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In-Silico Antioxidant Activity and GC-MS Analysis of Root Extract of High-Altitude Himalayan Plant: *Erigeron multiradiatus*

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Abstract: The chemical composition of methanolic extract of *Erigeron multiradiatus* root was determined by GC-MS analysis and its in-silico antioxidant activity was also assessed. GC-MS analysis led to the identification of seven compounds i.e 2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one, 6,7-Dioxabicyclo [3.2.2] nonane, 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-, 5-Hydroxy methyl furfural, 5-Acetoxymethyl-2-furaldehyde, D-Allose and 1,6-Anhydro- beta. -D-glucofuranose. Among these 5-Hydroxymethylfurfural was identified as major compound (56.24%). All the identified compounds displayed binding affinity in the range of −5.5 to −6.4 kcal/mol. The highest binding affinity (−6.4 kcal/mol) was recorded by compound 4 (5-Hydroxymethylfurfural) followed by compound 3 (4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-) that was -6.3 kcal/mol. Identified phytochemicals showed a better binding mechanism with the target protein myeloperoxidase. In silico prediction is useful for screening of potential antioxidant agents for further invitro study which gives clear explanation of antioxidant activity of selected extract.

Key words: GC-MS analysis • Antioxidant activity • In-Silico study

Introduction

Free radicals are highly reactive molecules produced in normal or pathological cell metabolism. Reactive oxygen species (ROS) react easily with free radicals to become radicals themselves. ROS are various forms of activated oxygen, which include free radicals such as superoxide anion radicals and hydroxyl radicals, as well as non-free radical species hydrogen peroxide and single oxygen, these molecules lead to oxidative stress and contribute to various diseases, including cancer, cardiovascular disorders, diabetes, and aging-related conditions (Kohen 2002).

It is well known that during the metabolism of arachidonic acid, the enzyme myeloperoxidase (MP) produces reactive oxygen species (ROS). By inhibiting MP, the cycle of ROS formation is broken, which reduces oxidative stress and maintains redox equilibrium (Dharmaraja 2017).

The antioxidant potential of compounds is the ability to neutralize the harmful effects of free radicals in the body. However, the widespread utilization of synthetic antioxidants, including butylated hydroxy anisole (BHA), tert-butyl hydroquinone (TBHQ), and butylated hydroxytoluene (BHT) occupied with adverse health effects ranging from carcinogenic potential to disrupting endocrine functions (Xu et al 2021). As a result of this, much attention has been focused on natural antioxidants to protect from damage due to free radicals.

Medicinal Plants serve as repositories for secondary phytochemicals, which are bioactive and possess significant antioxidant properties. Due to this characteristic, numerous researchers are currently engaged in

the exploration of the advantageous health impacts associated with phytochemicals (Saxena et al 2013).

A perennial herb *Erigeron multiradiatus* (Lindl.) Benth. belongs to the Asteraceae family and used as traditional medicine for years to treat various diseases such as rheumatism, hyperpiesia, hepatitis, adenolymphitis, hemiparalysis, and enteronitis. It is mainly distributed in an altitude range of 2600–4300 m (Li et al 2023).

The lack of reports on the phytochemical and antioxidant studies on *E. multiradiatus* inspired us to investigate and explore the chemical nature and In-silico antioxidant potential to analyse the interaction of identified compounds with myeloperoxidase enzyme.

Material and methods

Plant Material Collection and Identification

The plant material (*E. multiradiatus)* was collected in September month from the Chiplakedar forest of Himalayan region (Pithoragarh District), Uttarakhand, India, at an altitude of 3000 m with geographical coordinates 29° 96′ N latitudes and 80° 43′ E longitudes. Taxonomic identification was confirmed by the Botanical Survey of India (BSI), Dehradun, and voucher specimens were deposited for further reference with herbarium code (BSI-Accession no. 116031).

Preparation of Extract

The bulk mass of the plant root was brought into the laboratory, thoroughly washed and shade dried at room temperature. The dried root of *E. multiradiatus* ground using a mixture grinder. The powdered material was soaked into methanol (w/v1:6) in a conical flask and kept in an electrical shaker at 120rpm and 25ºC for 48 hours. After 48 hours, the mixture was filtered by using Whatman's filter paper no.1. to remove solid residues and particulate matter. The filtrate was collected and evaporated using a water bath at 40 ºC. After the evaporation of the solvent, the plant extract was stored at 4 ºC for further GC MS analysis.

Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

Gas Chromatography-Mass Spectrometry (GC-MS) analysis is a powerful technique used for the identification and quantification of phytochemicals present in plant extract. Detection and quantification of the chemical profile of methanolic extract of plant root was carried out using Shimadzu GC-MS QP 2010 Plus. Initially, the column oven temperature was set at 70^0C and held for 5 min., then increased to 250^0C at 10^0C per min. and held for 10 min., and finally to 300^0C at intervals of 10^0C per min. The instrument specifications are as follows: pressure: 110.8 kPa; total flow: 38.9 ml/min; solvent cut time: 3.5 min; detector gain mode: relative; injection temperature: 280^0C; purge flow:3 ml/min; column flow: 1.71 ml/min; and sample injection volume: 2µl, injection mode: splitless; helium used as a carrier gas. Phytocompounds were identified in the sample by comparing with the mass spectra with National Institute of Standard and Technology, and Wiley library. The name and molecular weight of the compounds of the tested material was determined (Mallard, 2008).

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) Analysis

To generate the physicochemical and pharmacokinetic properties of the identified compounds, chemical structures of compounds 1–7 were altered to their equivalent canonical simplified molecular-input line-entry system (SMILE) and submitted to the SwissADME web tool. The drug-likeness of seven identified compounds was evaluated using various parameters such as molecular weight, rotatable bond, lipophilicity, hydrogen bond donor, H-B acceptor, water solubility, Lipinski's Rule of Five, Bioavailability, polar surface area (TPSA), Lead likeness, PAINS, and BRINKS, along with pharmacokinetic properties

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including Gastrointestinal absorption, blood-brain barrier permeability, Skin permeability assay.

Molecular docking

In drug designing discovery, molecular docking is time saving and easiest way to prediction the ligand-receptor interaction. The docking calculations results include different parameters which are binding affinity (G) (Kcal\mol), the dipole moment of ligand (in Debye), number of H-bonds, drieding energy, and pictures of viable docked poses. The protein myeloperoxidase (PDB ID 1MHL) was used as the target protein. With the use of the standard protocol, Auto Dock Vina software (http://vina.scripps.edu/) was used to dock the identified compounds (1–7) into active sites of the target protein. 3 D structure of the protein was obtained from the Protein Data Bank (PDB). The protein was prepared using protein preparation protocol, (Madhavi et al 2013) and saved in pdbqt format. Similarly, 3D structure of the identified compounds (ligand) are obtained from the Pubchem data bank and are also synthesized with the help of pymol and Auto Dock vina and saved in pdbqt format. The algorithm of Auto Dock vina includes configuration parameters such as nine binding modes, energy difference = 4 kcal mol^{-1}, grid box with centre coordinates x = 26.154, y = 0.238, z = 15.210. Least binding energy configurations were selected for analysing interactions between compounds (ligands) and target proteins using the Discovery studio visualizer.

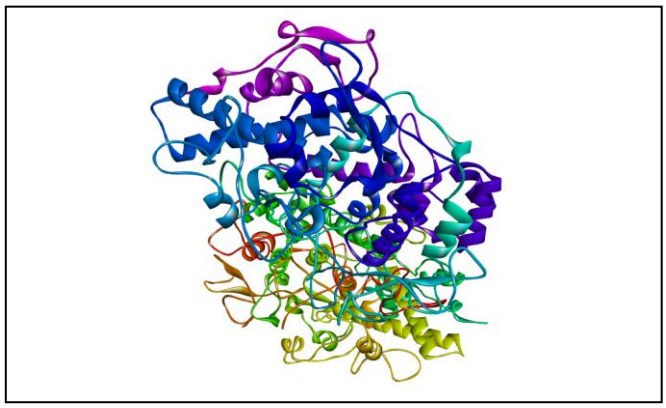

Fig 1. 3D image of protein myeloperoxidase

Results and discussion

GC-MS analysis: In the present study, the methanol extract of *E. Multiradiatus* root was analysed by gas chromatography-mass spectrometry (GC-MS) to identify the main phytochemical constituents. These compounds were identified by comparing their peak Retention Time (RT value), peak area (%), molecular weight, and mass spectral fragmentation patterns to those of the well-known compounds listed in the NIST library. Results revealed the presence of several compounds that contributed more than one percent, as given in Table (1), among these identified compounds 5-Hydroxymethylfurfural was found in the maximum percent area (56.24%) followed by 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-(20.42%). In our previous study, we found total 12 phytoconstituents using essential oil (EO) composition of the aerial parts of *E. multiradiatus* by gas chromatography−mass spectrometry with trans-2-cis-8-matricaria-ester (77.79%) as major constituents which also showed promising leishmanicidal effect against *Leishmania donovani* (Chandra Pandey et al 2019). In the present study, we obtained root extract of *E. multiradiatus* using a new purity method and accurately identified seven constituents using GC-MS analysis.

Table 1. Phytochemical constituents identified in the *E. multiradiatus* using Gas Chromatography-Mass Spectrometry (GC-MS)

Peak	R. Time	Name of Compounds	Percentage	Molecular Formula	Molecular weight
1.	6.442	2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one	1.21	$C_6H_8O_4$	144
2.	8.347	6,7-Dioxabicyclo [3.2.2]nonane	2.32	$C_7H_{12}O_2$	128
3.	9.478	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	20.42	$C_6H_8O_4$	144
4.	11.063	5-Hydroxymethylfurfural	56.24	$C_6H_6O_3$	126
5.	11.813	5-Acetoxymethyl-2-furaldehyde	1.28	$C_8H_8O_4$	168
6.	14.897	D-Allose	6.1	$C_6H_{12}O_6$	180
7.	16.349	1,6-Anhydro-.beta.-D-glucofuranose	3.23	$C_6H_{10}O_5$	162

Computational ADMET analysis: In recent years, with the development of in silico methods various molecules approved as drugs by the FDA (U.S. Food and Drug Administration). However, there are still lots of compounds that are unsuccessful in becoming drugs. Analysis of ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties provided the necessary information to make essential modifications to improve the drug potential. Therefore, it is necessary to find effective compounds with better ADMET properties.

All the seven phytochemicals were found to follow druglike properties and Lipinski's rule of five (Table 2). Lipinski used various molecular properties in formulating his "Rule of Five." The rule states that most molecules with good drug-likeness have an octanol-water partition coefficient not more than 5, molecular weight less than or equal to 500 D, number of HB donors less than or equal to 5, and the number of HB acceptors less than or equal to 10. All numbers are multiples of five so the rule is named as rule of 5 (RO5). The molecules that satisfy the RO5 criteria are eligible to become oral medications (Lipinski et al 2012).

There was no availability of PAINS and BRINK in the structures of these phytocompounds. Which indicates the absence of problematic structural motifs or certain unfavourable pharmacokinetic or toxicological attributes commonly associated with assay interference.

The Swiss ADME prediction indicated that four compounds have no rotatable bond and other identified compounds are less than 5 rotatable bonds. The lower number of rotatable bond (RB) values indicates the conformation stability of the compounds (Anza et al 2021).

The total polar surface (TPSA) impacts the bioavailability and permeability of a molecule. The TPSA value of all identified compounds is found to be less than 140 $Å^2$. while TPSA values of compound 2 (18.46) are found to be less enough than the margin value (140 $Å^2$), which specifies their maximum absorption in the intestine.

Table 3 indicates the pharmacokinetic properties of selected compounds in which log Kp value of the identified compounds was recorded within -5.95 to −9.7 cm/s. The less negative the log Kp (with Kp in cm/s), the more skin permeant the molecule (Pham et al 2022). Results revealed that compound 2 showed high skin permeability while compound 6(D-Allose) showed low skin permeability and low GI absorption, other identified compounds showed high gastrointestinal (GI), and compounds 2 and 5 have blood-brain barrier (BBB) permeability.

High gastrointestinal (GI) and blood-brain barrier (BBB) permeability indicates that effective absorption and distribution properties of drug molecules.

The ADME prediction result also demonstrate that all compounds under investigation are found to be non-inhibitors of selected cytochromes (CYP)and most of the compounds are non-substrate of permeability glycoprotein (P-gp), which indicates these compounds significant implication for their drug development potential.

Table 2. Drug likeness properties of the identified compounds

Phytocompounds	Parameter											
	Heavy atom	**RB**	**HA**	**HD**	**TPSA (Å2)**	**Log $P_{o/w}$**	**WS**	**B A**	**LRV**	**PA**	**B A**	**LL**
2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one	10	0	4	2	66.76	0.03	Very soluble	0.85	0	0	0	1
6,7-Dioxabicyclo [3.2.2]nonane	9	0	2	0	18.46	1.66	Very soluble	0.55	0	0	1	1
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	10	0	4	2	66.76	-0.22	Very soluble	0.85	0	0	0	1
5-Hydroxymethylfurfural	9	2	3	1	50.44	0.19	Very soluble	0.55	0	0	1	1
5-Acetoxymethyl-2-furaldehyde	12	4	4	0	56.51	0.84	Very soluble	0.55	0	0	1	1
D-Allose	12	1	6	5	110.38	-2.26	Highly soluble	0.55	0	0	0	1
1,6-Anhydro-.beta.-D-glucofuranose	11	0	5	3	79.15	-1.36	Highly soluble	0.55	0	0	0	1

RB- Rotatable bond, HD- hydrogen bond donor, HA-Hydrogen bond acceptor, TPSA- topological polar surface area, WS- Water solubility, BA- bioavailability, LRV - Lipinski's Rule violation, PA- PAIN, BA-BRINK, LL – Leadlikeness

Table 3. Pharmacokinetic properties of identified compounds

Phytocompounds	Parameters				
	GIA	**BBB**	**Pgp S**	**CYP1A2/ CYP2C19/ CYP2C9/ CYP2D6/ CYP3A4 inhibitors**	**SP log Kp (cm/s)**
2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one	High	No	No	No	-7.24
6,7-Dioxabicyclo [3.2.2]nonane	High	Yes	No	No	-5.95
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	High	No	No	No	-7.44
5-Hydroxymethylfurfural	High	No	No	No	-7.48
5-Acetoxymethyl-2-furaldehyde	High	Yes	No	No	-6.96
D-Allose	Low	No	Yes	No	-9.7
1,6-Anhydro-.beta.-D-glucofuranose	High	No	Yes	No	-8.82

GIA- Gastrointestinal absorption, BBB-blood-brain barrier permeability, SP- Skin permeability assay, PgpS- Phosphoglycoprotein substrate

Molecular docking

A molecular docking study was carried out to assess the binding affinity and binding interaction of identified compounds 1–7 toward the target protein myeloperoxidase (PDB ID 1MHL). The best docking score was selected among the nine poses that resulted in protein-ligand docking (Rana et al 2023;

Lakhera et al 2023). The docked compounds (1–7) displayed binding affinity in the range of −5.5 to −6.4 kcal/mol. Previous reports suggest that the lowest binding energy score showed the most stable protein-ligand binding complex and demonstrated the higher efficiency of bioactive compounds (Imana et al 2020). Results of molecular docking often focus on optimizing binding affinity. Drugs with high binding affinity are more likely to effectively inhibit or activate their target at lower concentrations, leading to greater potency. This can result in more efficient therapeutic outcomes. A more negative value of compound 4 (Table 4) indicates a lower binding energy G (−6.4 kcal/mol), reflecting a higher affinity for active site of the myeloperoxidase.

To study the interaction mechanism of the protein-ligand complex the results of the molecular docking were further analyzed and expressed in pictorial presentation. The 2D structures indicate the associated amino acid residues and the 3D structure demonstrates the hydrogen donor-acceptor surface around the ligand in the binding site shown in Table 5.

Table 4. List of phytochemicals of *E. multiradiatus* showed the best binding affinity

Ligand	Binding energy kcal/mol	No. of hydrogen bond	No. of hydrophobic bond interaction	Dipole moment	Dreiding energy
2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one	-6.2	2	2	1.236	24.23
6,7-Dioxabicyclo [3.2.2]nonane	-5.5	1	2	3.336	79.799
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	-6.3	2	0	0.476	27.93
5-Hydroxymethylfurfural	-6.4	1	4	2.372	7.39
5-Acetoxymethyl-2-furaldehyde	-6.0	0	1	2.387	8.35
D-Allose	-5.6	2	0	1.757	21.73
1,6-Anhydro-.beta.-D-glucofuranose	-5.8	1	0	2.964	39.81

5-Hydroxymethylfurfural (compound 4) also has the highest number of hydrophobic bond interactions in which the major amino acid residues involved are proline (PRO), leucine (LEU), and alanine (ALA). Myeloperoxidase is a heme-containing homodimeric glycoprotein. Glycosylation can strongly impact protein function and receptor interactions (Reiding et al.,2019). D-Allose and 1,6-Anhydro-beta-D-glucofuranose interact with mannose while 2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one, interact with fucose, which are the sugar residues of myeloperoxidase protein.

Although several research have been studied for myeloperoxidase-inhibition through hydrophobic and hydrogen bonding interactions with various phenolic compounds (Cidade et al 2020; de Almeida et al 2023).

Hassane et al. (2022) revealed that the well-known phenolic compound vanillin has low binding affinities with myeloperoxidase (-6.11kcal/mol) in comparison to the current investigation.

But there is still no information regarding Insilco antioxidant approach of compounds extracted from *E. multiradiatus* and other species of *Erigeron*. While, some previous studies on other species of *Erigeron* in antioxidant activity such as *E. sumatrensis,* (Puspa et al 2024*)* E. *Karvinskianus* (Rajalakshmi et al 2016) and *E. annuus (*Lee et al 2006*)* with different in vitro techniques validate effective antioxidant potential of *Erigeron*.

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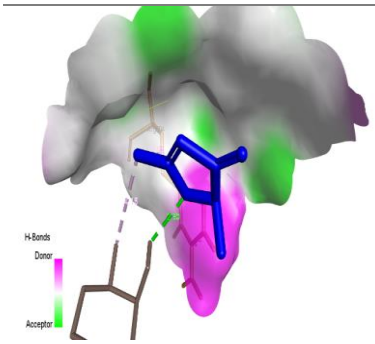
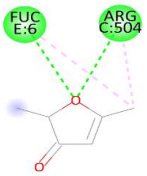
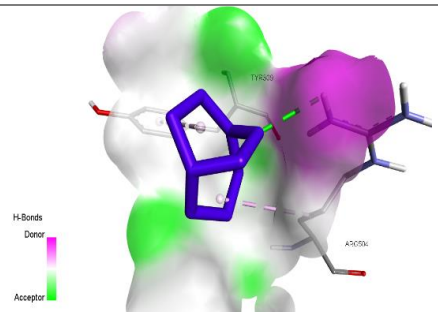
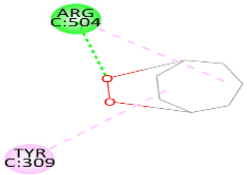
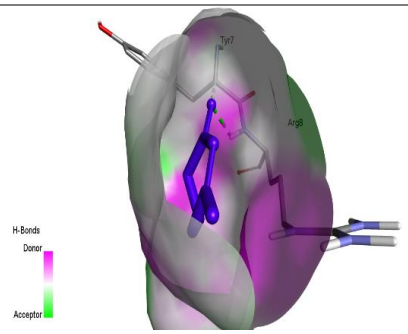
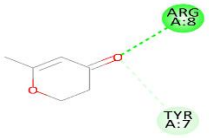
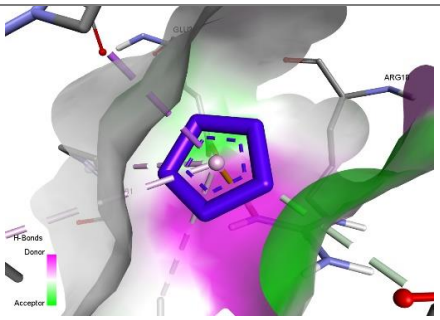
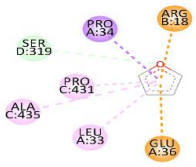
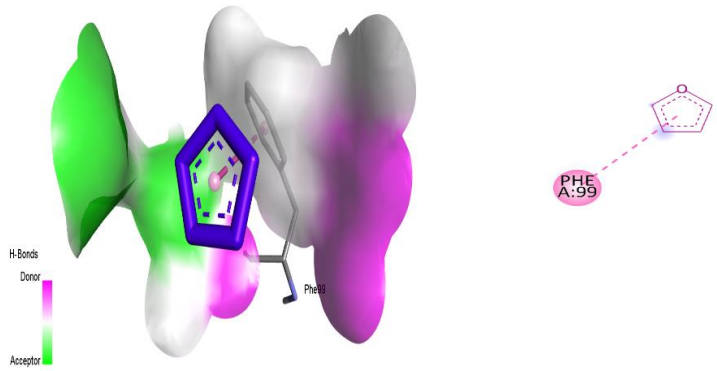
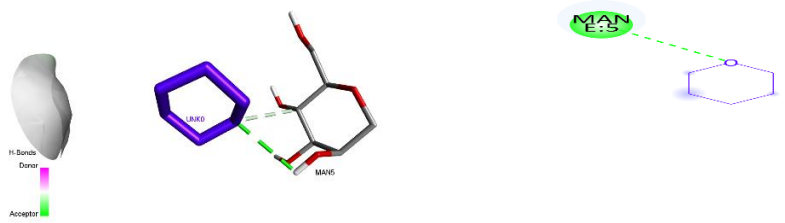
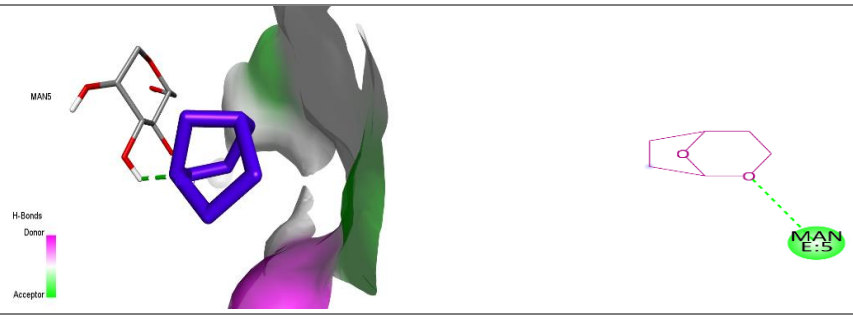
Table 5. 3D, 2D Pictorial presentation of the interaction of compounds with enzyme

Ligand	3D donor-acceptor surface around the ligand	2-D picture showing interaction of compounds with amino acids and carbohydrate
		
2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one		
6,7-Dioxabicyclo [3.2.2]nonane		
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-		
5-Hydroxymethylfurfural		

5-Acetoxymethyl-2-furaldehyde	
D-Allose	
1,6-Anhydro-.beta.-D-glucofuranose	

Conclusion

In silico approaches can also play a pivotal role in biodiversity conservation by providing sustainable alternatives to the physical bulk collection of high-altitude Himalayan plant root, particularly for species that are rare, and difficult to access.

Current study identified the seven phytoconstituents using GC-MS analysis with maximum percentage of 5-Hydroxymethylfurfural (56.24%). The overall molecular docking and post-docking analysis interpret that the selected phytochemicals showed a better binding mechanism with the target protein myeloperoxidase with maximum interaction with 5-Hydroxymethylfurfural. ADMET profiling of the all identified compounds indicates good acquiescence with druglikeness and pharmacokinetic properties suggesting their possibility as orally administered therapeutics. These findings provide significant and primary indication for further research for developing novel therapeutics drugs as the potential source of antioxidant activity of root of *E. multiradiatus.*

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