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In Silico Antioxidant Activity of Six Volatile Constituents in *Capsella bursa-pastoris*

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ABSTRACT

Capsella bursa-pastoris is a wild herb with high nutritional value that can be eaten raw or cooked in some countries. It is also used in the traditional medicine of many countries as an anti-bleeding agent and to relieve inflammation. This study aimed to identify the chemical composition of essential oil and assess the in silico antioxidant activity of six volatile constituents in *Capsella bursa-pastoris* grown in Syria. The essential oil was extracted and analyzed using gas chromatography-mass spectrometry (GC-MS). In addition, in silico pharmacokinetics and molecular docking of six volatile constituents (Phytone, Phytol, Farnesylacetone, Octa-3,5-dien-2-one, m-menthane, and beta-ionone) were performed on Xanthine oxidase (PDB ID: 1 FIQ). The results revealed the presence of thirty-eight compounds. The main compounds were hexahydrofarnesyl acetone (Phytone) at 20.2%, diacetyl-4,4',6,6'-tetramethoxy-2,2'-biphenyldiol at 8.46%, diisopropyl methylphosphonate at 6.45%, and beta-ionone at 5.24%. Farnesyl acetone and beta-ionone exhibited the highest binding affinity, ranging from -5.4 to -6.4 kcal/mol. The essential oil of *Capsella bursa-pastoris* is a potential source of antioxidants.

Keywords: *Capsella bursa-pastoris*, essential oil, antioxidant, molecular docking.

INTRODUCTION

Capsella bursa-pastoris, is one of the most important and widespread species in the genus Capsella. It belongs to the Brassicaceae family. *C. bursa-pastoris* is a small annual wild herb with a global distribution. It is distinguished by its inverted, triangular fruits that resemble a shepherd's purse. Hence its common name: Shepherd's purse[(1)].

C. bursa-pastoris grows in all parts of the world except tropical regions. The aerial parts are the medicinal component of the plant. The height of the plant is 2-40 cm. It has a simple, erect stem and a simple spindle root. The small flowers are distinguished by their white color and have four sepals, four petals, and six stamens. Its fruits are in the form of a green capsule containing many reddish-brown seeds[(2)].

C. bursa-pastoris has high nutritional value. In some countries, it is eaten fresh or cooked, commonly used as a salad ingredient[(3)]. It has been a staple in the diets of people in China and Japan for centuries[(4)] The plant is used internally for mild menstrual disorders such as menopause, and externally for nasal bleeds and bleeding surface skin wounds[(2)].

Studies have shown the presence of flavonoids and alkaloids, as well as minerals, vitamins A, C, and B (1, 2, 3, 6), and unsaturated fatty acids. It also contains many amino acids and organic acids (including formic, quinic, and caffeic), as well as glucosinolate, the production of which is characteristic of *C. bursa-pastoris*[(4)].

Studies have also shown that *C. bursa-pastoris* has anti-inflammatory[(5,6)] and antibacterial[(7)] efficacy, as well as antioxidant[(8)] and tumor growth inhibitory[(9)] effects.

This study aimed to identify the chemical composition

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of essential oil and assess the in silico antioxidant potential of major volatile constituents in *C. bursa-pastoris*.

MATERIALS AND METHODS:

Plant Material

The aerial parts of *C. bursa-pastoris* were collected in April 2020 from the park of the Faculty of Science at Damascus. The plant was identified and classified. The samples were dried immediately after collection by air drying at normal room temperature, away from sunlight.

Extraction

The essential oil was extracted from 90 grams of plant material using the steam distillation method.

Analysis of Essential Oil Ingredients

The analysis of the essential oil components was conducted according previous study[3], using Gas Chromatography-Mass Spectrometry (GC/MS) (Agilent Tecnologies 5957C). The following thermal program was applied: 60°C for 1 minute, increased to 70°C at 4°C/min, then to 130°C at 5°C/min, followed by 160°C at 4°C/min, then to 220°C at 5°C/min, and finally to 280°C at 15°C/min, with a total operation time of 44 minutes. Helium gas was used as the mobile phase at a flow rate of 1 mL/min and a pressure of 8.2317 Pa. The column used was HP-5MS 5% Phenyl Methyl Silox, with dimensions of 30 m x 250 µm x 0.25 µm, operated at 325 °C. Spectra were determined based on the NIST library (National Institute of Standards and Technology).

Drug Likeness and ADMET Properties

Drug-likeness rules are a set of guidelines for the fundamental properties of compounds. They are used for the rapid calculation of drug-like properties of a chemical compound. These rules are not supreme, nor do they aim to establish strict cutoff values to determine which property values are considered drug-like and which are not. However, they can be very viable and productive[10]. In this study, we utilized Swiss ADME to calculate drug likeness and pharmacokinetic properties[11], while toxicity risks were predicted using Osiris software[12].

Swiss ADME is an open-source virtual screening tool. Its calculation is based on various drug-likeness criteria such as Lipinski's rule[13], Ghose filter[14], Veber rule[15], Egan[16], and Muegge rule[17].

Swiss ADME was also used for predicting biological activity. It is a simple, accurate, and robust tool that enables the understanding of ADME properties of a compound. The parameters it provides include gastrointestinal absorption (GI) and permeation through the blood-brain barrier (BBB)[18]. The efflux pump P-glycoprotein, involved in pharmacokinetics and drug interactions, is an important parameter in discovery screening, particularly for drugs that need to penetrate the brain[19]. It is embedded in the Swiss ADME suite and built upon by the Support Vector Machine (SVM) model. The Swiss ADME package calculates the ability of a specific molecule to inhibit key cytochrome enzymes involved in drug metabolism[20].

Structures of the tested compounds were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and SMILES notations were copied and used as query files in the Swiss ADME tool.

The determination of the toxicity of chemical compounds is crucial for understanding their harmful effects on humans, animals, plants, and the environment. In vivo animal testing is limited by time, ethical considerations, and financial obstacles[21]. Computational methods are considered useful for assessing the toxicity of chemicals. In silico toxicology is proposed to assist in ongoing toxicity testing to predict toxicity, prioritize chemicals, guide toxicity testing, and minimize failures in the later stages of the drug design process[22]. The web tool Osiris Property Explorer was used to explore toxicity risks (https://www.organic-chemistry.org/prog/peo/). It is an easy and free tool to infer physicochemical and toxicological molecular properties. It provides the ability to estimate the risk of adverse effects, such as mutagenic, tumorigenic, irritant, and reproductive effects, as well as relevant drug properties, and an overall drug likeness

score. Mutagenicity structural alert refers to a set of molecular functions or substructures linked to the mutagenic activity of chemical compounds[23]. Several functional groups in chemical structures are suspected to be associated with tumorigenic effects[24]. The Osiris software enables the prediction of tumorigenic potentials, as well as irritant and reproductive effects, and provides a quantitative estimate of drug-likeness (QED).

Molecular Docking

Molecular docking is a technique that predicts the optimal binding mode of a ligand to a macromolecule[25]. The utilization of molecular docking in the process of natural products-based drug discovery provides insights into elucidating traditional uses and potentially identifying new applications for existing medicinal plants[26].

A molecular docking study was conducted using AutoDock Vina. It is one of the most popular protein-ligand docking software, besides being freely available and an open-source tool[27]. It provides a significant improvement in accuracy and a two-order magnitude of speed compared to AutoDock4. Molecular interactions were investigated for the compounds Phytone, Phytol, Farnesylacetone, Octa-3,5-dien-2-one, m-Menthane, Beta-ionone, and ascorbic acid as a reference compound. The process of molecular docking of our tested compounds went through the following steps:

Protein Preparation

The three-dimensional (3D) X-ray crystallographic structure of Xanthine oxidase was downloaded from the PDB website (https://www.rcsb.org/structure/1FIQ) with the ID: 1FIQ solved at a resolution of 2.5 Å.

The Protein Data Bank (PDB) file. The crystal structure of the enzyme is complexed with small molecules; therefore, the active site was emptied of all heteromolecules as a first step. Water molecules were removed, and all hydrogen atoms were added. Eliminating water molecules is essential because they can form unnecessary bonds with the ligand[28]. Kollman charges were added and spread on the protein, and there were no missing atoms to be added. The protein file was saved as a PDB file. Autodock Vina deals with PDBQT files. Consequently, the protein file was converted to PDBQT file format and saved for the docking process.

Ligand Preparation

The files of the studied compounds were downloaded from the https://pubchem.ncbi.nlm.nih.gov/ database as SDF files. The files were converted to PDB format using the OpenBabel software. To convert to PDBQT files, the torsion tree was selected, and rotation flexibility was maintained by default. Gasteiger charges were also added, and nonpolar hydrogens were merged. The structures were finally prepared for the docking process.

Grid Box Defining

The grid box position defines the space within the protein where the docking will take place. The grid box has dimensions of 40 x 40 x 40 units with a grid spacing of 0.375 units[29].

Docking Analysis

Once the docking was completed, the ligand poses with equal or lower affinity than the reference inhibitor, and root mean square deviation (RMSD) values lower than 2.5 Å were considered as potential inhibitors. To assist in the calculations and analysis of the results, the Protein-Ligand Interaction Profiler (PLIP) was used[30].

RESULTS AND DISCUSSION

The study focused on investigating the chemical composition of essential oil and the in silico antioxidant activity of major volatile constituents in *Capsella bursa-pastoris* .

Gas chromatography-mass spectrometry (GC-MS) analysis in Fig. 1 of the essential oil revealed the presence of thirty-eight compounds as shown in Table 1. The essential oil of C. bursa-pastoris contains various components: hydrogen carbonates constitute 19.25%, ketone compounds 23.9%, aldehydes 2.66%, terpenoid and terpenoid compounds 4.65%, and esters 28.22%. Among the most important ketone compounds is

Hexahydrofarnesyl acetone (Phytone), which constitutes the highest percentage in the oil at 20.2%. It is a ketone compound that may potentially demonstrate antibacterial activity against both gram-positive bacteria against both gram-positive and gram-negative bacteria[31]. Additionally, 3,5-Octadien-2-one is utilized as a flavoring agent and food additive[32]. Among the terpene compounds, Beta-ionone (5.24%) is a monoterpene with a structure similar to the cyclic structure of beta-carotene. Some studies have shown that it has anti-tumor activity[33] and is used in the manufacture of vitamins A, E, and K1[34].

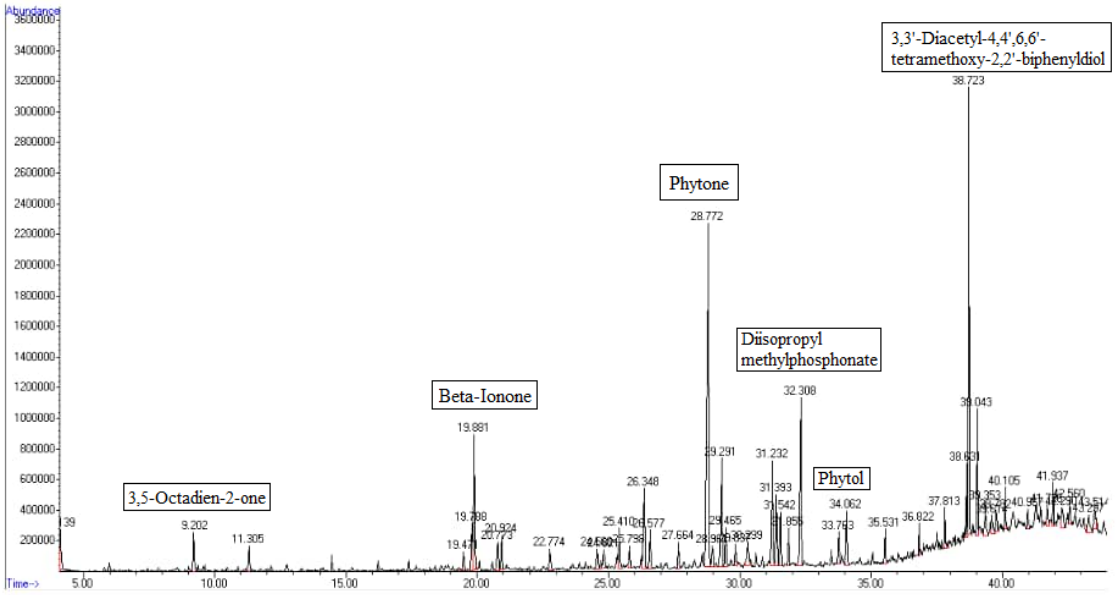


Fig. 1. GC-MS chromatogram of the essential oil of *Capsella bursa-pastoris*

Phytol (1.92%), an oxygenated diterpene, exhibits antibacterial activity and is utilized in the production of certain cosmetics, soaps, and detergents[31]. Farnesyl acetone (1.17%), a ketone terpenoid, and Menthane (1.55%), a monoterpenoid, are both utilized as flavoring agents and food additives[35]. When comparing the results of the analysis of essential oils in this study with other studies, it appears that there are some differences in the components of the oils, in addition to the presence of common components. **Table 2** displays the names of some common components along with a comparison of their percentage in the oil across different studies.

Drug Likeness and ADMET Properties

Drug Likeness and Bioavailability

The results obtained from the Swiss ADME suite showed that all the tested compounds followed the Lipinski rule, except for Beta ionone. However, only Beta ionone met the Ghose filter criteria. The concern was related to the logarithm of the partition coefficient (MLOGP) calculated using a topological method. The Ghose filter is a knowledge-based tool that aims to offer a qualitative and quantitative representation of drug-like chemical space for users. It can be utilized in drug discovery by assisting in the design of medicinal chemistry

or combinatorial libraries. The rules defined by this filter were as follows: 160 < molecular weight (MW) < 480, −0.4 < logP < 5.6, 20 < number of atoms < 70, and 40 < molar refractivity (MR) < 130[41].

Table 1. components of the essential oil compounds of *Capsella bursa-pastoris*

Peak no.	Compound	Peak area %	Retention time
1	3,5-Octadien-2-one	1.182	9.20
2	Methylcyclodecane	0.86	19.47
3	[(S)-2-nitro-2-cyclohexenyl]-acetate	1.75	19.79
4	Beta-Ionone	5.25	19.88
5	Cyclohexanecarboxylic acid, 4-cyanophenyl ester	1.27	20.77
6	2-Hydroxy-5-methoxybenzyl vinyl ether	1.21	20.92
7	Hexadecane	0.92	22.78
8	1-Heptadecene	0.92	24.82
9	Menthane	1.55	25.41
10	trans-Bicyclo[4.3.1]decan-10-one	3.68	26.35
11	Cinnamaldehyde, .alpha.-hexyl-	1.46	26.58
12	Octadecane	0.95	27.66
13	Phytone	20.21	28.77
14	Diisobutyl phthalate$$ 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	4.17	29.29
15	Cyclotetradecane	1.40	29.46
16	Nonadecane	0.77	29.84
17	Farnesyl acetone c	1.17	30.30
18	Dibutyl phthalate	4.16	31.23
19	Cyclohexane, 1-(cyclohexylmethyl)-2-methyl-, cis-	2.54	31.39
20	Sulfurous acid, cyclohexylmethyl hexyl ester	1.89	31.54
21	Eicosane	1.32	31.85
22	Diisopropyl methylphosphonate	6.45	32.31
23	Heneicosane	1.05	33.76
24	Phytol	1.93	34.06
25	Docosane	1.02	35.53
26	Tetracosane	0.84	37.81
27	Pentacosane	1.45	38.63
28	-3,3'-Diacetyl-4,4',6,6'-tetramethoxy-2,2'-biphenyldiol	8.46	38.72
29	1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester	3.08	39.04
30	9-Octylheptadecane	0.87	39.61
31	Heptacosane	0.95	39.78
32	Octacosane	0.77	40.97
33	Cholestane	0.91	41.72
34	Nonacosane	1.34	41.93
35	Pentanamide, N-(2-methyl-3-trifluoromethyl)phenyl-	1.25	42.29
36	i-Propyl 5,9,17-hexacosatrienoate	0.82	42.56
37	Stigmastane	1.11	43.30
38	5-[5'-Ethynyl(thien-2'-yl)]thiophene-2-carbaldehyde	1.21	43.51

Table 2. Comparison of essential oil components between the current study and other studies

Components	Area Pct						
	current study	Gao *et al*[36]	Choi *et al.* [37]	LIU Yu *et al.*[38]	Miyazawa *et al.*[39]	Lee *et al.*[40]	Gümüşok *et al.*[3]
3,5-Octadien-2-one	1.18		0.78			0.54	
Beta-Ionone	5.24		0.18			1.24	0.2
Hexadecane $$ n-Cetane	0.92				1.5		
1-Heptadecene $$ Hexahydroaplotaxene	0.92				0.3		
Octadecane	0.95		0.1		0.3		
Hexahydrofarnesyl acetone $$ Phytone	20.2	9.6	1.21	10.15		6.11	
Nonadecane	0.76		0.2				19.6
Eicosane	1.31				0.3	1.14	
Phytol	1.92	18	21.12			7.57	19.3
Tetracosane	0.84					4.84	
Pentacosane	1.44		0.65				13.5
Heptacosane	0.94		0.96				9.9
Octacosane	0.76			4.73			

Neither Phytone nor Phytol adhere to Veber and Egan filters. The Veber filter states only two rules regarding polar surface area (PSA) and the number of rotatable bonds (Rotors), which should not exceed 140 Å2 and 10, respectively[42]. The Egan filter utilizes multivariate statistics to assess membrane permeability for poorly absorbed compounds. LOGP and TPSA are the chosen descriptors in the Egan filter[43]. Both Phytone and Phytol exhibited a calculated WLOGP (calculated by atomistic method) of more than 5.8. The compounds were non-drug-like according to the Muegge rule. The nominated drugs must acquire two to seven pharmacophore points to pass the Muegge filter[44]. Violations occurred when the molecular weight (MW) was less than 200 and when XLOGP values were calculated using both atomistic and knowledge-based methods. All the investigated compounds exhibited moderate bioavailability, with values exceeding 50%. Results of drug likeness are presented in **Table 3**.

Pharmacokinetics and ADME Properties

The prediction of gastrointestinal absorption (GI) using in silico models has emerged as a widely used and promising complement to traditional in vitro assays[45]. With the exception of Phytol and m-Menthane, all the tested compounds demonstrated good gastrointestinal absorption. The blood-brain barrier permeability filters determine which compounds are included or excluded in both central nervous system (CNS) and non-CNS drug development processes[18]. Phytone, Phytol, and Farnesylacetone showed no ability to penetrate the blood-brain barrier (BBB), while Octa-3,5-dien-2-one, m-Menthane, and Beta-ionone are expected to cross the BBB. P-glycoprotein is a crucial factor in discovery screening, especially for drugs that need to penetrate the blood-brain barrier[46]. Only Phytone and Phytol are considered substrates for P-gp. Phytone, Phytol, Farnesylacetone, and m-Menthane are expected to inhibit CYP2C9. Farnesylacetone was found in a previous in silico study to exhibit convenient pharmacokinetics and bioavailability due to the polar carbonyl moiety[47]. Among the bioactive compounds studied, Octa-3,5-dien-2-one and Beta-ionone did not inhibit any CYP isoform, while Phytone, Phytol, Farnesylacetone, and m-Menthane were moderately metabolized as they only inhibited specific liver isozymes.

Previous computational analysis of the pharmacokinetic profile of phytol revealed that it does not permeate the blood-brain barrier (BBB) or the skin[48]. **Table 4** presents the pharmacokinetic properties of the bioactive components of Phytone, Phytol, Farnesylacetone, Octa-3,5-dien-2-one, m-menthane, and Beta-ionone.

Table 3: Drug Likeliness of the Selected Phytoconstituents from *Capsella bursa-pastoris* ….

	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Phytone	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
Phytol	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Heteroatoms<2	0.55
Farnesylacetone	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	Yes	Yes	No	0.55
Octa-3,5-dien-2-one	Yes; 0 violation	No; 2 violations: MW<160, MR<40	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
m-Menthane	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Beta ionone	Yes	Yes	Yes	Yes	No: 2 violations: MW<200, Heteroatoms<2	0.55
Ascorbic acid	Yes; 0 violation	No; 2 violations: WLOGP<-0.4, MR<40	Yes	Yes	No; 1 violation: MW<200	0.56

Table 4. Pharmacokinetic properties of the bioactive components of Phytone, Phytol, Farnesylacetone, Octa-3,5-dien-2-one, m-menthane, and Beta ionone

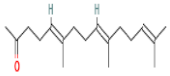
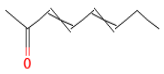
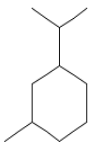
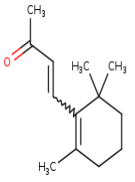
	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 Inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Phytone	High	No	Yes	No	No	Yes	No	No	-3.00
Phytol	Low	No	Yes	No	No	Yes	No	No	-2.29
Farnesylacetone	High	No	No	Yes	No	Yes	No	No	-3.95
Octa-3,5-dien-2-one	High	Yes	No	No	No	No	No	No	-5.74
m-Menthane	Low	Yes	No	No	No	Yes	No	No	-3.93
Beta ionone	High	Yes	No	No	No	No	No	No	-5.41
Ascorbic acid	High	No	No	No	No	No	No	No	-8.54

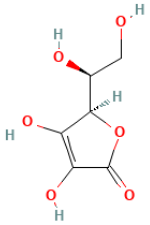
Toxicity risks

The key substructures responsible for certain toxicity are known as structural alerts (SAs). Medicinal chemists can rely on them during structural optimization to reduce the risk, as they are directly linked to toxicity. Certain substructures are associated with mutagenicity, while others are linked to carcinogenicity[49]. Octa-3,5-dien-2-one has mutagenic potential characteristics in addition to tumorigenic ones. Risk assessment of eye and skin irritation is crucial in the cosmetics and pharmaceutical

industries. Except for Phytol and m-menthane, the other tested constituents have a moderate risk of potential irritant properties. **Table 4** Essential ingredients chemical structures with their physicochemical properties. The toxicity risk results are represented in **Table 5**.

Table 5. The toxicity risks of Phytone, Phytol, Farnesylacetone, Octa-3,5-dien-2-one, m-menthane, Beta-ionone.

	Mutagenic	Tumorigenic	Irritant	Reproductive effects	Structure	Drug likeness	MW
Phytone CC(C)CCCC(C)CCCC(C)CCCC(=O)C	No	No	Yes	No		-7.06	268.48
Phytol CC(C)CCCC(C)CCCC(C)CCCC(=CCO)C	No	No	No	No		-3.77	296.53
Farnesylacetone CC(=CCCC(=CCCC(=CCCC(=O)C)C)C)C	No	No	Yes	No		-4.59	262.43
Octa-3,5-dien-2-one CCC=CC=CC(=O)C	Medium Risk	Yes	Yes	No		-5.92	124.18
m-menthane CC1CCCC(C1)C(C)C	No	No	No	No		-6.17	140.27
Beta ionone CC1=C(C(CCC1)(C)C)C=CC(=O)C	No	High Risk	Yes	No		-6.41	192.30

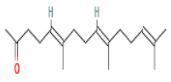
	Mutagenic	Tumorigenic	Irritant	Reproductive effects	Structure	Drug likeness	MW
Ascorbic acid C(C(C1C(=C(C(=O)O1)O)O)O)O							176.12

Molecular Docking

Molecular docking plays a vital role in drug discovery, where natural components from herbal origins are the main source of drugs[50].

The molecular docking of Phytone, Phytol, Farnesylacetone, Octa-3,5-dien-2-one, m-menthane, and Beta-ionone was performed on Xanthine oxidase (PDB ID: 1FIQ). We analyzed the active phytochemical compounds using binding free energy scores and molecular interaction profiles. The results of molecular docking and amino acid interactions are represented in **Table 7**. Farnesyl acetone and Beta-ionone displayed the best binding affinity, ranging from -5.4 to -6.4 kcal/mol. Ascorbic acid was utilized as a reference antioxidant, and the binding affinity of the bioactive components was compared to it. Phytone, farnesyl acetone, and beta-ionone showed higher affinity compared to ascorbic acid. Python, in turn, formed hydrogen bonds with some residues in the active site of the enzyme. Although lower than the affinity of ascorbic acid, phytol, octa-3,5-dien-2-one, and m-menthane showed binding affinities very close to that of ascorbic acid.

Table 6. The toxicitTable 6. Essential ingredients chemical structures with their physicochemical properties

Name	Structure	MW	BP	Density	Refraxtive index
Phytone		268.48	-	-	-
Phytol		296.53	202.00 to 204.00 °C	-	-
Farnesylacetone		262.43	-	0.885-0.895	1.478-1.483

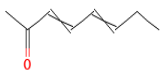
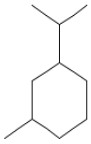
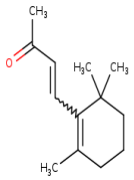
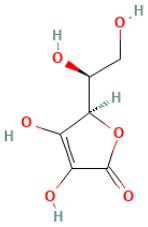
Name	Structure	MW	BP	Density	Refraxtive index
Octa-3,5-dien-2-one		124.18	-	0.880-0.890	1.508-1.516
m-menthane		140.27	-	-	-
Beta ionone		192.30	271 °C	-	-
Ascorbic acid		176.12	-	0.9461	1.517-1.522

Table 7. Molecular Docking results: Binding affinity and amino acid interactions

Ligand	Binding Affinity, ΔG (Kcal/mol)	Hydrogen-Bond Interactions	Hydrophobic Interactions	Salt Bridges
Phytone	-6.3	VAL259, ASN261	LEU257, 287, 404, GLU263, ILE264, 353	
Phytol	-5.6	ARG32, ASP594	LEU27,41, PHE604, ALA678, MET826	
Farnesylacetone	-6.4		LEU257, 398, ILE264, 353, ALA302, GLU263	
Octa-3,5-dien-2-one	-5.4		LEU257, 245, 287, ILE284, ALA301, 302, VAL259	
m-menthane	-5.6		ILE353, 398, ILE353	
Beta ionone	-6.4		LEU257, 398, ILE353	
Ascorbic acid	-5.9	LEU605, GLU676, 679, ALA678, MET826		ARG32

Previous studies proved interactions to be through hydrogen bonding and hydrophobic forces[51]. Phenylalanine, glutamate and arginine are key residues at the active site of the enzyme[52]. Fig. 2 represents the 3D binding mode of the phytoconstituents with the active site of 1 FIQ. Many Natural products showed antioxidant activity[53-55].

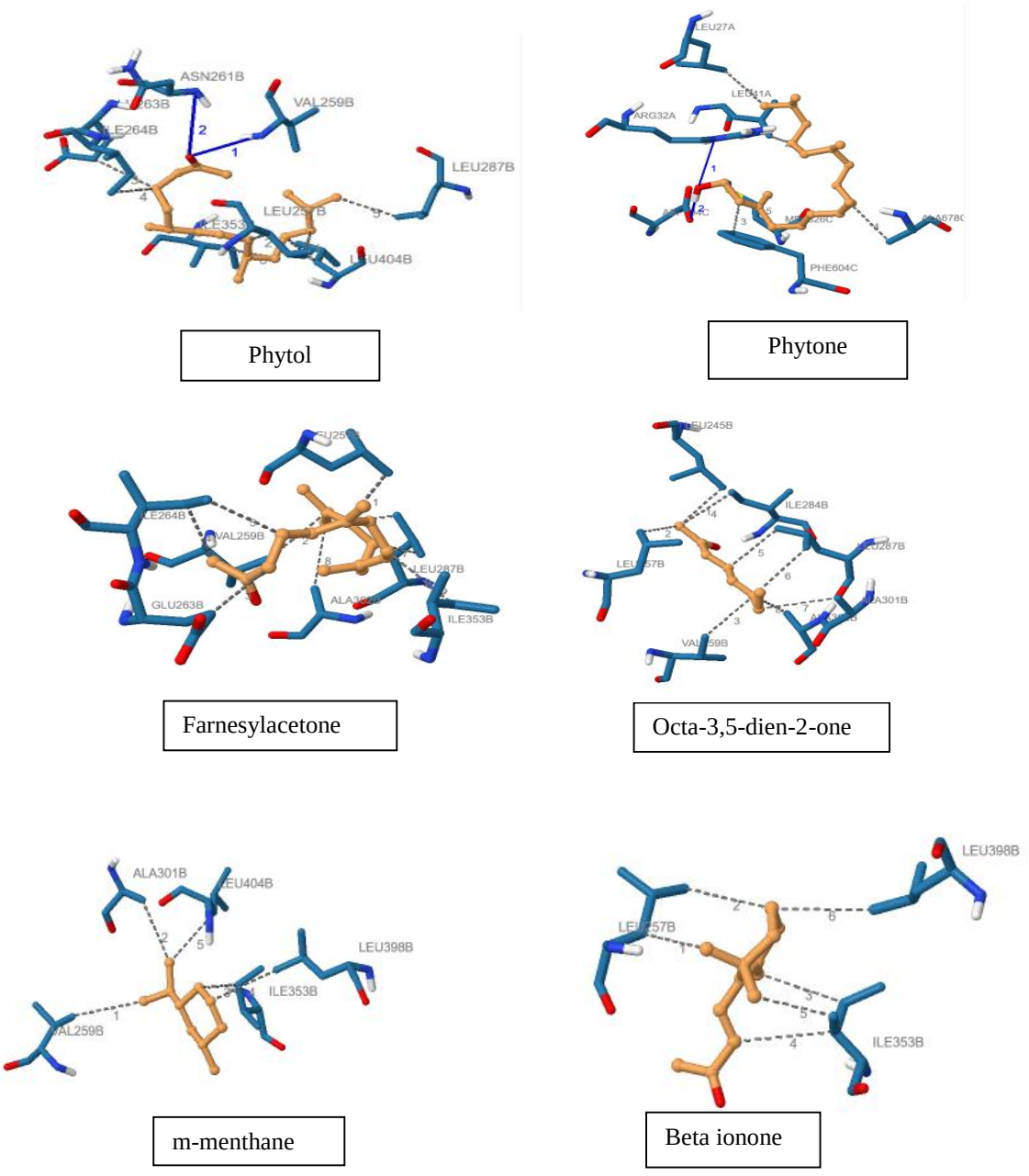


Fig 2. Binding mode of the phytochemical components with the active site of 1 FIQ

CONCLUSIONS

The in silico study demonstrated the antioxidant activity of farnesyl acetone and beta-ionone, which exhibited binding affinity to Xanthine oxidase. This suggests that they possessed important biological activities that require evaluation in the future.

REFERENCES

1. Grieve M. *A Modern Herbal, Volume 1, Shepherd's Purse, Capsella bursa-pastoris.* Electronic version by Ed Greenwood, Arcata, California, USA; 1995. Available at: http://botanical.com/botanical/mgmh/s/shephe47.html.
2. Gruenwald J., Brendler T., Jaenicke C. *Herbal Monograph in PDR for Herbal Medicines.* 2nd ed. Medical Economics Company; 2000. p. 690-691.
3. Gümüşok S., Kirci D., Demirci B., Kiliç C.S. Essential Oil Composition of *Capsella bursa-pastoris* (L.) Medik. Aerial Parts. *Turk. J. Pharm. Sci.* 2023; 20(5):341-344.
4. Al-Snafi A.E. The Chemical Constituents and Pharmacological Effects of *Capsella bursa-pastoris* - A Review. *Int. J. Pharmacol. Toxicol.* 2015; 5(2):76-81.
5. Kuroda K., Takagi K. Physiologically Active Substance in *Capsella bursa-pastoris*. *Nature.* 1968; 220:707-708.
6. Cha J.M., Kim D.H., Lee T.H., Subedi L., Kim S.Y., Lee K.R. Phytochemical Constituents of *Capsella bursa-pastoris* and Their Anti-Inflammatory Activity. *Nat. Prod. Sci.* 2018; 24(2):132-138.
7. Park C.J., Park C.B., Hong S.S., Lee H.S., Lee S.Y., Kim S.C. Characterization and cDNA Cloning of Two Glycine- and Histidine-Rich Antimicrobial Peptides from the Roots of Shepherd's Purse, *Capsella bursa-pastoris*. *Plant Mol. Biol.* 2000; 44(2):187-197.
8. Grosso C., Vinholes J., Silva L.R., Pinho P.G.D., Gonçalves R.F., Valentão P., Andrade P.B. Chemical Composition and Biological Screening of *Capsella bursa-pastoris*. *Rev. Bras. Farmacogn.* 2011; 21(4):635-643.
9. Riaz I., Bibi Y., Ahmad N., Nisa S., Qayyum A. Evaluation of Nutritional, Phytochemical, Antioxidant, and Cytotoxic Potential of *Capsella bursa-pastoris*, a Wild Vegetable from Potohar Region of Pakistan. *Kuwait J. Sci.* 2021; 48(3):1-11.
10. Kuroda K, Akao M, Kanisawa M, Miyaki K. Inhibitory effect of Capsella bursa-pastoris extract on growth of Ehrlich solid tumor in mice. *Cancer Research*. 36(6), 1900-1903, (1976).
11. Protti Í.F., Rodrigues D.R., Fonseca S.K., Alves R.J., Oliveira R.B. de, Maltarollo V.G. Do Drug-Likeness Rules Apply to Oral Prodrugs? *ChemMedChem.* 2021; 16(9):1446–1456.
12. Daina A., Michielin O., Zoete V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness, and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* 2017; 7:1-13.
13. Ayati A., Falahati M., Irannejad H., Emami S. Synthesis, *In Vitro* Antifungal Evaluation and *In Silico* Study of 3-Azolyl-4-Chromanone Phenylhydrazones. *DARU J. Pharm. Sci.* 2012; 46(20).
14. Lipinski C.A., Lombardo F., Dominy B.W., Feeney P.J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* 1997; 23(1-3):3-25.
15. Ghose A.K., Viswanadhan V.N., J.J.W. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery: 1. A Qualitative and Quantitative Characterization of Known Drug Databases. *J. Comb. Chem.* 1999; 1(1):55-68.
16. Veber D.F., Johnson S.R., Cheng H.Y., Smith B.R., Ward K.D.K. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* 2002; 45(12):2615.
17. Kralj S., Jukić M. Molecular Filters in Medicinal Chemistry. *Encyclopedia.* 2023; 3(3):501-511.
18. Muegge I., Heald S.L., Brittelli D. Simple Selection Criteria for Drug-like Chemical Matter. *J. Med. Chem.* 2001; 44(12):1841-1846.
19. Sahin S. A Single-Molecule with Multiple Investigations: Synthesis, Characterization, Computational Methods,

Inhibitory Activity Against Alzheimer's Disease, Toxicity, and ADME Studies. *Comput. Biol. Med.* 2022; 146:105514.

20. Li N., Kulkarni P., Badrinarayanan A., Kefelegn A., Manoukian R., Li X., Prasad B., Karasu M., McCarty W.J., Knutson C.G. P-glycoprotein Substrate Assessment in Drug Discovery: Application of Modeling to Bridge Differential Protein Expression Across *In Vitro* Tools. *J. Pharm. Sci.* 2021; 110(1).
21. Beck T.C., Beck K.R., Morningstar J., Benjamin M.M., Norris R.A. Descriptors of Cytochrome Inhibitors and Useful Machine Learning-Based Methods for the Design of Safer Drugs. *Pharmaceuticals.* 2021; 15(5):472.
22. Van Norman G.A. Limitations of Animal Studies for Predicting Toxicity in Clinical Trials. *JACC Basic Transl. Sci.* 2020; 5(4):387-397.
23. Rim K-T. *In Silico* Prediction of Toxicity and Its Applications for Chemicals at Work. *Toxicol. Environ. Health Sci.* 2020; 12:192-202.
24. Ridings J.E., Barratt M.D., Cary R., Earnshaw C.G., Eggington C.E., Ellis M.K., et al. Computer Prediction of Possible Toxic Action from Chemical Structure: An Update on the DEREK System. *Toxicology.* 1996; 106(1-3):267-279.
25. Enoch S.J., Cronin M.T.D. A Review of the Electrophilic Reaction Chemistry Involved in Covalent DNA Binding. *Crit. Rev. Toxicol.* 2010; 40(8):728-748.
26. Taghizadeh M.S., Taghizadeh M.S., Moghadam A., Afsharifar A. Experimental, Molecular Docking and Molecular Dynamic Studies of Natural Products Targeting Overexpressed Receptors in Breast Cancer. *PLoS One.* 2022; 17(5): e0267961.
27. Asiamah I., Obiri S.A., Tamekloe W., Armah F.A., Borquaye L.S. Applications of Molecular Docking in Natural Products-Based Drug Discovery. *Sci. African.* 2023; 20: e01593.
28. Vieira T.F. Comparing AutoDock and Vina in Ligand/Decoy Discrimination for Virtual Screening. *Appl. Sci.* 2019; 9(21):4535.
29. Trott O., Olson A.J. AutoDock Vina: Improving the Speed and Accuracy. *J. Comb. Chem.* 2010; 31(2):455–461.
30. Gurivelli P., K.S. Pharmacognostic, Phytochemical Evaluation, and Antioxidant Activity of the Leaves of *Grewia Billamellata* Gangeb (Tiliaceae). *Bull. Pharm. Sci. Assiut Univ.* 2023; 46(2):817-833.
31. A.M.F., L.K., B.S.N., K.F., S.S., H.V.J., et al. Expanding the Scope of the Protein–Ligand Interaction Profiler to DNA and RNA. *Nucleic Acids Res.* 2021; 49:530–554.
32. Nopsiri W., Chansakaow S., Putiyanan S., Natakankitkul S., Nantachit K., Khantawa B., Santiarworn D. Chemical Constituents and Antibacterial Activity of Volatile Oils of *Combretum latifolium* Bl. and *C. quadrangulare* Kurz Leaves. *CMUJ Nat. Sci.* 2015; 14:245-256.
33. National Center for Biotechnology Information. PubChem Compound Summary for CID 10408, 6,10,14-Trimethylpentadecan-2-one. *PubChem.* https://pubchem.ncbi.nlm.nih.gov/compound/6_10_14-Trimethylpentadecan-2-one. Accessed Nov. 2, 2020.
34. Heidor R., Vargas-Mendez E., Moreno F.S. Epigenetic Aspects of Hepatocellular Carcinoma Chemoprevention. In *Epigenetics of Cancer Prevention.* Academic Press, 2019: 231-249.
35. National Center for Biotechnology Information. PubChem Compound Summary for CID 638014, beta-Ionone. *PubChem.* https://pubchem.ncbi.nlm.nih.gov/compound/beta-Ionone. Accessed Nov. 2, 2020.
36. National Center for Biotechnology Information. PubChem Compound Summary for CID 1711945, Farnesylacetone. *PubChem.* https://pubchem.ncbi.nlm.nih.gov/compound/Farnesylacetone. Accessed Nov. 2, 2020.
37. Gao Y.X., Zhou X.J. Chemical Constituents of Essential Oil from Leaves of *Capsella bursa-pastoris. Resour. Dev. Market.* 2009; 25:1070-1071.
38. Choi H.S., Kang E.J., Kim K.H. Analyses of Essential Oil and Headspace Compositions of *Capsella bursa-pastoris* Medicus by SDE and SPME Methods. *Korean J. Food Preserv.* 2006; 13(1):108-114.
39. Liu Y., Li Y.H., Ning W., Zhao X., Wu J., Li X.L. GC-MS Analysis of Essential Oil from *Capsella bursa-pastoris. Lishizhen Med. Mater. Med. Res.* 2009; 5:1050-1051.
40. Miyazawa M., Uetake A., Kamoka H. The Constituents of the Essential Oils from *Capsella bursa-pastoris* Medik. *Yakugaku Zasshi.* 1979; 99(10):1041-1043.

41. Lee M.S., Choi H.S. Volatile Flavor Components of *Capsella bursa-pastoris* as Influenced by Drying Methods. *Korean J. Food Sci. Technol.* 1996; 28(5):814-821.
42. Kralj S., Jukič M., Bren U. Molecular Filters in Medicinal Chemistry. *Encyclopedia.* 2023; 3(2):501–511.
43. Veber D.F., Johnson S., Cheng H-Y., Smith B., Ward K., Kopple K. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* 2002; 45:2615–2623.
44. Egan W., Merz K., Baldwin J. Prediction of Drug Absorption Using Multivariate Statistics. *J. Med. Chem.* 2000; 43:3967–3877.
45. Halder S.K., Elma F. In Silico Identification of Novel Chemical Compounds with Anti-TB Potential for the Inhibition of InhA and EthR from *Mycobacterium tuberculosis. bioRxiv.* 2020; 12(4):411967.
46. Sjögren E., Thörn H., Tannergren C. In Silico Modeling of Gastrointestinal Drug Absorption: Predictive Performance of Three Physiologically Based Absorption Models. *Mol. Pharm.* 2016; 13(6):1763–1778.
47. Mando H., Allous I. Hierarchical Virtual Screening of SARS-CoV-2 Main Protease Potential Inhibitors: Similarity Search, Pharmacophore Modeling, and Molecular Docking Study. *Anti-Infective Agents.* 2024.
48. Mostafa E.M., El-Ghorab A.H., Ghoneim M.M., Ebrahim H.A., Abulfaraj M., Abdelgawad M.A., et al. Cytotoxic and Antioxidant Potential of *Launaea mucronata* Forssk Essential Oil Growing in Northern Saudi Arabia. *Molecules.* 2023; 28(20):7025.
49. Asra F., Thathapudi D., Ajra F., Katari S., Dumala N. In Silico Pharmacokinetic and Pharmacodynamic Screening Methods of Phytol; An Antitubercular Lead Discovery Study. In: Murahari M., Nalluri B.N., Chakravarthi G., editors. *Current Trends in Drug Discovery, Development and Delivery (CTD4-2022).* Royal Society of Chemistry Books; 2023:822.
50. Yang H., Sun L., Li W., Liu G., Tang Y. In Silico Prediction of Chemical Toxicity for Drug Design Using Machine Learning Methods and Structural Alerts. *Front. Chem.* 2018; 6(30).
51. Moussa N., Mando H. Novel and Predictive QSAR Model and Molecular Docking: New Natural Sulfonamides of Potential Concern against SARS-CoV-2. *Anti-Infective Agents.* 2023; 21(5).
52. Chen X., Guan W., Li Y., Zhang J., Cai L. Xanthine Oxidase Inhibitory Peptides from *Larimichthys polyactis*: Characterization and In Vitro/In Silico Evidence. *Foods.* 2023; 12(5):982.
53. Hille R. Xanthine Oxidase—A Personal History. *Molecules.* 2023; 28(4):1921.
54. Alkhatib R. Chemical Composition of Essential Oils, Total Phenols, and Antioxidant Activity of *Achillea fragrantissima* and *A. santolina* Grown in Syria. *Jordan Journal of Pharmaceutical Sciences.* 2024; 17(3).
55. Alkhoury R., Alkhatib R. *Rumex conglomeratus* Murr. Grown Wild in Syria: Phytochemical Analysis and In Vitro Activities of Aerial Parts and Rhizomes Extracts. *Jordan Journal of Pharmaceutical Sciences.* 2024; 17(4).
56. Al-Halaseh L., Issa R., Said R., Al-Suhaimat R. Antioxidant Activity, Phytochemical Screening, and LC/MS Characterization of Polyphenol Content of Jordanian Habitat of *Pennisetum setaceum* Aqueous Leaf Extract. *Jordan Journal of Pharmaceutical Sciences.* 2024; 17(4).

النشاط المضاد للأكسدة في الحاسوب لستة مكونات متطايرة في نبات *Capsella bursa-pastoris*

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ملخص

يعتبر نبات *Capsella bursa-pastoris* عشبة برية ذات قيمة غذائية عالية ويمكن تناولها نيئة أو مطبوخة في بعض البلدان. كما يستخدم في الطب التقليدي في العديد من البلدان كعامل مضاد للنزيف وتخفيف الالتهاب. هدفت هذه الدراسة إلى تحديد التركيب الكيميائي للزيت العطري وتقييم النشاط المضاد للأكسدة في الحاسوب لستة مكونات متطايرة في نبات *Capsella bursa-pastoris* المزروع في سوريا. تم استخلاص الزيت العطري وتحليله باستخدام كروماتوغرافيا الغاز–مطياف الكتلة (GC-MS). بالإضافة إلى ذلك، تم إجراء الحركية الدوائية الحاسوبية والالتحام الجزيئي لستة مكونات متطايرة (Phytone و Phytol و Farnesylacetone و Octa-3,5-dien-2-one و m-menthane و Beta ionone) على أكسيداز الزانثين (PDB ID: 1 FIQ). أظهرت النتائج وجود ثمانية وثلاثين مركبًا. كانت المركبات الرئيسية هي أسيتون هيكساهيدروفارنيسيل (فيتون) بنسبة 20.2٪، وداي أسيتيل–4،4'،6،6'–تيتراميثوكسي–2،2'–بيفينيل ديول بنسبة 8.46٪، وثنائي إيزوبروبيل ميثيل فوسفونات بنسبة 6.45٪، وبيتا أيونون بنسبة 5.24٪. أظهر أسيتون فارنيسيل وبيتا أيونون أعلى تقارب ارتباط، يتراوح من –5.4 إلى –6.4 كيلو كالوري / مول. يعد الزيت العطري لـ *Capsella bursa-pastoris* مصدرًا محتملًا لمضادات الأكسدة.

الكلمات الدالة: *Capsella bursa-pastoris*، الزيت العطري، مضاد الأكسدة، الالتحام الجزيئي.

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