Avicenna Journal of Pharmaceutical Research
2020 December;1(2):65-71 http://ajpr.umsha.ac.ir

Research Article

doi:10.34172/ajpr.2020.12

Investigation on Chemical Constituents of *Foeniculum vulgare* Essential Oil and the Molecular Docking Studies of its Components for Possible Matrix Metalloproteinase-13 Inhibition

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Abstract

Background: *Foeniculum vulgare* (Fennel) has a wide range of applications. Previous studies revealed the presence of different compounds in the essential oil (EO) of fennel fruit (FF). Matrix metalloproteinase-13 (MMP-13) participates in several human biological processes including the degradation of extracellular matrix proteins, activation or degradation of some significant regulatory proteins, and tumor cell invasion. Furthermore, the up-regulation of MMP-13 is associated with many disorders such as tooth caries and periodontitis, as well as the degradation of enamel and tissues around the implant and Alzheimer's disease. Therefore, the aims of the present study were to investigate the compounds of the EO of FF (EOFF) from the Hamedan district, along with performing molecular docking analysis to assess the binding affinity of four compounds originated from *F. vulgare* with the MMP-13. Finally, the study focused on evaluating the pharmacokinetic and toxicity characteristics of the compounds.

Methods: Hydrodistillation method was used for obtaining the EO from FF. Then, gas chromatography-mass spectrometry was applied to identify the components of the EO. Molecular docking analysis was carried out using AutoDock software. Eventually, the pharmacokinetic and toxicity features of compounds were evaluated using bioinformatics webservers.

Results: The results revealed the presence of fourteen compounds, among which e-anethole (86.86%), fenchone (743%), estragole (165%), and thymol (1.21%) were the main components. Based on the results, thymol, fenchone, e-anethole, and estragole could potentially bind to the MMP-13 active site, respectively.

Conclusion: Regardless of several studies on the chemical constituents of EOFF, the subject has its own pharmacognostical importance. According to computational studies, EOFF has the potential for study on several human disorders such as cancer, tooth decay, and Alzheimer's disease.

Keywords: *Foeniculum vulgare*, Essential oil, Alzheimer's disease, Bioinformatics, Docking, Matrix metalloproteinase-13

Received 20 September 2020, **Accepted**: 25 October 2020, **ePublished**: 30 December 2020

Introduction

The genus *Foeniculum* (Apiaceae) has two species in Iran, including *Foeniculum carvi* (L.) and *Foeniculum vulgare* Miller. The scientific synonyms are *Carum carvi* and *Foeniculum officinale* All., respectively. *Foeniculum vulgare* Miller. is recognized by "fennel", "Razianeh", and "Shamr" as English, Persian, and Arabic names, respectively. The plant is scattered around the Mediterranean region and central Europe. Due to the wide applications of the plant (e.g., culinary and medicinal uses), the plant is widely cultivated in Iran. It is noteworthy that it grows wild in Mazandaran province. Fennel can be an annual, perennial, or biennial herb. It has feathery leaves resembling *Anethum* and umbelliferous golden yellow flowers. The fruits become fully grown at the end of summer or early autumn (1). The fruit dimensions vary based on the plant growth region (2). Fennel fruit (FF) has an intense aroma such as the anise fruit and is used as a flavouring in alcoholic beverages, baked goods, ice cream, meat and seafood dishes, and herbal mixtures. The savor of the FF is used as a culinary supplement and its essential oil (EO) composition establishes therapeutic effects such as anti-inflammatory, analgesic, anti-spasmodic, anti-oxidant, and diuretic (4) and anti-thrombotic (5) effects.

Moreover, these fennels can motivate menstruation and lactation, provide remarkable improvements in infantile colic (6), and is useful for the treatment of diarrhea and digestive complications. Additionally, FF is extensively used in folk medicine for different ailments such as cough remedies, digestive upset, and diarrhoea (7). According to previous research, EOFF may be considered as a potential candidate in studies on cognitive disorders such as depression, anxiety, dementia, and Alzheimer's (8). For example, Joshi et al found that *Foeniculum vulgare* had a memory-enhancing effect related to the involvement of the cholinergic system (9). EO composition between the plants in a species is not completely similar. Internal and external factors such as the genetic structure or the climate condition create these differences, leading to significant changes in the composition and the EO yield (10(. Thus, valuable pharmacognostic studies on the chemical constituents of EOs are considered necessary in order to reach-high quality EOs in terms of yields and compositions (11). Considering the wide range of the effects and uses and despite various reports on the chemical constituents of the EOFF, it remains a subject focus for researchers. Matrix metalloproteinase-13 (MMP-13) is a calcium-containing enzyme, and zinc is a cofactor of the protein. MMP-13 is involved in the degradation of extracellular matrix proteins such as fibrillar collagen, fibronectin, tenascin-C, and aggrecan. Moreover, MMP-13 hydrolyses many other proteins including type I, type II, type III, type IV, type XIV, and type X collagen (12). The up-regulation of MMP-13 has been demonstrated in several disorders such as tooth decay, periodontitis, Alzheimer's disease, and cancer progression (1-4,13-16). Therefore, the inhibition of MMP-13 may result in the prevention of mentioned disorders. In silico techniques such as molecular docking are fast and low-cost methods for predicting the affinity of small molecules to the active site of enzymes for therapeutic aims (17). In the present study, the molecular docking approach was performed to evaluate the binding affinity of four plant-based compounds, originated from *Foeniculum vulgare,* to the active site of MMP-13 using Autodock software. The results of the current study could be useful in the prevention approaches of a number of human disorders such as dental caries, cancer progression, periodontitis, and Alzheimer's disease. However, wet-lab experiments are required to validate the results of the current study. Considering the importance of EOFF, variations in the type and amount of available compounds in different EOFF, the current study evaluated the chemical constituents of EOFF and the binding affinity of four compounds more than 1% in EFF to the active site of MMP-13 using Autodock software.

Methods

Preparation of the Essential Oil

Foeniculum fruits (FF) were purchased from a market in the Hamedan district. The authentication of the plant material was performed on the herbarium of the School of Pharmacy, Hamadan University of Medical Sciences. FF was washed and dried, and then the powdered FF was subjected to a Clevenger-type apparatus for 3 hours, and the oil was obtained by the hydrodistillation method (18). The oil was dried by anhydrous sodium sulfate and kept in a refrigerator until use.

Identification of Oil Components

EOFF was injected into the gas chromatography-mass spectrometry system (GC-MS) and the system was ThermoQuest GC-coupled to the Thermo Finnigan mass system. The GC apparatus was equipped with a DB-5 column ((5%-Phenyl)-methylpolysiloxane, 30 m * 0.25 mm * 0.25 µm)) and the carrier gas was He by a flow rate of 1.1 mL/min. The split ratio and the run time were 1:50 and 40 minutes, respectively. The oven temperature was 60˚C which increased to 250˚C by a ramp of 5˚/minute and continued for 2 minutes at 250˚C. The temperature of the detector and the injector was 250°C. The mass analyzer was the Quadropole system operating at 70 eV ionization energy. Accurate mass spectra and electron ionization mass spectra (EIMS) were recorded at m/z and m/e ranges of 50-700 and 40-460 amu in the scan mode, respectively. Further, n-alkanes were injected into GC-MS at the same condition as the oil, and their retention times were used for calculating retention indices (RIs). Then, the EIMS fragmentation pattern of constituents was compared by the published data and those held in the Wiley library of mass spectra. For accurate identification, the calculated RI of compounds was compared by previous reports (19).

Molecular Structure Preparing

The three-dimensional (3-D) structure of MMP-13 was attained from the Research Collaboratory for Structural Bioinformatics (https://www.rcsb.org, PDB ID: 5b5o) at 1.2 Å x-ray resolution (18). Chain A in the 5b5o file was selected for molecular docking analysis. Moreover, the Swiss-PdbViewer, version 4.1.0 (http://www.expasy.org/spdbv) was utilized for the energy minimization (EM) of MMP-13 (19). Four herbal compounds were considered as the candidates for MMP-13 inhibition, including thymol (PubChem ID: 6989), fenchone (PubChem ID: 14525), trans-anethole (PubChem ID: 637563), and methyl chavicol (PubChem ID: 8815). The 3-D structures of all small molecules were obtained as a structure data file (SDF) format from the PubChem database (cactus webtool (http://cactus.nci.nih.gov/chemical/structure) was utilized to convert the SDF to PDB format. All ligands were structurally and geometrically optimized by EM and using the HyperChem software, version 8.0.10.

Physical and Chemical Properties of Small Molecules

The PubChem database (https://pubchem.ncbi.nlm.nih.gov) was applied to evaluate the drug-likeness of herbal compounds according to the theoretical method of

pharmacokinetic parameters in consonance with the Rule of Five (RO5) defined by Lipinski et al (20). The molecular mass and oil/water partition coefficient in addition to the number of donors and the acceptors of hydrogen bonds were studied as well.

Pharmacokinetic and Toxicological Properties (e.g., absorption, distribution, metabolism, and excretion, ADMET)

The SwissADME webserver (http://www.swissadme.ch/) was used to predict the pharmacokinetic properties of herbal compounds, including ADME (21). Furthermore, the toxicological features of small molecules were considered using the PreADMET (https://preadmet.bmdrc.kr/) webserver in order to predict the carcinogenicity of compounds in the mouse and rat models, in addition to estimating the possible inhibition of the human ether-a-go-go-related gene (hERG) channel in the heart.

Molecular Docking Analysis

A windows-based operating system was used to carry out bioinformatic analyses. The basic information of the system included installed memory (32 GB), processor (Intel Core i7), and system type (64-bit). The molecular docking analysis was performed using AutoDock software, version 4.0 (http://autodock.scripps.edu). The AutoDock tool predicts the conformation of the ligand bounded to the receptor with a predicted Gibbs free energy of the connection. Furthermore, it estimates the free energy of binding ($\Delta G_{binding}$) from the following formulas (22):

$\Delta G_{binding}$ = *Intermolecular Energy + Total Internal Energy + Torsional Free Energy - Energy of Unbound System*

The catalytic domain of the MMP-13 was considered as the receptor of the ligands. The grid box options were set as spacing (0.375 Å), X-dimension (52), Y-dimension (52), and Z-dimension (60). Based on the study by Nara et al (23), the main amino acids are located in the active site of MMP-13, in addition to the 3-D view of the interaction between the MMP-13 active site and the inhibitor of the protein (https://www.rcsb.org/structure/5B5O). These key amino acids were selected as the docking box containing 16 residues such as His187, Ala186, Leu185, Val219, Leu218, Tyr244, Thr245, Ile243, Pro242, Ala238, His232, Phe241, His226, His222, Leu239, and Glu223 (23). The number of conformations for each ligand was set as 50. Finally, the BIOVIA Discovery Studio Visualizer (version 19.1.0.18287) was used for visualizing the interaction modes between ligands and the residues within the MMP-13 active site.

Results

The EO of *Foeniculum vulgare* was extracted by the hydrodistillation method. The EFF yield was 0.5% w/w, and the oil was studied by GC-MS (Figure 1). The list of EFF components is reported in Table 1. Based on the results, 14 compounds were identified representing 99.2% of EFF. The major components of the oil were e-anethole (86.86%), fenchone (7.43%), estragole (1.65%), and thymol (1.21%). Other ten compounds have an amount of less than 1%. Based on the obtained data (Table 1), the main components of EFF belongs to phenylpropanoids (88.51%), monoterpene ketones (7.53%), monoterpene phenols (1.21%), and monoterpene hydrocarbons (1.17%).

Molecular Docking

The molecular docking approach was performed to evaluate the binding affinity of four compounds more than 1% to the active site of MMP-13. Table 2 presents the details of binding energies between the MMP-13 and the tested compounds in this study, along with the inhibition constant estimated for each ligand obtained from docking results. All four compounds were identified with an inhibition constant at the micromolar (μM) scale.

Physical and Chemical Properties of the Compounds

The physical and chemical features of the compounds were studied based on the RO5 as described by Lipinski et al (20). According to RO5, an appropriate compound must illustrate a molecular mass of ≤500 g/mol, logarithm of the partition coefficient between n-octanol and water (LogP) ≤ 5, a hydrogen bond acceptor count ≤10, and a hydrogen bond donor count ≤ 5 (12-15,24-26). According to the results, all four compounds were in agreement with the RO5 and considered to be drug-like molecules for oral use. Table 3 provides the details of characteristics related to the RO5 for each compound.

Pharmacokinetic and Toxicological Properties (ADME/Tox) of Compounds

Further analyses focused on the compounds for predicting the ADMET of each ligand. The pharmacokinetic features evaluated by the SwissADME webserver were gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, P-gp (P-glycoprotein) substrate, cytochrome

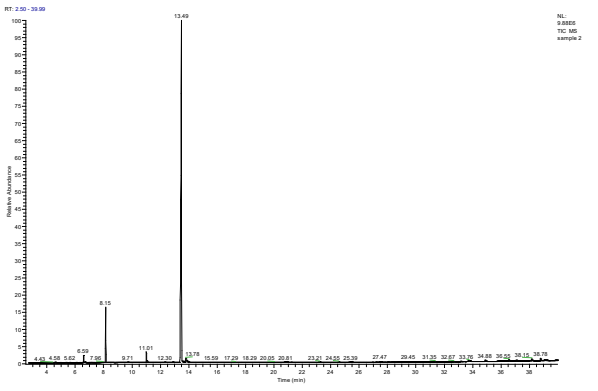

Figure 1. GC Chromatogram of the Essential Oil of *Foeniculum vulgare*. *Note*. GC: Gas chromatography.

Table 1. Composition of the Essential Oil of Fennel Fruits

RI Calculated	Area GCMS%	Compound	RI Reference
933	0.06	α-pinene	932
972	0.12	Sabinene	969
987	0.08	β-myrcene	988
1025	0.03	p-Cymene	1020
1028	0.88	Limonene	1024
1033	0.18	1,8-Cineol	1026
1091	7.43	Fenchone	1083
1155	0.1	Camphor	1141
1206	1.65	p-Allylanisole	1247
1291	86.86	E-Anethol	1282
1301	1.21	Thymol	1289
1889	0.16	Nonadecane	1900
2285	0.2	Tricosane	2300
2385	0.24	tetracosane	2400
Phenylpropanoid		88.51	
Monoterpene ketone		7.53	
Monoterpene phenol		1.21	
Monoterpene hydrocarbon		1.17	

Note. RI: Retention index; GC-MS: Gas chromatography-mass spectrometry.

Table 2. Details of Binding Energies Between the Matrix Metalloproteinase-13 and the Four Compounds of Fennel Fruit Essential Oil Tested in This Study

Ligand ID	Ligand Name	Final Intermolecular Energy (kcal.mol)	Final Total Internal Energy (kcal.mol)	Torsional Free Energy (kcal.mol)	Unbound System Energy (kcal.mol)	Estimated Free Energy of Binding (kcal/mol)	Inhibition Constant (μM)
6989	Thymol	-6.72	-0.16	0.6	-0.16	-6.13	32.37
14525	Fenchone	-5.58	0	0	0	-5.58	81.14
637563	Trans-anethole	-6.21	-0.18	0.89	-0.15	-5.35	120.44
8815	Methyl chavicol	-6.18	-0.2	0.89	-0.17	-5.31	128.26

Note. ID: identifier, μM, micromolar.

Table 3. Properties of Lipinski's Rule of Five Associated with the Compounds

Ligand Name	Molecular Weight (g/mol)	XLogP3	Hydrogen Bond Donor Count	Hydrogen Bond Acceptor Count	Agreement With RO5
Thymol	150.22	3.3	1	1	Yes
Fenchone	152.23	2.3	0	1	Yes
Trans-anethole	148.2	3.3	0	1	Yes
Methyl chavicol	148.2	3.4	0	1	Yes

Note. LogP: The logarithm of the partition coefficient between n-octanol and water.

P-450 inhibition, and the skin permeation coefficient (k_p). The possible inhibition of the human cardiac potassium channel hERG and the carcinogenicity of the compounds in mouse and rat models were considered as the toxicological properties of the compounds. Thymol and fenchone were predicted to have lower toxicity effects as compared with other compounds. The ADMET results of the current study are presented in Table 4.

Discussion

The present study revealed that the *F. vulgare* EO contains fourteen compounds, in which phenylpropanoids (88.51%), monoterpene ketones (7.53%), monoterpene phenols (1.21%), and monoterpene hydrocarbons (1.17%) are the main classes.

E-anethole and estragole belonging to phenylpropanoids constitute 86.86% and 1.65% of EOFF, respectively. Bahmani et al studied the oils of FFs from 12 regions in Iran and they found that the content of e-anethole in Khash and Sari was 88.455% and 1.47%, respectively, whereas that of estragole was 0.221% and 55.09% in the EFF of Khash and Sari, respectively. The amounts of e-anethole and estragole were 14.7% and 59.1% in Kalibar (27). Likewise, Mehrpour et al studied FF growing in Hamedan and concluded that anethole and estragole constituted 78.6% and 3.2% of the EFF. They used the

Table 4. Predicted Pharmacokinetic and Toxicological Properties of the Compounds in This Study

Ligand Name	Pharmacokinetics									Toxicity		
	GI Abs	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log K_p	Carcino_ mous	Carcino_ rat	hERG Inhibition
Thymol	High	Yes	No	Yes	No	No	No	No	-4.87	Negative	Negative	Low risk
Fenchone	High	Yes	No	No	No	No	No	No	-4.73	Negative	Positive	Low risk
Trans-anethole	High	Yes	No	Yes	No	No	No	No	-4.86	Positive	Positive	Medium risk
Methyl chavicol	High	Yes	No	Yes	No	No	No	No	-4.71	Positive	Positive	Medium risk

GI: Gastrointestinal; Abs: Absorption; BBB: Blood-brain barrier; P-gp: P-glycoprotein; CYP: Cytochrome p-450; K_p: Skin permeation coefficient; hERG: Human ether-a-go-go related gene.

hydrodistillation method for the isolation of the EO (28). Fenchone, monoterpene ketone, constituted 7.43% of the available EFF. Bahmani et al reported a range between 1.226% and 14.74% from Sanandaj and Sari, respectively (27) .Mehrpour et al examined the EFF from Hamedan province and reported that it contained 11.29% of the oil (28).

Thymol is a monoterpene phenol. EFF in the present study had 1.21% thymol while none of the 12 studied regions by Bahmani et al contained thymol (27) .In their study, Abdossi et al examined the EFF of Hamedan, Kermanshah, and Shahrekord. Only the specimen of Hamedan contained 0.16% of thymol (29). This wide diversity was observed among different growing populations in Hamedan and some regions of Iran. Additionally, there are different reports on the chemical constituents of EFF in other countries.

For instance, Miguel et al found that estragole (79-88%) was the major compound of EFF in plants growing in Portugal (30). According to previous evidence, they reported that there are estragole, estragole/anethole, and estragole fenchone chemotypes in different geographical regions. They also found that the isolation procedure did not affect the chemotype in one distinct growing population.

In the present study, the computational screening approach was carried out using AutoDock software to identify compounds originated from *Foeniculum vulgare* capable of inhibiting the MMP-13. Thymol, as an oxygenated monoterpene (31) was estimated to be the most effective compound from the tested ligands in this study, followed by trans-anethole, methyl chavicol, and fenchone.

In the present study, thymol demonstrated one hydrogen interaction and seven hydrophobic interactions with Leu185, Ala186, Val219, His222, His226, His232, and Tyr244 residues within the MMP-13 active site. Methyl chavicol revealed three hydrophobic interactions with Leu185, Val219, and His222 residues within the MMP-13 active site. Moreover, fenchone showed one hydrogen interaction and five hydrophobic interactions with Gly183, Leu185, His222, His226, His232, and Pro242 residues within the MMP-13 active site. Moreover, trans-anethole formed three hydrophobic interactions with Leu185, Val219, and His222 residues within the MMP-13 active site. The interaction modes between each of the compounds and the MMP-13 active site are presented in Table 5. Figure 2 shows the images of ligand-amino acid interactions for the four studied compounds.

According to the results of the present study, no significant correlation was found between the structures of phenylpropanoid compounds (i.e., trans-anethole and methyl chavicol) and monoterpene compounds (i.e., thymol and fenchone) in the inhibition of MMP13.

Conclusion

Considering the wide diversity in the type of EFF components, it seems that the geographical growth region of *F. vulgare* is one of the most important affected factors. Accordingly, despite the large number of studies conducted in this regard, it is the subject of interest for researchers. The present study successfully found that all four compounds in the EO of *F. vulgare* are capable of inhibiting the MMP-13 according to their estimated $\Delta G_{binding}$ and the inhibition constant. In addition, they all revealed drug-like features according to Lipinski's RO5. Furthermore, thymol and fenchone showed lower toxicity effects as compared with other compounds. Therefore, they may be considered as potential drug candidates for the next steps of drug discovery. The findings of the present study may be helpful for the prevention and/or therapeutic procedures of several human disorders

Table 5. Molecular Interactions Between the Compounds and the Residues Incorporated in the Matrix Metalloproteinase-13 Active Site

Ligand Name	Hydrogen Bond (distance Å)	Hydrophobic Interaction (Distance Å)
Thymol	Ala186 (4.07)	Val219 (3.26); Leu185 (5.25); His226 (7.26); His232 (5.73); His222 (7.06, 4.72); Leu185 (4.51); Tyr244 (5.51)
Methyl chavicol	NA	VAL219 (6.55); leu185 (5.33); His222 (5.75)
Fenchone	Gly183 (5.01)	His232 (6.79); Leu185 (5.41); Pro242 (4.52); His222 (5.97); His226 (7.12)
Trans-anethole	NA	His222 (5.78); Leu185 (5.33); Val219 (6.58)

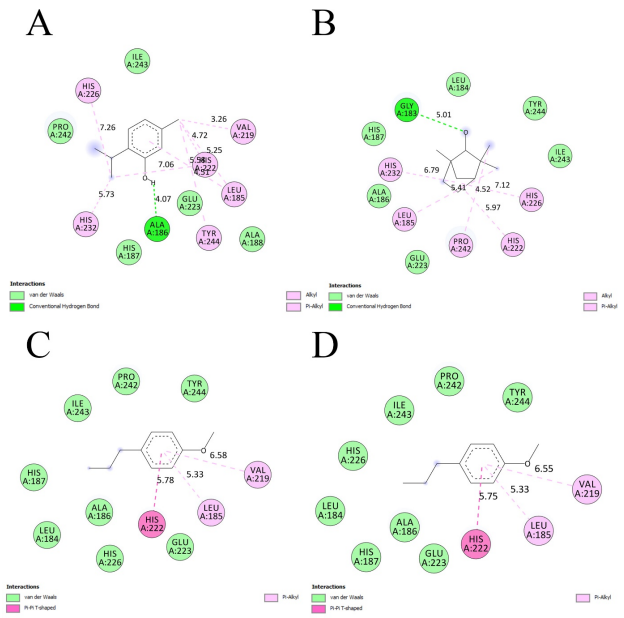

Figure 2. Receptor Ligand Interaction for (A) Thymol (A), Methyl chavicol (B), Fenchone (C), and Trans-anethole (D) Within the MMP-13 Active Site. *Note*. MMP-13: Matrix metalloproteinase-13.

such as dental caries, Alzheimer's disease, periodontitis, and tumor cell invasion and migration. Nevertheless, validation is necessary in the future.

Acknowledgments

The authors would like to appreciate the Vice-chancellor of Research and Technology for financial support (grant number: 9807305692).

Competing Interests

The authors declare that they have no competing interests.

References

1. Mozaffarin V. Identification of Medicinal and Aromatic Plants of Iran. Tehran: Farhang Moaser Publishers; 2012. [Persian].
2. Rather MA, Dar BA, Sofi SN, Bhat BA, Qurishi MA. *Foeniculum vulgare*: a comprehensive review of its traditional use, phytochemistry, pharmacology, and safety. Arab J Chem. 2016;9:S1574-S83. doi: 10.1016/j.arabjc.2012.04.011.
3. García-Jiménez N, Péerez-Alonso MJ, Velasco-Negueruela A. Chemical composition of fennel oil, *Foeniculum vulgare* Miller, from Spain. Journal of Essential Oil Research. 2000;12(2):159-62. doi: 10.1080/10412905.2000.9699487.
4. Aprotosoaie AC, Şpac A, Hancianu M, Miron A, Tănăsescu VF, Dorneanu V, et al. The chemical profile of essential oils obtained from fennel fruits (*Foeniculum vulgare* Mill.). Farmacia. 2010;58(1):46-53.
5. Tognolini M, Barocelli E, Ballabeni V, Bruni R, Bianchi A, Chiavarini M, et al. Comparative screening of plant essential oils: phenylpropanoid moiety as basic core for antiplatelet activity. Life Sci. 2006;78(13):1419-32. doi: 10.1016/j.lfs.2005.07.020.
6. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (*Foeniculum vulgare*) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. Altern Ther Health Med. 2003;9(4):58-61.
7. Napoli EM, Curcuruto G, Ruberto G. Screening the essential oil composition of wild Sicilian fennel. Biochem Syst Ecol. 2010;38(2):213-23. doi: 10.1016/j.bse.2010.01.009.
8. Cioanca O, Hancianu M, Mircea C, Trifan A, Hritcu L. Essential oils from Apiaceae as valuable resources in neurological disorders: *Foeniculi vulgare aetheroleum*. Ind Crops Prod. 2016;88:51-7. doi: 10.1016/j.indcrop.2016.02.064.
9. Joshi H, Parle M. Cholinergic basis of memory-strengthening effect of *Foeniculum vulgare* Linn. J Med Food. 2006;9(3):413-7. doi: 10.1089/jmf.2006.9.413.
10. Telci I, Demirtas I, Sahin A. Variation in plant properties and essential oil composition of sweet fennel (*Foeniculum vulgare* Mill.) fruits during stages of maturity. Ind Crops Prod. 2009;30(1):126-30. doi: 10.1016/j.indcrop.2009.02.010.
11. Telci I, Toncer OG, Sahbaz N. Yield, essential oil content and composition of *Coriandrum sativum* varieties (var. *vulgare* Alef and var. *microcarpum* DC.) grown in two different locations. J Essent Oil Res. 2006;18(2):189-93. doi: 10.1080/10412905.2006.9699063.
12. UniProt: a worldwide hub of protein knowledge. Nucleic Acids Res. 2019;47(D1):D506-D15. doi: 10.1093/nar/gky1049.
13. Sabogal-Guáqueta AM, Muñoz-Manco JI, Ramírez-Pineda JR, Lamprea-Rodriguez M, Osorio E, Cardona-Gómez GP. The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice. Neuropharmacology. 2015;93:134-45. doi: 10.1016/j.neuropharm.2015.01.027.
14. Grenier D, Chen H, Ben Lagha A, Fournier-Larente J, Morin MP. Dual action of myricetin on *Porphyromonas gingivalis* and the inflammatory response of host cells: A promising therapeutic molecule for periodontal diseases. PLoS One. 2015;10(6):e0131758. doi: 10.1371/journal.pone.0131758.
15. Koo H, Schobel B, Scott-Anne K, Watson G, Bowen WH, Cury JA, et al. Apigenin and tt-farnesol with fluoride effects on S. mutans biofilms and dental caries. J Dent Res. 2005;84(11):1016-20. doi: 10.1177/154405910508401109.
16. Hyuga S, Hyuga M, Yoshimura M, Amakura Y, Goda Y, Hanawa T. Herbacetin, a constituent of ephedrae herba, suppresses the HGF-induced motility of human breast cancer MDA-MB-231 cells by inhibiting c-Met and Akt phosphorylation. Planta Med. 2013;79(16):1525-30. doi: 10.1055/s-0033-1350899.
17. Huang SY, Zou X. Advances and challenges in protein-ligand docking. Int J Mol Sci. 2010;11(8):3016-34. doi: 10.3390/ijms11083016.
18. Mojab F, Khalaj N. Chemical constituents of the essential oil of *Stachys fruticulosa* M. Bieb. from Iran. Avicenna J Pharm Res. 2020;1(1):33-6. doi: 10.34172/ajpr.2020.06.
19. Abdoli P, Moradkhani SH, Dastan D. Comparative analysis of *Nepeta crispa* essential oil composition in flowering and vegetative stages. American Journal of Phytomedicine and Clinical Therapeutics.2016;4(4):106-12.
20. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26. doi:10.1016/s0169-409x(00)00129-0.
21. Berman HM, Battistuz T, Bhat TN, et al. The Protein Data Bank. Acta Crystallogr D Biol Crystallogr. 2002;58(Pt 6 No 1):899-907. doi:10.1107/s0907444902003451.
22. Dhanachandra Singh Kh, Kirubakaran P, Manikandaprabhu S, Nagamani S, Srinivasan P, Karthikeyan M. Docking Studies of Adenosine Analogues with NS5 Methyltransferase of Yellow Fever Virus. Indian J Microbiol. 2012;52(1):28-34.

doi:10.1007/s12088-011-0201-7.
23. Nara H, Kaieda A, Sato K, et al. Discovery of Novel, Highly Potent, and Selective Matrix Metalloproteinase (MMP)-13 Inhibitors with a 1,2,4-Triazol-3-yl Moiety as a Zinc Binding Group Using a Structure-Based Design Approach. J Med Chem. 2017;60(2):608-626. doi:10.1021/acs.jmedchem.6b01007.
24. Muthusamy K, Prasad S, Nagamani S. Role of Hydrophobic Patch in LRP6: A Promising Drug Target for Alzheimer's disease. Indian Journal of Pharmaceutical Sciences. 2016;78(2):240-51. doi: 10.4172/pharmaceutical-sciences.1000109.
25. Huey R, Morris GM, Olson AJ, Goodsell DS. A semiempirical free energy force field with charge-based desolvation. J Comput Chem. 2007;28(6):1145-1152. doi:10.1002/jcc.20634.
26. de Amorim AL, de Lima AVM, de Almeida do Rosário AC, dos Santos Souza ÉT, Ferreira JV, da Silva Hage-Melim LI. Molecular modeling of inhibitors against fructose bisphosphate aldolase from *Candida albicans*. In Silico Pharmacol. 2018;6(1):2. doi: 10.1007/s40203-018-0040-x.
27. Bahmani K, Darbandi AI, Ramshini HA, Moradi N, Akbari A. Agro-morphological and phytochemical diversity of various Iranian fennel landraces. Ind Crops Prod. 2015;77:282-94. doi: 10.1016/j.indcrop.2015.08.059.
28. Mehrpoor Sh, Ahmadi N, Jamallou F, Zandmonfared MR. Investigation of essential oil analysis and antioxidant properties of Foeniculum vulgare Mill. Before and after seed cryopreservation. Scientific Research Applied Biology. 2018;8(1):11-19.
29. Abdossi V, Ghahremani A, Hadipanah A, Ardalani HR, Aghaee K. Quantitative and qualitative responses in chemical composition of three ecotypes of fennel (Foeniculum vulgare Mill.) cultivated in Iran climatic conditions. Journal of Biodiversity and Environmental Sciences. 2015;6:401-407.
30. Miguel MG, Cruz C, Faleiro L, Simões MT, Figueiredo AC, Barroso JG, et al. *Foeniculum vulgare* essential oils: chemical composition, antioxidant and antimicrobial activities. Nat Prod Commun. 2010;5(2):319-28. doi: 10.1177/1934578x1000500231.
31. Bahmani K, Darbandi AI, Ramshini HA, Moradi N, Akbari A. Agro-morphological and phytochemical diversity of various Iranian fennel landraces. Ind Crops Prod. 2015;77:282-94. doi: 10.1016/j.indcrop.2015.08.059.