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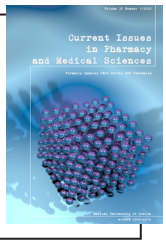

Exploring the antihypertensive potential of natural compounds from *Zygophyllum sp* plant: An *in-silico* investigation of ACE inhibition

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ABSTRACT

Hypertension, a major contributor to global mortality, requires comprehensive management including lifestyle changes and medication. This study explores the potential of natural compounds from *Zygophyllum sp* as Angiotensin-converting enzyme (ACE) inhibitors, a key class of antihypertensive drugs. Using molecular docking methodology, we investigated the inhibitory effects of these compounds on the ACE enzyme (PDB: 1UZF). Our work demonstrated that several molecules exhibited promising binding scores compared to established reference ligands, suggesting potential ACE-inhibiting properties. Myristic acid showed the most favorable score (-9.2454 kcal/mol), surpassing conventional reference drugs. Geranyllinalool, Pseudophytol, Methyl linoleate and Phytol also demonstrated superior scores. 1-Octadecene and linoleic acid outperformed captopril and aligned closely with other reference ligand scores. The computational scores, largely exceeding those of established drugs, indicate strong affinities between *Zygophyllum sp's* chemical constituents and the ACE enzyme. This suggests potential antihypertensive properties of the plant and its bioactive components, supporting its traditional use as an antihypertensive remedy. The notable efficacy scores of select known therapeutic agents further validate this potential. However, additional *in-vitro* and *in-vivo* investigations are necessary to robustly establish the ACE-inhibitory capability of *Zygophyllum sp* compounds. This study provides a foundation for further research into natural antihypertensive treatments, potentially offering new avenues for managing this widespread health concern.

INTRODUCTION

Hypertension is a major cause of premature death worldwide. According to the World Health Organization (WHO), hypertension significantly increases the risk of heart, brain and kidney diseases, and is one of the top causes of death and disease throughout the world [1]. The number of adults aged 30-79 years with hypertension has increased from 650 million to 1.28 billion in the last thirty years [2]. Categorically, there are two main types of hypertension. The first type is primary hypertension, which develops gradually over many years and has no identifiable cause [2]. The second type is secondary hypertension, which is caused by an underlying condition such as kidney disease, diabetes, long-term kidney infections, certain medications, smoking, obesity, lack of physical activity, stress, genetic and obstructive sleep apnea [3].

There are many drugs used in the treatment of hypertension. Some of the most common types of drugs used in treatment include: diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers and beta blockers [4]. Like all medications, they can have negative side effects. The specific side effects may vary depending on the drug class and the individual's response to the medication [5].

Nowadays, the prioritization of researchers lies in the development and identification of novel drugs characterized by reduced or negligible side effects. Nature, with its botanical heritage, continues to serve as an invaluable reservoir

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of natural medicinal resources derived from medicinal plants, which are now being explored as novel therapeutic approaches for hypertension treatment [6]. ACE inhibition is regarded as a promising therapeutic approach for hypertension treatment [7]. ACE inhibitors exert their pharmacological effect by impeding the synthesis of angiotensin II, a potent vasoconstrictor hormone that induces arterial constriction and elevates blood pressure levels [8]. Through this inhibition, ACE inhibitors facilitate vasodilation, leading to relaxation of blood vessels and subsequent reduction in blood pressure [9].

Biology and computational chemistry play crucial roles in discovering new drugs. Computer-aided drug discovery (CADD) has emerged as a powerful and promising technology for faster, cheaper, and more effective drug design [10]. The application of computational tools to drug discovery has grown steadily over the past few years, and has had a significant impact on the design of drugs and drug candidate [11]. Computational biology, especially biomacromolecular simulation, is a powerful method for revealing the molecular mechanism of the target protein and providing new perspectives for drug design [12]. Computational chemistry has also been harnessed in drug search and design. It is drug employed to predict the binding affinity between small molecules and target proteins. Moreover, computational chemistry can also be applied to predict the pharmacokinetic properties of small molecules [13].

Some species of the *Zygophyllum* genus have been reported to possess medicinal properties. For instance, a study published in BioMed Research International investigated the anti-inflammatory activity of *Zygophyllum coccineum* extract in an arthritis animal model and discovered that it has efficient and safe anti-inflammatory potential [14]. Additionally, a review article published in Herbal Medicines Journal provides phytochemical profiles and *in-vitro* as well as *in-vivo* biological activities of several *Zygophyllum* plants with hypoglycemic properties, based on research from selected research articles and books published between 1939 and 2017 [15]. For the first time, our present study examines the interaction between molecules derived from the *Zygophyllum sp* plant, and ACE enzyme to establish the plant's use as a hypotensive agent.

In the present study, we use molecular docking which is one of the major computational and bioinformatics tools exploited in the drug-discovery process to predict the binding geometries and binding energy of the ligand-target complex. The purpose of drawing on this technique is to predict the most probable 'binding scenarios' between the Angiotensin-converting enzyme (ACE) and a ligand (phytochemicals from *Zygophyllum sp* plant), based on their respective three-dimensional structures. This endeavor aims to identify novel molecules that can effectively inhibit ACE and demonstrate potential as antihypertensive agents.

MATERIAL AND METHODS

Selection of phytochemical molecules and ligand preparation

The selection of *Zygophyllum sp* plant was based on a local ethnopharmacological survey concerning use of medicinal plants as hypertensive and antidiabetic [16]. *Zygophyllum sp* is a genus of flowering plants in the family *Zygophyllaceae*. The genus is distributed in arid and semi-arid regions of Africa, the Mediterranean Basin, central Asia and Australia [17].

In the present investigation, we thoroughly examined numerous manuscripts to ascertain the principal chemical constituents of these plants cultivated in diverse geographical locations. By analyzing the existing literature, we detected a significant number of chemical compounds in the essential oil derived from various *Zygophyllum sp.* species cultivated in distinct Mediterranean regions [18-22]. We obtained the molecules (ligands) in 3D format from the PubChem and ChemSpider databases [23-24].

PubChem is recognized as one of the most extensive openly accessible chemical databases worldwide, facilitating the investigation of physicochemical properties using diverse molecular identifiers, including Trivial, systematic or IUPAC names, formulas and molecular structures. When 3D structures were absent, ChemDraw software was employed to draw the molecules.

To obtain the most stable conformer of molecules obtained from *Zygophyllum sp* (lowest energy), the ligand energies were minimized using Molecular Operating Environment software (MOE) [25]. The minimization process employed the Molecular Orbital Package (MOPAC) integrated into MOE, which is a versatile program designed to predict and study electronic structures, chemical properties and chemical reactions. MOPAC is a semi-empirical quantum chemistry program based on the Dewar and Thiel NDDO approximation. In the electronic calculation, the semi-empirical Hamiltonians MNDO, MINDO/3, AM1 and PM3 were utilized to obtain molecular orbitals, heat of formation and derivatives concerning molecular geometry.

Merck Molecular Force Field (MMFF94x) was also employed in this study. MMFF94x represents an extension of the MMFF94 force field, initially introduced in 1994, specifically tailored to accommodate organic compounds. It exhibits high precision in predicting molecular structures and chemical properties, particularly for small and medium-sized molecules. The force field encompasses various types of chemical bonds, bond angles, torsions, Van der Waals interactions and electrostatic interactions. MMFF94x was meticulously designed to offer a superior depiction of molecular structures and relative energies compared to its predecessor, MMFF94. This step is of utmost significance in acquiring energetically stable ligands. Molecules (ligands) identified in essential oil were assembled in a database in *mdb format for further docking studies. Reference ligands (drugs) were also optimized by same method as molecules from *Zygophyllum sp*.

Enzyme preparation (receptor)

Angiotensin-converting enzyme (ACE) plays a crucial role in the regulation of blood pressure and hypertension. ACE is part of the renin-angiotensin-aldosterone system (RAAS), which is a hormone system that helps maintain blood pressure, fluid and electrolyte balance in the body [26-27]. The primary function of ACE is to convert

angiotensin I, an inactive precursor, into angiotensin II, a potent vasoconstrictor [28].

ACE inhibitors are a class of medications commonly prescribed to treat hypertension. These drugs block the activity of ACE, which results in reduced production of angiotensin II and decreased vasoconstriction and aldosterone release. As a result, blood vessels dilate, blood pressure decreases, and the workload on the heart is reduced [29]. The 3D crystal structure of Angiotensin-converting enzyme (ACE) was downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) [30] under the code 1UZF, with three-dimensional resolutions of 2.00 Å [31].

Following the methodology outlined by Soga *et al*. [32], we employed the MOE software to discern and isolate the largest active site of the enzyme, to which specific substrates were subsequently attached using the "site finder" module. Prior to commencing the docking procedure, a crucial step involved the validation of the method through redocking of the reference ligand. This validation process is of paramount importance in ensuring the successful execution of the subsequent operations. The assessment of docking success rate in the redocking protocol was established based on the ratio of samples in which the Root Mean Square Deviation (RMSD) of the top-ranked pose was found to be less than 2 Å [33-34]. In the present study, the obtained RMSD value was 1.82 Å, which demonstrated that our procedure is valid. Figure 1 shows the superposition of the co-crystallized ligand in the active site after re-docking.

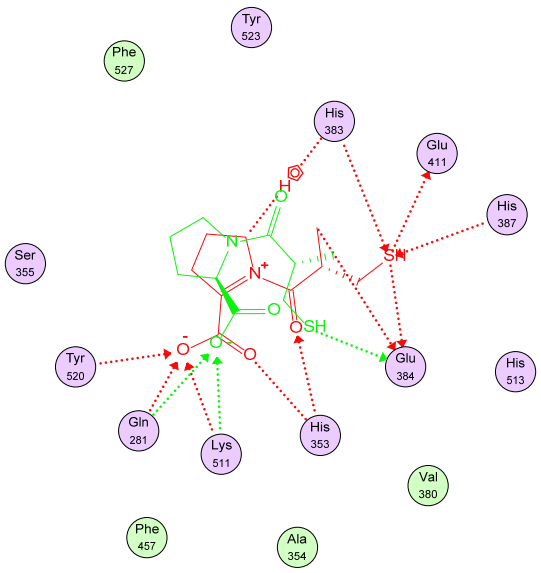

Figure 1. Superposition of the co-crystallized ligand in the active site of the ACE enzyme (PDB ID 1UZF)

Molecular docking results and discussions

Docking serves as a crucial element in virtual screening strategies. This pivotal process entails accurately positioning a ligand within the enzyme's active site to discern the interactions that occur between the ligand and the pre-arranged amino acids within the active site. By employing a scoring function ΔG [U total in kcal/mol], which accounts for the summation of electrostatic and Van der Waals energies, the affinity between the ligand and the enzyme can be quantified. Subsequently, candidate poses can be ranked based on this calculated affinity, enabling the identification of potential ligand-receptor interactions [35-36].

Docking algorithms employ a combination of scoring functions and search methods to accurately predict ligand binding. The operational performance of these algorithms is largely determined by two theoretical aspects of the scoring function. The first aspect is the presence of a global extremum in the ligand pose landscape at the correct location, which reflects the ability of the scoring function to accurately predict ligand binding. The second aspect is the accuracy of the magnitude of the scoring function at this extremum, which reflects the ability of the scoring function to accurately predict binding affinity [37]. The scoring value serves as a valuable thermodynamic parameter for evaluating and comparing multiple ligands. Notably, certain scoring functions have the capability to predict the dissociation constant between two molecules. These scoring functions play a pivotal role in assessing ligand-receptor interactions and can provide crucial insights into the binding affinities of ligands, aiding in the selection and prioritization of potential candidate molecules [39-41].

These interactions are then used to evaluate the potential for inhibition of the enzyme by the ligand. Docking simulations were conducted using default conditions, including a temperature of 300 K and a pH of 7. As benchmarks for comparison, reference ligands (medicaments) were employed. These reference ligands are approved drugs known for their established efficacy and strong affinity towards a specific receptor. The docking process allowed for a direct comparison of the binding affinity between the ligands under investigation and the known medicaments for the same receptor. Table 1 presents the top scores obtained after docking of molecules from *Zygophyllum sp*, and also docking results of the reference ligands in order to make comparison. In order to identify the best ligands which may be developed to drug (according to Lipinski's rule) we also studied the physicochemical properties of the top molecules as shown in Table 2.

To ensure compliance with the extended Lipinski's rule of five, the following criteria (ADME/T) were checked: molecular weight (MW) should be less than or equal to 500 g/mol, hydrophobicity (log P) should be less than or equal to 5, solubility (log S) should be greater than -4, the number of hydrogen bond donors (HBD) should be less than or equal to 5, the number of hydrogen bond acceptors (HBA) should be less than or equal to 10, and the topological polar surface area (TPSA) should be less than or equal to 140 Å^2. For a ligand to be compatible with orally administered drugs, it is necessary for it to satisfy at least two of Lipinski's rule properties [42-43]. However, these rules are not strict and there are many examples of oral drugs that do not meet all the criteria. In general, a molecule is considered as good candidate for an orally administered drug if it satisfies at least 2 out of the 5 rules, but it is important to note that these rules are not absolute-– and exceptions do exist [44]. We used the SwissADME tool which is an open-access tool for calculating physicochemical, pharmacokinetic, drug-like, and other parameters related to a molecule intended to be developed for a drug [45].

Table 1. Docking results of molecules from *Zygophyllum sp*. and ligands reference with Angiotensin-converting enzyme ACE (PDB ID 1UZF)

Reference ligands	Score (kcal/mol)
Ramipril (altace) _CID_5362129	-8.0242
Trandolapril_CID_5484727	-8.1235
Quinapril (accupril) _CID_54892	-7.8807
Benazepril (lotensin) _CID_5362124	-8.2364
Enalaprilat_CID_5462501	-7.4271
l-captopril_CID_44093	-7.0339
Molecules from *Zygophyllum sp*. (CID)	Score (kcal/mol)
11005	-9.2454
5365872	-7.6573
6437979	-7.6454
5284421	-7.5734
5280435	-7.5615
10408	-7.2542
8217	-7.2359
5280450	-7.0952

The obtained results show that many natural molecules from *Zygophyllum sp* yielded important scores. Moreover, these outnumbered known inhibitors of ACE, suggesting higher affinity and good interaction. Myristic acid (CID 11005) has the best score – equal to -9.2454 kcal/mol - which is higher than the score given by all reference ligands. We note as well that geranyllinalool (CID 5365872), pseudo phytol (CID 6437979), methyl linoleate (CID 5284421) and Phytol (CID 5280435) also gave good scores. In addition, 6,10,14-Trimethylpentadecan-2-one (CID 10408) , 1-Octadecene (CID 8217) and linoleic acid (CID 5280450) give score better than captopril and closer to the cited reference ligands. Types of interactions exhibited by the top selected ligands are summarized in Table 3. Figures 2-9 depict the interactions between ACE (PDB ID 1UZF) and the studied ligands as showcased through both 2D and 3D diagrams. Figure 10 illustrates the 2D diagram legend.

Table 2. Main physicochemical properties of the selected top ligands

Compound (CID)	Toxicity	Weight (g/mol)	LogP	LogS	H-bond donor	H-bond acceptor	TPSA Å2	Drug likeness
11005	No	228.37	4.77	-4.31	1	2	37.30	1 violation
5365872	No	290.49	6.12	-5.79	1	1	20.23	2 violations
6437979	No	292.51	6.35	-5.82	1	1	20.23	2 violations
5284421	No	294.48	5.97	-7.18	0	1	26.30	2 violations
5280435	No	296.54	6.36	-8.27	1	1	20.23	2 violations
10408	No	268.48	6.01	-7.35	0	1	17.07	2 violations
8217	No	252.48	7.04	-8.76	0	0	0.00	2 violations
5280450	No	280.45	5.88	-6.77	1	2	37.30	2 violations

Table 3. Scores and types of interactions of the best selected ligands docked in the active site of the Angiotensin-converting enzyme ACE (PDB ID 1UZF)

Ligands (CID)	Score (kcal/mol)	Bonds between atoms of compounds and residues of the active site					
		Atoms of compound	Involved Receptor atoms	Involved Receptor residues	Type of interaction bond	Distances (Å)	Energy (kcal/mol)
11005	-9.2454	O1 O1 O1 O1 O2	NE2 NZ OH NZ NE2	GLN 281 LYS 511 TYR 520 LYS 511 HIS 353	H-acceptor H-acceptor H-acceptor Ionic Ionic	3.00 2.86 2.98 2.86 3.85	-6.2 -2.7 -1.3 -5.5 -0.8
5365872	-7.6573	O1 C12	O 6-ring	ALA 354 TYR 523	H-donor H-pi	3.22 4.30	-0.7 -0.7
6437979	-7.6454	O1 O1	OE2 CA	GLU 384 SER 355	H-donor H-acceptor	3.17 3.35	-0.7 -0.5
5284421	-7.5734	Only electrostatic interactions are perceptible					
5280435	-7.5615	O1 O1	OE2 NH1	GLU 411 ARG 522	H-donor H-acceptor	3.31 3.05	-0.8 -1.9
10408	-7.2542	O1 O1	NE2 NE2	HIS 383 HIS 387	H-acceptor H-acceptor	3.05 3.02	-3.9 -3.2
8217	-7.2359	Only electrostatic interactions are perceptible					
5280450	-7.0952	O1 C11	OD1 5-ring	ASP 453 HIS 387	H-donor H-pi	2.88 4.02	-4.0 -1.2

Figures 2(a) and 2(b) illustrate the interactions between myristic acid (CID 11005) and the Angiotensin-converting enzyme (ACE) (PDB 1UZF). Myristic acid forms three hydrogen bonds with GLN 281, LYS 511 and TYR 520, with bond distances of 3.00 Å, 2.86 Å and 2.98 Å, respectively. The interaction energies for these hydrogen bonds are -6.2 kcal/mol, -2.7 kcal/mol and -1.3 kcal/mol, respectively. Additionally, myristic acid forms two ionic bonds with LYS 511 and HIS 353, with bond distances of 2.86 Å and 3.85 Å, respectively. The interaction energies for the ionic bonds are -5.5 kcal/mol and -0.8 kcal/mol, respectively.

Myristic acid, known also as tetradecanoic acid, is a common saturated fatty acid which has been shown in previous study to be anti-diabetic by interaction with DPP-4 and alpha amylase enzymes [46]. Myristic acid has been associated with potential negative effects on blood pressure. While investigations are still in progress, certain studies propose that increased consumption of myristic acid might play a role in unfavorable cardiovascular effects, which could encompass heightened blood pressure. [47]. However, more comprehensive research is needed to establish a clear and definitive relationship between myristic acid consumption and its influence on blood pressure regulation.

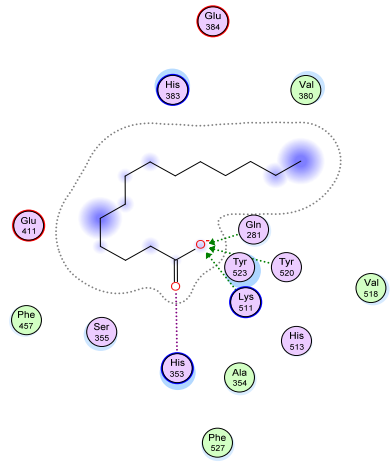

Figure 2(a). 2D interaction between myristic acid and ACE (PDB ID 1UZF)

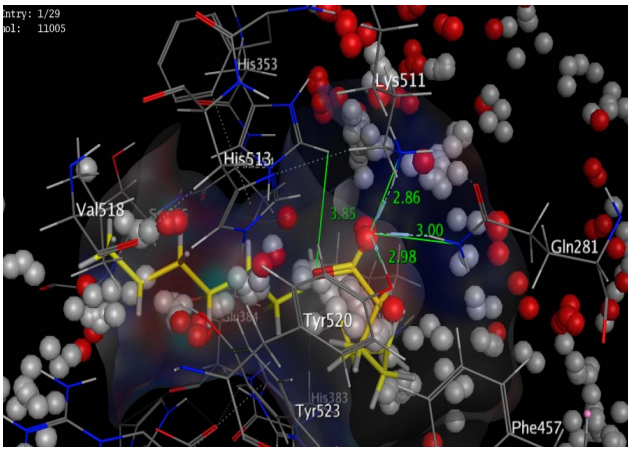

Figure 2(b). 3D interaction between myristic acid and ACE (PDB ID 1UZF).

The 2D and 3D interactions between Geranyllinalool (CID 5365872) and ACE (PDB ID 1UZF) are illustrated in Figure 3(a) and 3(b). Geranyllinalool is a natural compound found in various plants and essential oils. A comprehensive range of research primarily concentrated on its immediate impact on hypertension is lacking. Nevertheless, investigations into related compounds and essential oils that encompass the precursor of geranyllinalool, namely linalool, have indicated potential advantages for cardiovascular health and hypertension in certain studies [48-49].

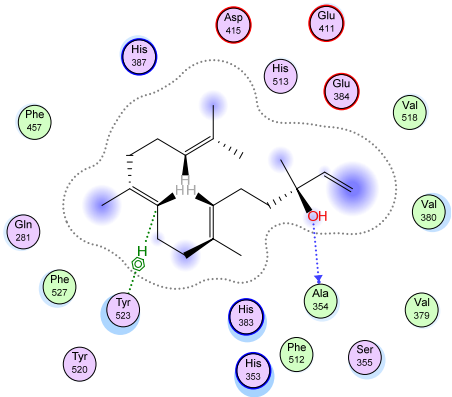

Figure 3(a). 2D interaction between Geranyllinalool and ACE (PDB ID 1UZF)

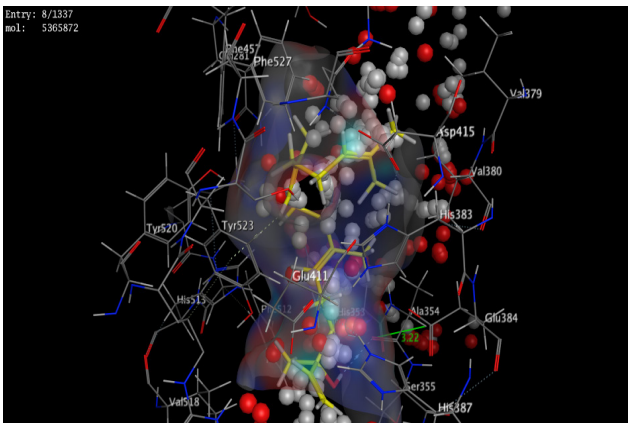

Figure 3(b). 3D interaction between Geranyllinalool and ACE (PDB ID 1UZF)

Pseudo phytol (CID 6437979), also known as 6-methyl-5-hepten-2-ol, is a chemical compound that belongs to the class of branched-chain fatty alcohols. It is structurally similar to phytol, which is a component of chlorophyll, the green pigment found in a plant that is involved in photosynthesis. Pseudo phytol is primarily a chemical compound used in various research and industrial applications, and its direct relationship with hypertension is not a well-studied topic within the existing scientific literature. Figures 4(a) and 4(b) show the 2D and 3D interactions between Pseudo phytol and ACE (PDB ID 1UZF).

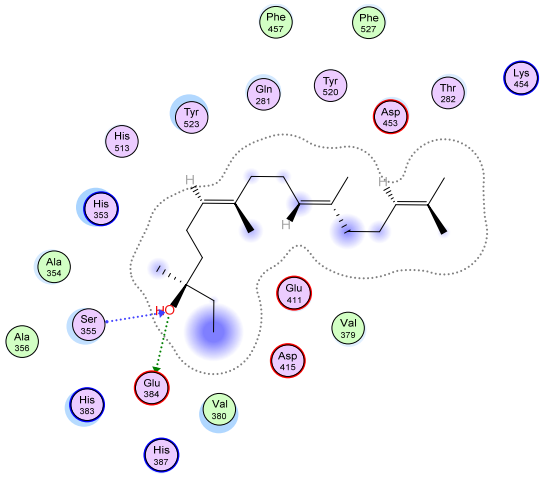

Figure 4(a). 2D interaction between Pseudo phytol and ACE (PDB ID 1UZF)

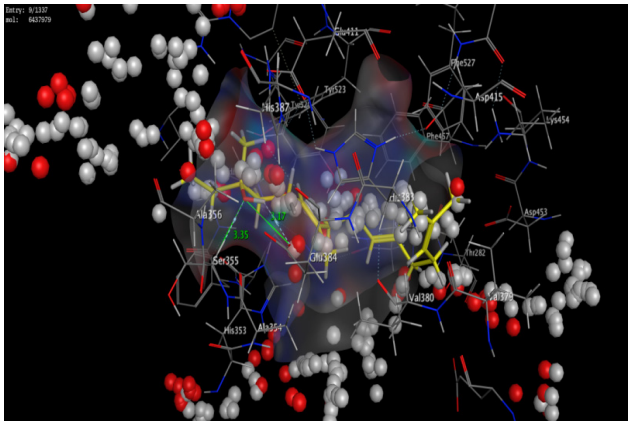

Figure 4(b). 3D interaction between Pseudo phytol and ACE (PDB ID 1UZF)

As indicated in the 2D and 3D diagrams illustrating interactions between Methyl linoleate (CID 5284421) and ACE (PDB ID 1UZF), no interactions are detected, only electrostatic interactions are possible, as shown in Figures 5(a) and 5(b). Methyl linoleate is a chemical compound that belongs to the class of compounds known as fatty acid esters. It is derived from linoleic acid, which is an essential omega-6 polyunsaturated fatty acid. Linoleic acid is important for the human body as it cannot be synthesized internally and must be obtained from the diet. According to literature, there is no direct relation between Methyl linoleate and hypertension.

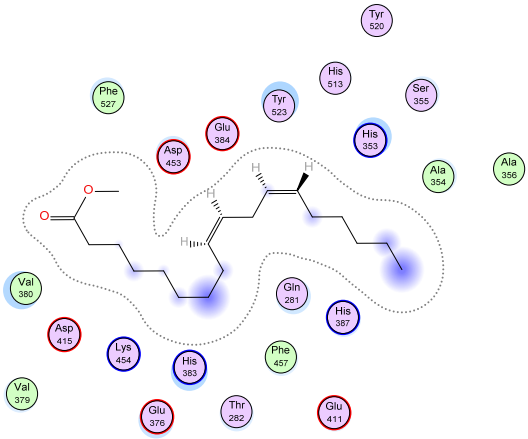

Figure 5(a). 2D interaction between Methyl linoleate and ACE (PDB ID 1UZF)

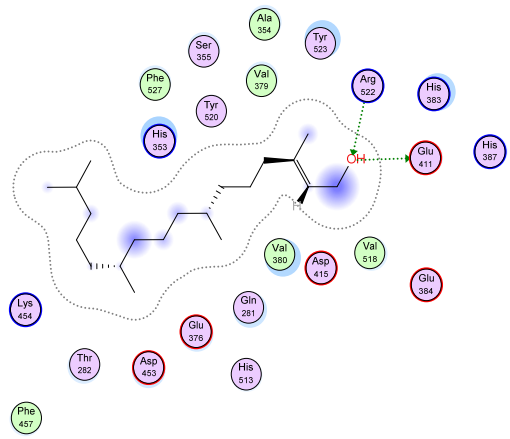

Figure 6(a). 2D interaction between Phytol and ACE (PDB ID 1UZF)

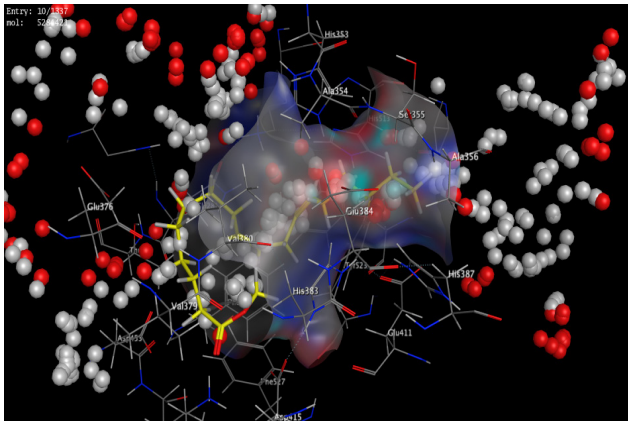

Figure 5(a). 3D interaction between Methyl linoleate and ACE (PDB ID 1UZF)

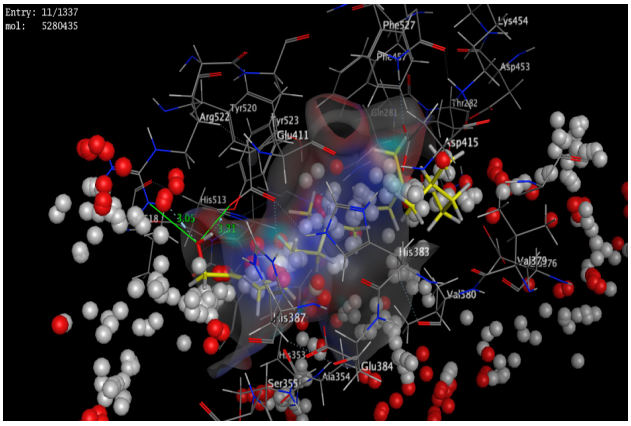

Figure 6(b). 3D interaction between Phytol and ACE (PDB ID 1UZF)

Figures 6(a) and 6(b) show 2D and 3D diagrams interactions between phytol (CID 5280435) and Angiotensin-converting enzyme ACE (PDB ID 1UZF) Phytol emerges as a naturally occurring diterpene compound obtainable from the chlorophyll found in green plants [50]. Subject to examination for numerous decades, it has been proposed to possess metabolic characteristics alongside robust anti-inflammatory impacts [50]. Phytol stands as a naturally derived molecule exhibiting lipid-modulating attributes, aligning with the contemporary requirement for novel therapeutics to manage conditions associated with the Westernized diet and lifestyle [50]. Phytol's advantageous impacts on well-being emerge as a captivating naturally sourced element within novel holistic treatments and functional dietary items aimed at addressing the swiftly escalating worldwide health challenges stemming from cardiovascular and chronic inflammatory conditions [50]. Investigations into the impacts of this substance indicate potential for aiding in anxiety reduction, pain alleviation and various additional advantages. While existing literature does not establish a direct correlation between phytol and hypertension, there is a need for studies to elucidate the significance of phytol concerning cardiovascular disease and hypertension.

The compound 6,10,14-Trimethylpentadecan-2-one (CID 10408) interacts with the ACE enzyme (PDB ID 1UZF) and forms two hydrogen-bond acceptor interactions with HIS 383 and HIS 387 at distances of 3.05 Å and 3.02 Å, respectively. The corresponding energies for these interactions are -3.09 kcal/mol and -3.2 kcal/mol. The 2D and 3D diagrams interactions are illustrated in Figures 7(a) and 7(b). The available literature does not show any biological activity of the compound nor a direct relationship with hypertension, hence the need to deeply study this compound.

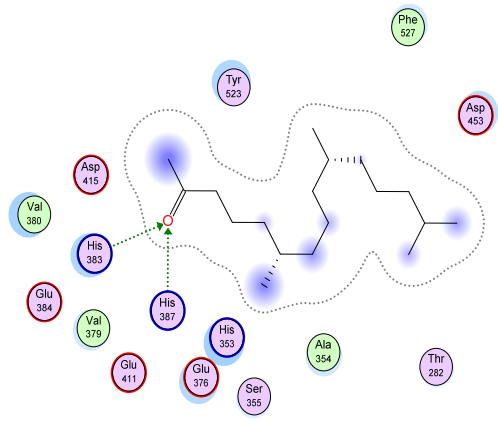

Figure 7(a). 2D interaction between 6,10,14-Trimethylpentadecan-2-one and ACE (PDB ID 1UZF)

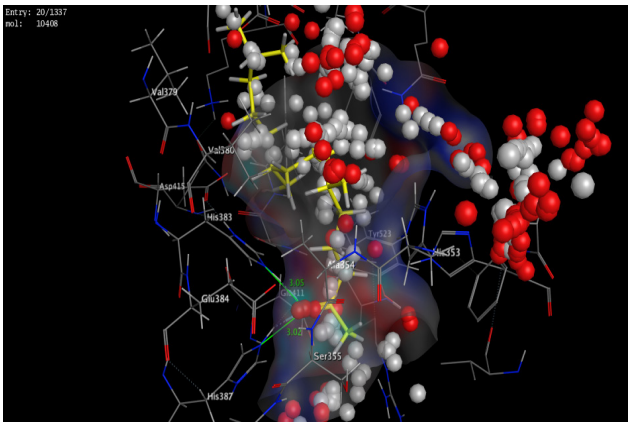

Figure 7(b). 3D interaction between 6,10,14-Trimethylpentadecan-2-one and ACE (PDB ID 1UZF)

The compound 1-Octadecene (CID 8217) does not react with the enzyme ACE (PDB ID 1UZF). As illustrated in the 2D and 3D diagrams of Figures 8(a) and 8(b), only electrostatic interactions are possible. Current scientific literature does not list any therapeutic interest or biological activity of this compound. Consideration of this compound in future studies is recommended.

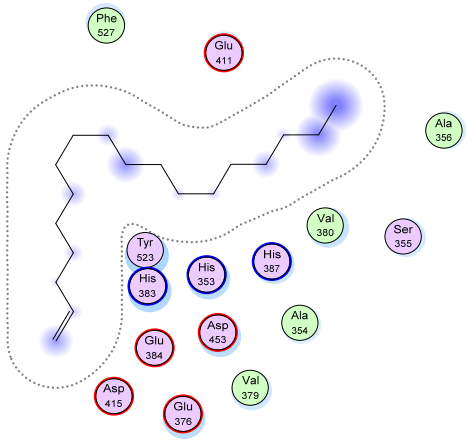

Figure 8(a). 2D interaction between 1-Octadecene and ACE (PDB ID 1UZF)

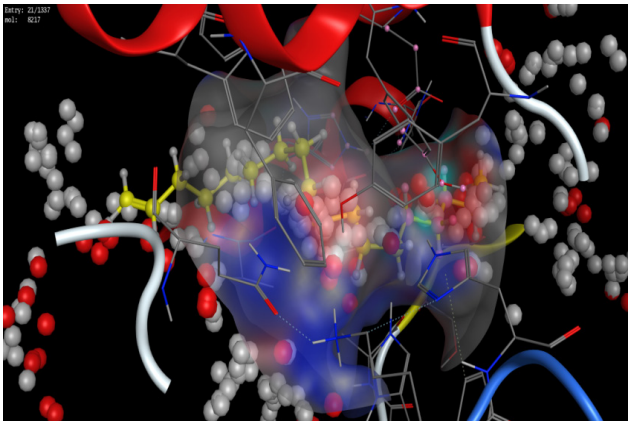

Figure 8(b). 3D interaction between 1-Octadecene and ACE (PDB ID 1UZF)

The compound linoleic acid (CID 5280450) exhibits an H-donor interaction with ASP 453 at a distance of 2.88 Å, accompanied by an energy of -4.0 kcal/mol. Additionally, it demonstrates an H-pi interaction with HIS 387, with a distance of 4.02 Å and an energy of 1.2 kcal/mol, as depicted in Figures 9(a) and 9(b). Categorized as a polyunsaturated fatty acid (PUFA), linoleic acid is prominently found in vegetable and seed oils, and plays a pivotal role as a primary supplier of dietary PUFAs in modern human dietary practices. Functioning as an omega-6 fatty acid, linoleic acid (LA) holds a crucial position as one of the two necessary fatty acids essential for maintaining human physiological health. It serves as a foundational element for the synthesis of various indispensable compounds within the human body. Its prominence is especially noteworthy in human tissue constitution, solidifying its status as an indispensable fatty acid. The documented issue of insufficient intake of essential fatty acids among adults has persisted over an extended span.

The physiological effects of LA on both animal and human systems have been subject to thorough investigation. Maintaining a balanced and evolutionarily aligned intake of LA has been linked to reduced vulnerability to a range of conditions, encompassing atherosclerosis and hypercholesterolemia. Additionally, when coupled with supplementation of omega-3 fatty acids, it has shown potential to alleviate chronic health issues like headaches and others [51].

A study published in the journal 'Hypertension' underscores that dietary intake of linoleic acid could potentially contribute to the prevention and management of adverse blood pressure levels within general populations [52]. The International Study of Macro-Micronutrients and Blood Pressure encompasses a cross-sectional epidemiological analysis involving 4680 men and women aged 40 to 59, drawn from 17 population samples across The People's republic of China, Japan, the United Kingdom and the United States. Employing diverse models to account for potential confounding factors, be they dietary or other, the study's linear regression analyses indicate a statistically non-significant inverse correlation between linoleic acid intake (expressed as a percentage of kilocalories) and systolic, as well as diastolic, blood pressure levels across all participants [52]. However, a more pronounced relationship becomes evident when focusing on 2238 individuals not subject to specific interventions (those not following specialized diets, refraining from nutritional supplements, lacking diagnosed cardiovascular diseases or diabetes, and not using medication for hypertension, cardiovascular diseases, or diabetes). After adjusting for fourteen variables, the estimated differences in systolic and diastolic blood pressure associated with a 2-standard deviation increase in linoleic acid intake (equivalent to 3.77% kcal) amounted to 1.42/0.91 mm Hg (with p-values exceeding 0.05 for both), emphasizing the stronger association among no intervened participants [52]. Deeper investigations are needed to understand and establish a clear relation between linoleic acid and hypertension.

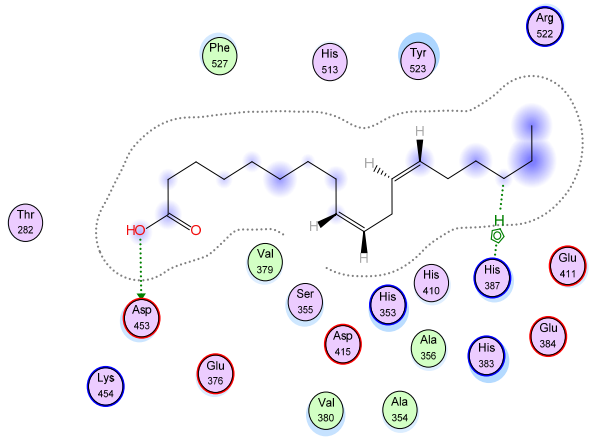

Figure 9(a). 2D interaction between linoleic acid and ACE (PDB ID 1UZF)

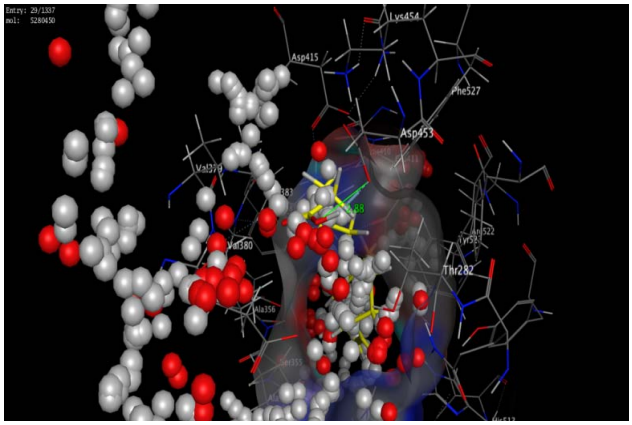

Figure 9(b). 3D interaction between linoleic acid and ACE (PDB ID 1UZF)

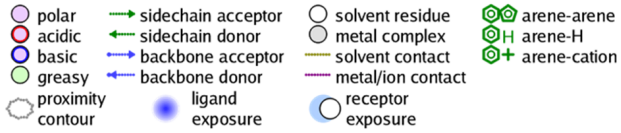

Figure 10. 2D diagrams legend

CONCLUSION

Many conducted studies show the therapeutic effect of *Zygophyllum sp* and its medicinal properties. In the present *in-silico* study, the molecular docking results suggest that several natural molecules from *Zygophyllum sp*. have higher affinity and better interaction with ACE than known inhibitors and may be developed into antihypertensive drugs, especially since they mostly respect Lipinski's rules. Myristic acid has the best score among all tested compounds, while several other compounds also show promising results. Alongside interesting results, these findings confirm the very probable effect of linoleic acid from *Zygophyllum sp*. as an antihypertensive molecule in accordance with previous studies and in accordance to the importance of the molecule. The present study highlights the folk use of *Zygophyllum sp* as an antihypertensive. These findings may provide a basis for further research into the potential therapeutic use of these natural molecules as ACE inhibitors.

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REFERENCES

1. *WHO*; 2023. [https://www.who.int/news-room/fact-sheets/detail/hypertension]
2. Kitt J, Fox R, Tucker KL, McManus RJ. New approaches in hypertension management: a Review of current and developing technologies and their potential impact on hypertension care. *Curr Hypertens Rep.* 2019;21(6):44.
3. Ott C, Schmieder RE. Diagnosis and treatment of arterial hypertension 2021. *Kidney Int.* 2022;101(1):36-46.
4. Khalil H, Zeltser R. Antihypertensive medications. In: *StatPearls. Treasure Island* (FL): StatPearls Publishing; 2023. [http://www.ncbi.nlm.nih.gov/books/NBK554579/]
5. Tedla YG, Bautista LE. Drug side effect symptoms and adherence to antihypertensive medication. *Am J Hypertens.* 2016;29(6):772-9.
6. Verma T, Sinha M, Bansal N, Yadav SR, Shah K, Chauhan NS. Plants used as antihypertensive. *Nat Prod Bioprospect.* 2021;11(2):155-84.
7. Bhuyan BJ, Mugesh G. Angiotensin converting enzyme inhibitors in the treatment of hypertension. *Curr Sci.* 2011;101(7):881-7.
8. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation.* 1998;97(14):1411-20.
9. Hilleman DE. Role of angiotensin-converting-enzyme inhibitors in the treatment of hypertension. *Am J Health-Syst Pharm.* 2000;1 (57 suppl_1):S8-11.
10. Cui W, Aouidate A, Wang S, Yu Q, Li Y, Yuan S. Discovering anti-cancer drugs via computational methods. *Front Pharmacol.* 2020;11:733.
11. Cox PB, Gupta R. Contemporary computational applications and tools in drug discovery. ACS Med Chem Lett. 2022;13(7):1016-29.
12. Zhang Y, Luo M, Wu P, Wu S, Lee TY, Bai C. Application of computational biology and artificial intelligence in drug design. *Int J Mol Sci.* 2022;23(21):13568.
13. Min KA, Zhang X, Yu J yu, Rosania GR. Computational approaches to analyse and predict small molecule transport and distribution at cellular and subcellular levels. *Biopharm Drug Dispos.* 2014;35(1):15-32.
14. Yosri M, Elaasser MM, Abdel-Aziz MM, Hassan MM, Alqhtani AH, Al-Gabri N, et al. Determination of therapeutic and safety effects of Zygophyllum coccineum extract in induced inflammation in rats. *BioMed Res Int.* 2022;18:1-17.
15. Mohammedi Z. Phytochemical, antidiabetic and therapeutic properties of Zygophyllum. *Herb Med J.* 2021;5(4):163-77.
16. Rachid A, Rabah D, Farid L, Zohra SF, Houcine B, Nacéra B. Ethnopharmacological survey of medicinal plants used in the traditional treatment of diabetes mellitus in the North Western and South Western Algeria. *J Med Plants Res.* 2012;6(10):97-103.
17. Zygophyllum L. WFO; 2023. [*http://worldfloraonline.org/taxon/wfo-4000041345*].
18. Akhgar MR, Rajaei P, Poshteshirani F. Composition of the essential oil of Zygophyllum eurypterum from Iran. *Chem Nat Compd.* 2015;51(3):577-8.
19. Kchaou M, Salah HB, Mnafgui K, Abdennabi R, Gharsallah N, Elfeki A, et al. Chemical composition and biological activities of Zygophyllum album (L.) Essential oil from Tunisia. *J Agr Sci Tech.* 2016;18:1499-510.
20. Mnafgui K, Kchaou M, Ben Salah H, Hajji R, Khabbabi G, Elfeki A, et al. Essential oil of Zygophyllum album inhibits key-digestive enzymes related to diabetes and hypertension and attenuates symptoms of diarrhea in alloxan-induced diabetic rats. *Pharm Biol.* 2016;54(8):1326-33.
21. Mostafavi H, Vahiddost M, Solimanzadeh R. Chemical composition of essential oil of Zygophyllum fabago L. from North-West Iran. *Int J Herb Med.* 2015;2(6): 34-37.

22. Tigrinekordjani N, Meklati B, Chemat F. Analysis by gas chromatography–mass spectrometry of the essential oil of Zygophyllum album L., an aromatic and medicinal plant growing in Algeria. *Int J Aromatherapy.* 2006;16(3-4):187-91.
23. *PubChem.* [https://pubchem.ncbi.nlm.nih.gov/]
24. *ChemSpider.* [http://www.chemspider.com/]
25. Chemical, Computing Group Inc. *Molecular Operating Environment* (MOE). 1010 Sherbooke St. West, Suite #910. Montreal, QC, Canada. H3A 2R7; 2014.
26. Bernstein KE, Giani JF, Shen XZ, Gonzalez-Villalobos RA. Renal angiotensin-converting enzyme and blood pressure control. *Curr Opin Nephrol Hypertens.* 2014;23(2):106-12.
27. Herman LL, Padala SA, Ahmed I, et al. Angiotensin-Converting Enzyme Inhibitors (ACEI). In: *StatPearls. Treasure Island* (FL): StatPearls Publishing; 2023. [https://www.ncbi.nlm.nih.gov/books/NBK431051/].
28. Ibrahim SL, Jiroutek MR, Holland MA, Sutton BS. Utilization of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in patients diagnosed with diabetes: Analysis from the National Ambulatory Medical Care Survey. *Prev Med Rep.* 2016;3:166-70.
29. Khurana V, Goswami B. Angiotensin converting enzyme (ACE). *Clin Chim Acta.* 2022;524:113-22.
30. RCSB Protein Data. [https://www.rcsb.org/search]
31. Natesh R, Schwager SLU, Sturrock ED, Acharya KR. Crystal structure of the human angiotensin-converting enzyme-lisinopril complex. *Nature.* 2003;421(6922):551-4.
32. Soga S, Shirai H, Kobori M, Hirayama N. Use of amino acid composition to predict ligand-binding sites. *J Chem Inf Model.* 2007;47(2):400-6.
33. Zheng L, Meng J, Jiang K, Lan H, Wang Z, Lin M, et al. Improving protein–ligand docking and screening accuracies by incorporating a scoring function correction term. *Brief Bioinform.* 2022;23(3):1-15.
34. Grinter S, Zou X. Challenges, Applications, and recent advances of protein-ligand docking in structure-based drug design. *Molecules.* 2014;19(7):10150-76.
35. Li J, Fu A, Zhang L. An overview of scoring functions used for protein–ligand interactions in molecular docking. *Interdiscip Sci Comput Life Sci.* 2019;11(2):320-8.
36. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: a review. *Biophys Rev.* 2017;9(2):91-102.
37. Jain AN. Scoring functions for protein-ligand docking. *Curr Protein Pept Sci.* 2006;7(5):407-20.
38. Guedes IA, Pereira FSS, Dardenne LE. Empirical scoring functions for structure-based virtual screening: Applications, critical aspects, and challenges. *Front Pharmacol.* 2018;9:1089.
39. Pason LP, Sotriffer CA. Empirical scoring functions for affinity prediction of protein-ligand complexes. *Mol Inform.* 2016;35(11-12):541-8.
40. Wang Z, Wang X, Kang Y, Zhong H, Shen C, Yao X, et al. Binding affinity and dissociation pathway predictions for a series of USP7 inhibitors with pyrimidinone scaffold by multiple computational methods. *Phys Chem Chem Phys.* 2020;22(10):5487-99.
41. Liu J, Wang R. Classification of current scoring functions *J. Chem. Inf. Model.* 2015;55(3):475-82
42. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem.* 2002;45(12):2615-23.
43. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov Today Technol.* 2004;1(4):337-41.
44. Violeta I, Miroslav R, Biljana A, Aleksandra P. Lipinski's rule of five, famous extensions and famous exceptions. *Chem N.* 2020;3(1):171-81.
45. 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):42717.
46. Arbi B, Bouchentouf S, EL-Shazly M. Investigation of the potential antidiabetic effect of *Zygophyllum sp.* by studying the interaction of its chemical compounds with Alpha-Amylase and DPP-4 enzymes using a molecular docking approach. *CEI.* 2023;19(2):100-8.
47. Ke C, Zhu X, Zhang Y, Shen Y. Metabolomic characterization of hypertension and dyslipidemia. *Metabolomics.* 2018;14(9):117.
48. Anjos PJC, Lima AO, Cunha PS, De Sousa DP, Onofre ASC, Ribeiro TP, et al. Cardiovascular effects induced by linalool in normotensive and hypertensive rats. *Z Naturforsch C J Biosci.* 2013;68(5-6):181-90.
49. Camargo SB, Simões LO, Medeiros CFDA, De Melo Jesus A, Fregoneze JB, Evangelista A, et al. Antihypertensive potential of linalool and linalool complexed with β-cyclodextrin: Effects of subchronic treatment on blood pressure and vascular reactivity. *Biochem Pharmacol.* 2018;151:38-46.
50. Olofsson P, Hultqvist M, Hellgren LI, Holmdahl R. Phytol: A chlorophyll component with anti-inflammatory and metabolic properties. In: Jacob C, Kirsch G, Slusarenko A, Winyard PG, Burkholz T (eds). *Recent advances in redox active plant and microbial products.* Netherlands: Springer; 2014:345-59.
51. Mercola J, D'Adamo CR. Linoleic Acid: A narrative review of the effects of increased intake in the standard American diet and associations with chronic disease. *Nutrients.* 2023;15(14):3129.
52. Miura K, Stamler J, Nakagawa H, Elliott P, Ueshima H, Chan Q, et al. Relationship of dietary linoleic acid to blood pressure: The international study of macro-micronutrients and blood pressure study. *Hypertension.* 2008;52(2):408-14.