamma muurolene, (Z, E)-alpha-farnesene, Nootkatone, Aromadendrene oxide-(2), 7-Acetyl-2-hydroxy-2-methyl-5-isopropylbicyclo[4.3.0] nonane, Rosifoliol, 9,10-dehydro isolongifolene, Ylangenol, 4,7,10,13,16,19-Docosahexaenoic acid

Table 1. Phytocompounds detected in the methanolic root extract of *C. zizanioides* by GC-MS

Sl. No.	Compound	RT	Area %
	Monoterpene		
1	Cyclopentane acetaldehyde2-formyl-3-methyl-.alpha.-methylene-[DOLICHODIAL]	32.531	0.57
2	Ocimene	32.89	0.74
	Sesquiterpene		
3	Gamma Himachalene	26.046	0.57
4	Naphthalene, 1,2,3,4,4a,8a-hexahydro-4,7-dimethyl1-(1-methylethyl)-naphthalene [ALPHA AMORPHENE]	26.439	0.46
5	alpha.-Cubebene	27.004	0.54
6	1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-, (Z,E)- [(Z,E)-ALPHA-FARNESENE]	27.340	0.19
7	cyclohexene 3-methyl-6-(1-methylethenyl)- (3r-trans)- [TRANS LIMONENE]	27.565	0.42
8	1H-Cycloprop[e]azulene, decahydro 1,1,7-trimethyl-4-methylene-,[1aR (1a.alpha.,4a.beta.,7.alpha.,7a.beta.,7b.alpha.)]- [AROMADENDRENE]	28.001	0.21
9	2-Naphthalenemethanol, 2,3,4,4a,5,6,7,8-octahydro.alpha.,.alpha.,4a,8-tetramethyl[2R-(2.alpha.,4a.beta.,8.beta.)]-	29.087	1.61
10	Caryophyllene oxide	29.459	0.56
11	alpha.-Bisabolol	29.792	0.24
12	Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2-(1-methylethenyl[2R-(2.alpha.,4a.alpha.,8a.beta.)]- [AROMADENDRENE]	30.102	0.31
13	2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl-, (Z,E)- [FARNESOL]	30.318	0.71
14	1,4-Methanoazulene, decahydro-4,8,8-trimethyl-9-methylene-, [1S-(1.alpha.,3a.beta.,4.alpha.,8a.beta.)]- [LONGIFOLENE]	30.5	1.44
15	2-Naphthalenemethanol, decahydro alpha.,.alpha.,4a-trimethyl-8-methylene-, [2R-(2.alpha.,4a.alpha.,8a.beta.)]- [BETA EUDESMOL]	30.714	1.05
16	Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-7-methyl-4-methylene-1-(1-methylethyl)-, (1.alpha.,4a.alpha., 8a.alpha.)- [GAMMA MUUROLENE]	31.211	2.83
17	2(3H)-Naphthalenone, 4,4a,5,6,7,8- hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-, [4R-(4.alpha.,4a.alpha.,6.beta.)]- [NOOTKATONE]	31.571	2.47
18	Isolongifolene 9,10-dehydro	31.751	1.61
19	Aromadendrene oxide-(2)	32.002	1.97
20	Tricyclo[4.4.0.02,7]dec-3-ene-3-methanol, 1-methyl-8-(1-methylethyl)-, [YLANGENOL]	32.41	1.53
21	1H-Cycloprop[e]azulen-7-ol decahydro-1,1,7-trimethyl-4-methylene [1ar-(1a.alpha.,4a.alpha.,7.beta., 7a.beta.,7b.alpha.)]- [SPTHULENOL / ESPATULENOL]	32.763	3.31
22	.beta.-Cedren-9-.alpha.-ol	33.128	4.45
23	1H-Cycloprop[e]azulen-4-oldecahydro-1,1,4,7-tetramethyl-, [1ar-(1a.alpha.,4.beta.,4a.beta.,7.alpha., 7a.beta.,7b.alpha.)]- [D VIRIDIFLOROL]	33.494	0.36
24	beta.-Vatirenene	34.097	7.24
25	alpha.-Farnesene	34.195	2.61

26	1H-3a,6-Methanoazulene-3-carboxylic acid, octahydro-7,7-dimethyl-8-methylene- [3S-(3.alpha.,3a.alpha.,6.alpha.,8a.alpha.)]- [VETIVENIC ACID / KHUSENIC ACID]	34.854	38.9
	Ester		
27	4,7,10,13,16,19-Docosahexaenoic acid, methyl ester(all-Z)-	33.732	1.48
28	Carbonic acid, propargyl 2,2,2-tri chloroethyl ester	33.732	1.48
	Hydrocarbon		
29	Toluene	4.295	0.64
30	Hexane	26.758	0.48
31	3,4-Dimethoxytoluene	29.323	0.36
	Alcohol		
32	beta.-Ethylphenethyl alcohol	33.281	12.73
	Fatty acid		
33	2-Nonynoic acid	30.99	0.23
	Others		
34	3-Aminopyrrolidine	26.758	0.48
35	1-Methoxy-1,4-cyclohexadiene	29.928	0.28
36	Cyclopentane-3'-spirotricyclo[3.1.0.0(2,4)]hexane-6'-spirocyclopentane	30.186	0.22
37	1,4-Methanoazulenedecahydro-4,8,8-trimethyl-9-methylen	30.496	1.44
39	Cyclopropane1,1-dichloro-2,2,3,3 -tetramethyl-	32.27	2.27
40	7-Acetyl-2-hydroxy-2-methyl-5-isopropylbicyclo[4.3.0]nonane	33.004	1.82
41	Oxacyclotetradeca-4,11-diyne	34.549	1.35

Table 2. Reported pharmacological activities of compounds identified in *C. zizanioides* roots

Sl. No.	Pharmacological Activities	*C. zizanioides*
1	Anicancer, AntianoxicAnti ulcer, Hepatoprotective, Pesticide	Beta eudesmol (18)
2	Antiinflammatory	alpha.-Cubebene (19) alpha.-Bisabolol (20) Spathulenol (21) D Viridiflorol (22) Caryophyllene oxide (23)
3	Antimicrobial	beta.-Vatirenene (24) Ocimene (25) gamma himachelene (26) alpha.-Cubebene (19) alpha.-Bisabolol (27) Spathulenol (21) Vetivenic acid (28) 2-Nonynoic acid (29) D Viridiflorol (22)
4	Antioxidant	D Viridiflorol (22) Isolongifolene 9,10-dehydro (30) Spathulenol (21)
5	Skin problems	alpha.-Bisabolol (27) aromadendrene (31)
6	Anticancer	Caryophyllene oxide (18) Aromadendrene (18)
7	Antiulcer	Beta eudesmol (18) alpha.-Bisabolol (27) Nootkatone (18)
8	Perfumes	Ylangenol (32) alpha.-Farnesene (33) Ocimene (18) alpha.-Bisabolol (27)
9	Flavour	Farnesol (18)
10	Insecticide	Dolichodial (18) Ocimene (25) Nootkatone (34) alpha.-Farnesene (33)

methyl ester, Carbonic acid, propargyl 2,2,2-tri chloroethyl ester, Oxacyclotetradeca-4,11-diyne, beta eudesmol and longifolene were evaluated *in silico*. The observed values are tabulated (Table 3) and the graphical output in the form of “BOILED-egg” model is represented (Fig. 2). All the studied compounds proved to obey Lipinski's rule-of-five and were water soluble. Vetivenic acid showed a good bioavailability score of 85% while the others showed 55%. None of the compounds were substrates to P glycoprotein.

Discussion

C. zizanioides root are a rich source of bioactive compounds. GC-MS analysis of the crude root extract of *C. zizanioides* in methanol, indicated the presence of sesquiterpenes, monoterpenes, esters, alcohols and fatty acids. Of the 41 compounds identified, sesquiterpenes were the major group. Vetivenic acid was the compound identified with major peak area. The presence of gamma himachelene, nootkatone, aromadendrene oxide, vetivenic acid, betavetirene, alpha farnesene, alpha bisabolol, gamma murolene,

Table 3. Result of ADME prediction of phytoconstituents identified in GC-MC of methanolic root extract of *C. zizanioides*

Sl. No.	Compound	Molecular mass	Lipophilicity	Water Solubility	GI absorption	BBB permeability	P-gp substrate	Skin permeation cm/s	Drug likeliness	Bio availability score
1	1H-3a,6-Methanoazulene-3-carboxylic acid, octahydro-7,7-dimethyl-8-methylene- [3S-(3.alpha.,3a.alpha.,6.alpha.,8a.alpha.)]- [VETIVENIC ACID / KHUSENIC ACID]	234.33	3.21	Soluble	High	Yes	No	-5.15	Yes	0.85
2	Beta Vatirenene	202.34	4.13	Soluble	Low	No	No	-4.38	Yes	0.55
3	.beta.-Cedren-9-.alpha.-ol	220.35	3.35	Soluble	High	Yes	No	-5.12	Yes	0.55
4	1H-Cycloprop[e]azulen-7-ol decahydro-1,1,7-trimethyl-4-methylene [1ar-(1a.alpha.,4a.alpha.,7.beta., 7a.beta.,7b.alpha.)]- [SPTHULENOL / ESPATULENOL]	222.37	3.43	Soluble	High	Yes	No	-5.00	Yes	0.55
5	Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-7-methyl-4-methylene-1-(1-methylethyl)-, (1.alpha.,4a.alpha., 8a.alpha.)- [GAMMA MUUROLENE]	204.35	4.17	Soluble	Low	No	No	-4.49	Yes	0.55
6	alpha.-Farnesene	204.35	4.96	Soluble	Low	No	No	-3.20	Yes	0.55
7	2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-, [4R-(4.alpha.,4a.alpha.,6.beta.)]- [NOOTKATONE]	218.33	3.57	Soluble	High	Yes	No	-4.89	Yes	0.55
8	Aromadendrene oxide-(2)	220.35	3.54	Soluble	High	Yes	No	-5.03	Yes	0.55
9	7-Acetyl-2-hydroxy-2-methyl-5-isopropylbicyclo[4.3.0]nonane	238.37	2.8	Soluble	High	Yes	No	-5.94	Yes	0.55
10	2-Naphthalenemethanol, 2,3,4,4a,5,6,7,8-octahydro.alpha.,.alpha.,4a,8-tetramethyl[2R-(2.alpha.,4a.beta.,8.beta.)]- (Rosifoliol)	222.37	3.58	Soluble	High	Yes	No	-4.90	Yes	0.55
11	Isolongifolene 9,10-dehydro	202.34	4.18	Soluble	Low	No	No	-4.01	Yes	0.55
12	Tricyclo[4.4.0.02,7]dec-3-ene-3-methanol, 1-methyl-8-(1-methylethyl)-,[YLANGENOL]	220.35	3.26	Soluble	High	Yes	No	-5.36	Yes	0.55
13	4,7,10,13,16,19-Docosahexaenoic acid, methyl ester(all-Z)-	324.51	6.32	Moderately soluble	Low	No	No	-3.77	Yes	0.55
14	Carbonic acid, propargyl 2,2,2-tri chloroethyl ester	231.46	2.21	Soluble	High	Yes	No	-5.94	Yes	0.55
15	Oxacyclotetradeca-4,11-diyne	190.28	3.21	Soluble	High	Yes	No	-5.01	Yes	0.55
16	2-Naphthalenemethanol, decahydro alpha.,.alpha.,4a-trimethyl-8-methylene-, [2R-(2.alpha.,4a.alpha.,8a.beta.)]- [BETA EUDESMOL]	222.37	3.61	Soluble	High	Yes	No	-5.00	Yes	0.55
17	1,4-Methanoazulene, decahydro-4,8,8-trimethyl-9-methylene-, [1S-(1.alpha.,3a.beta.,4.alpha.,8a.beta.)]- [LONGIFOLENE]	204.35	4.50	Soluble	Low	No	No	-3.94	Yes	0.55

beta eudesmol were identified. Similar findings were reported earlier in the essential oil of *C. zizanioides* (10–12). But the methodology followed in this study is simpler and cheaper than other distillation methods followed (13).

Reported pharmacological action of the compounds identified (Table 2) supports the suggested medicinal use of root of *C. zizanioides* in Ayurveda (2). The findings support the traditional use of roots of *C. zizanioides* (well known as *Ramacham*) as body scrubber.

Of the 41 compounds identified, compounds with ADME information and peak area above 1% were tabulated.17 compounds thus tabulated showed molecular weight less than 500 Daltons which indicated ability of trans cutaneous permeation for these compounds. Topical dermatological therapy focusses on development of innovative compounds under 500 daltons (14). All the 17 compounds selected satisfied the Lipinski rule of five indicating drug likeliness. All the studied compounds in *C. zizanioides* showed water solubility thus favouring more bioavailability. This finding is an added advantage as more than 40% new chemical entities developed in pharmaceutical industry are known to be practically insoluble in water. Solubility has become major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption (15). Carbonic acid, propargyl 2,2,2-tri chloroethyl ester and 7-Acetyl-2-hydroxy-2-methyl-5-isopropylbicyclo [4.3.0] nonane showed log P (lipophilicity) less than 2 indicating lower toxicity (16). None of the compounds were substrates to P-

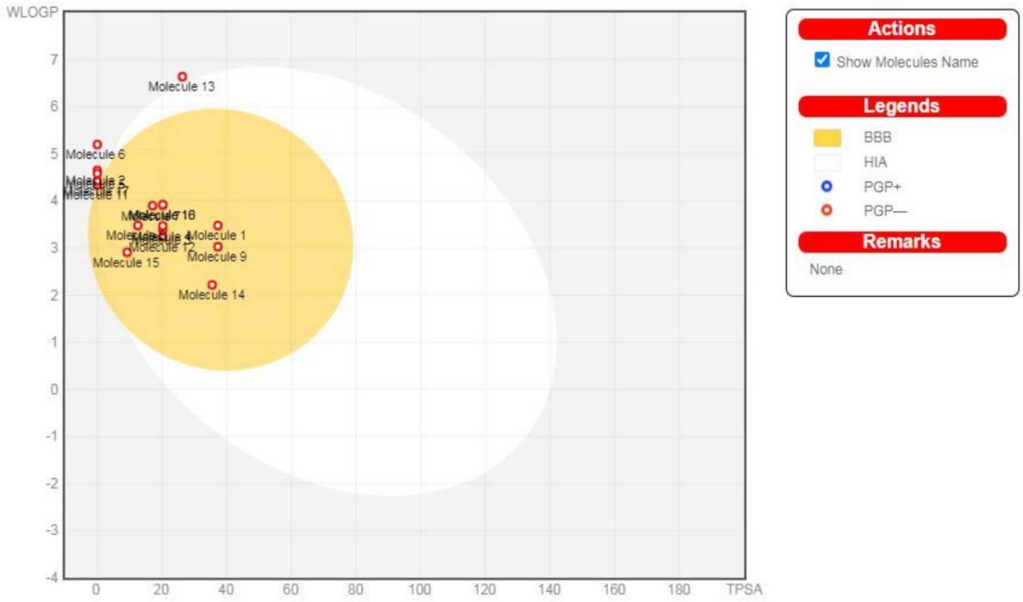

Fig. 2. Boiled Egg Model of the Phytoconstituents of *C. zizanioides* roots.

glycoprotein and thus indicating a better bio availability as reported previously (17). The graphical output of the analysed parameters in the form of "BOILED-Egg" gives a global evaluation about passive absorption (inside/outside the white), passive brain access (inside/outside the yolk) and active efflux from the CNS or to the gastrointestinal lumen by colour-coding: blue dots for P-gp substrates (PGP+) and red dots for P-gp non-substrate (PGP-) (Fig. 2) (8).

Thus, the study shows that many of the volatile components present in the oil of *C. zizanioides* can be extracted by simple maceration method of extraction using methanol. Among the identified compounds, compounds with ADME information indicated transcutaneous permeation, proved to obey Lipinski's rule-of-five and were water soluble. Vetivenic acid showed a good bioavailability score of 85% while the others showed 55%. None of the compounds were substrates to P glycoprotein. The pharmacokinetic parameters studied indicate drug likeliness for the studied compounds but require further *in vitro* and *in vivo* studies for validation. The values predicted may be used for preliminary evaluation of pharmacological properties of *C. zizanioides* and also as monographs for the development of potential semisynthetic or synthetic drugs.

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Authors' contributions

SVCN carried out the experiments and wrote the entire manuscript. IN gave overall direction and helped in interpreting the results.

Conflict of interests

The authors declare no conflict of interest.

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