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Ascertain of Antihypertensive Bioactive Compounds from Rosemary and Hawthorn; A Molecular Docking Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Blood pressure disorder causes serious diseases in the cardiovascular system such as arterial hypertension. According to the World Health Organization, an estimated 1.13 billion people worldwide have hypertension, and most of them (two-thirds) live in low- and middle-income countries. It is poorly controlled and constitutes one of the leading causes of premature death. In Africa, nearly 40% of adults in many countries have high blood pressure, but most wouldn't even know it. In 2019, Algeria announced that 24% of the population suffers from the arterial hypertension and around 72% of those who were tested positive had not received treatment. Among the processes related to hypertension, the angiotensin converting enzyme I (ACE) plays an important role in the regulation of the blood pressure. The talk about the high potential of the hawthorn and rosemary plants to treat hypertension was so spread in the Algerian culture, which prompted to

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study the molecules of these plants and descript they behavior with the angiotensin-converting enzyme by calculating energy affinity. Using molecular docking approach, identification and evaluation of the inhibitory potential of ACE by selected herbs was attempted. In addition, and in order to identify the most suitable molecules which can be developed to oral drugs considering their adsorption, distribution, metabolism, and excretion (ADME), Lipinski's rules were applied using free SwissADME tool. Our study provides clearer insight interaction properties of known putative inhibitors of ACE such as Caffeic acid, Quercetin, Luteolin, Eugenol, Rosmaquinone, and Rosmaquinone β, which may be developed into drugs after *in-vitro* and *in-vivo* tests and also encourage use of medicinal herbs for treatment of arterial hypertension.

Keywords: Blood pressure; angiotensin-converting enzyme I (PDB ID 1O8A); hawthorn; rosemary; molecular docking; SwissADME.

ABBREVIATIONS

WHO: World Health Organization
ACE: Angiotensin converting enzyme
MOE: Molecular Operating Environment
MOPAC: Molecular Orbital PACkage
AM1: Austin Model 1
PDB: Protein Data Bank
RCSB: Research Collaboratory for Structural Bioinformatics
RMSD: Root mean square deviation
CID: Compound ID
MW: Molecular weight
TPSA: Topological polar surface area
RT: Number of rotatable bonds
HBA: H-bond acceptor
HBD: H-bond donor
MR: Molar refractivity
VdW: Van der Waals
SHRs: Spontaneously hypertensive rats

1. INTRODUCTION

High blood pressure is often referred to as the silent killer, meaning the disease is asymptomatic and leads to complications that can cause death [1]. It is the main risk factor for stroke and an important risk factor for cardiovascular morbidity and mortality, and also the cause of other pathologies such as renal failure, heart failure, arterial aneurysm, aortic dissection, arrhythmia, and dementia [2]. According to the world health organization (WHO), more than 10 million annual deaths are attributable to hypertension, in fact, cardiovascular mortality doubles for each increase of 20/10 mmHg in systolic/diastolic blood pressure [3]. Arterial hypertension disease in sub-Saharan Africa is a problem of immense medical and economic significance because of its high prevalence in urban areas, its late or incomplete detection, the economic problems associated with its treatment, and the consequences of its complications[4]. According to research, a quarter of adults from half of African countries may have high blood pressure in their lifetime [5]. During 2019 year, the Algerian Ministry of Health announced that 23.6% of the population is suffering from high blood pressure disease, which represents more than 8 million people affected, while 71.9% of them don't receive treatment [6]. On the other hand, statistics confirmed that high blood pressure is prevalent at 23.1% for men and 24.1% for women where this percentage reaches 67% for the 60 years age group. Statistical studies also confirmed that 30% of the youth groups had never taken blood pressure tests and 71.9% of those who tested positive had not received definitive treatment [6]. Among the processes related to hypertension, the angiotensin converting enzyme I (ACE) plays an important role in the regulation of blood pressure where ACE promotes the conversion of angiotensin-I into potent and inactive vasoconstrictor angiotensin-II (ACE II), where the inhibition of ACE is considered as a useful therapeutic approach in the treatment of hypertension [7]. The high blood pressure treated by the inhibition of ACE approach using synthetic drugs with antihypertensive effect such as captopril and lisinopril may have certain harmful side effects such as cough, taste disturbances, skin rashes, which could all be intrinsically linked to the synthetic molecules, therefore, the research and development to find a safer, more innovative and economical treatment was necessary to start with the new phase of drug development based on natural herbal medicines in order to get out of the current synthetic method which costs more expensive and requires sophisticated materials in addition to a significant amount of time consumed during the development [7]. Recently, several ethno-pharmacological studies carried out in different regions of the world have shown that hundreds of

herbs are used for the empirical treatment of high blood pressure because they are cheap and available from nature which is the greatest source of remedy in many health problems [8]. Today, herbal remedies can be used alone or with chemicals to treat various illnesses [8]. Algeria enjoys a very diverse climate; plants grow in abundance in coastal, mountainous and also Saharan regions, these plants are potential natural remedies that can be used in curative and preventive treatment [9]. Medicinal plants occupy an important place in traditional Algerian medicine which is widely used in various fields of diseases treatment [10]. Old and recent publications have indeed reported that a large number of medicinal plants are used for the treatment of various diseases [10]. Nowadays, the identification of natural molecules for the treatment of hypertension is based on molecular modeling such as molecular docking [11]. In a simple definition, docking is a molecular modeling technique used to predict how a protein (enzyme) interacts with small molecules (ligands), it shows the ability of a protein (enzyme) and a nucleic acid to interact with small molecules to form a supramolecular complex playing a major role in the dynamics of the protein which enhance or inhibit a biological function [12]. Molecular docking is a growing application in medicinal chemistry [13]. Where the behavior of small molecules in the active sites of the targeted proteins can be described and understood by molecular docking, this method aims to identify the correct poses of ligands in the binding pocket of a protein and to predict the affinity between the ligand and the protein [12]. Docking has gradually become common practice in drug research and design, discovery of new compounds, identification of binding sites or conformations, and even allowed reuse of the drug to treat other diseases [14]. The human immunodeficiency virus (HIV) epidemic around the world has prompted researchers to use cost-effective means to find new HIV therapy. So it was achievable thanks to molecular docking, because bringing a drug to the market can take many years and cost astronomical sums of money around 2 billion dollars. In addition, molecular docking also allows researchers to make accurate predictions of what is happening at the molecular level [14].

In this paper, we study the behavior and interactions of natural molecules from medicinal plants used in the Algerian tradition with ACE enzyme in order to identify potential inhibitors and therefore validate the use of medicinal plants in the Algerian customs. We opted for rosemary (*Rosmarinus Officinalis*) and hawthorn (*Crataegus Oxyacantha*/*laevigata*) after an ethno-pharmacological survey in the Algerian tradition on the best plants with anti-hypertensive power. Grandmothers, herbalists and even some specialists in medicinal plants have been questioned in order to opt for these two widely used plants, but whose anti-hypertensive mechanism action remains sparsely exploited.

2. MATERIALS AND METHODS

Rosemary (*Rosmarinus Officinalis)* is a plant popularly known as rosemary, it belongs to the Lamiaceae family and is native to the Mediterranean [15]. However, this plant is found all over the world [15]. It is a perennial and aromatic plant, in the form of a shrub with branches full of leaves, having a height of up to two meters with green leaves that releases a characteristic fragrance [16].

Hawthorn *(Crataegus laevigata*) is a shrub of the Rosaceae family considered as Euro-Mediterranean species that develops spontaneously [17]. Its shiny green leaves are lobed and its flowers are white or slightly pink, while its fruit is a small red drupe [17]. In Algeria, the plant is known as 'zaârour el barri' it is also observed in the region of Aurès [18].

2.1 Ligand Preparation

Ligands are the molecules which exist in the various extracts of rosemary and hawthorn. The molecules and their structure were collected from the literature related to the studies of the phytochemical composition of the selected plants. Based on studies of Martinez et al [19], Einbond et al [20], Ojulari et al [21], Verma et al [22], Hellenbrand et al [23], Nadim et al [24], and de Souza and collaborators [25], component molecules of the studied plants were collected. The "PubChem" [26] database was consulted in order to download the three-dimensional structure of the main ligands; however the three dimensional structure of two molecules; Delphinidin and Sterol were obtained from the ChemSpider database [27]. The downloaded molecules files were in sdf* format, and converted to .mol* format. The molecular docking study and all steps necessary for the study were done with Molecular Operating Environment software (MOE) which includes other programs [28].

2.2 Energy Ligands Minimization

The docking procedure requires minimization of the ligands energy. The theory of minimizing ligands energy before initiating docking consists in eliminating conflicts between ligand atom's and developing a reasonable starting pose [25]. Using Molecular Orbital PACkage (MOPAC) and Austin Model 1 (AM1) programs included in MOE software the energy of the ligands was minimized [29].

2.3 Database Preparation

Database preparation is the way to add multiple ligands into a single file (*.mol) to prepare all molecules together (energy minimization and docking) and making easy the docking process allowing saving time and getting grouped results.

For the choice of the PDB code of the enzyme (ACE), it has been noticed according to numerous molecular docking published studies on hypertension [30,31] that the most studied PDB code was:1O8A.

The ACE enzyme 3D structure was downloaded from the RCSB Protein Data Bank (Research Collaboratory for Structural Bioinformatics) [32] with a three-dimensional resolution equal to 2.00 Å as shown in Fig. 1 [33].

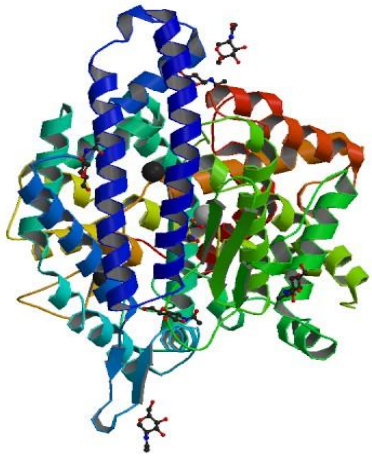

Fig. 1. Three dimensional structure of the enzyme ACE (PDB ID 108A)

2.4 Preparation of Enzyme and Active Site Identification

The enzyme preparation steps consist in removing water molecules and co-crystallization ligands and also maintaining a single reference ligand which is NXA (N-CARBOXYALANINE) as shown in Fig. 2. The active site of an enzyme is the region where specific substrates bind to the enzyme. Using the "site finder" module implanted in MOE software, the largest active site of the enzyme was identified as shown in Figure 3. The Docking procedure has been validated by re-Docking of the reference ligand to obtain an root mean square deviation (RMSD) value less than 2Å [34]. The docking results of the reference ligand are shown in Table 1.

2.5 Docking

After preparation of enzyme and ligands; databases containing ligands from each plant was created and this in the form of database 1 and database 2. In the interface of the MOE, the Compute then Dock commands have been selected in order to dock molecules from database 1 and database 2.

3. RESULTS AND DISCUSSION

Molecular docking gives several results after simulation of all possible poses that ligands can have in the active site of the enzyme. Interest has been accorded to the most important score (lowest complex energy) while results interpretation.

3.1Description of the Interactions between Hawthorn's Compounds and ACE Enzyme (PDB ID 1O8A)

The obtained results from Hawthorn's ligands docking revealed that several ligands have a higher score than the reference ligand. Caffeic acid gives a score of -5,4157 Kcal/mol as shown in figure 4, allowing H-donor interaction to Alanine (354) with a distance of 2,99 Å and energy equal to -3,6 kcal/mol. Two H-acceptor interactions to Histidine (383) with a distance of 2,98 Å and energy of -4,8 kcal/mol, and interaction to Histidine (387) with a distance of 3,07 Å and energy equal to -3,9 kcal/mol are also possible. H-π interaction is also detected to Tyrosine (523) with a distance of 4,54 Å and energy equal to -0,7 kcal/mol.

Hyperoside gives a score of **-**7**.**2448 Kcal/mol. As shown in Fig. 5 two H-donor interactions are observed; one to aspartic acid (415) with a distance of 3.34 Å and energy of -1.2 kcal/mol, and another interaction to Aspartic acid (377) with a distance of 2.99 Å and energy equal to -4.2 kcal/mol. Two H-acceptor interactions to Histidine (353) with a distance of 3.12 Å and

energy of -0.9 kcal/mol, and to Glutamine (281) with a distance of 3.09 Å and energy of -1.7 kcal/mol are also observed respectively. H-acceptor interaction to Lysine (511) is also detected with a distance of 3.41 Å and energy equal to -0.7 kcal/mol.

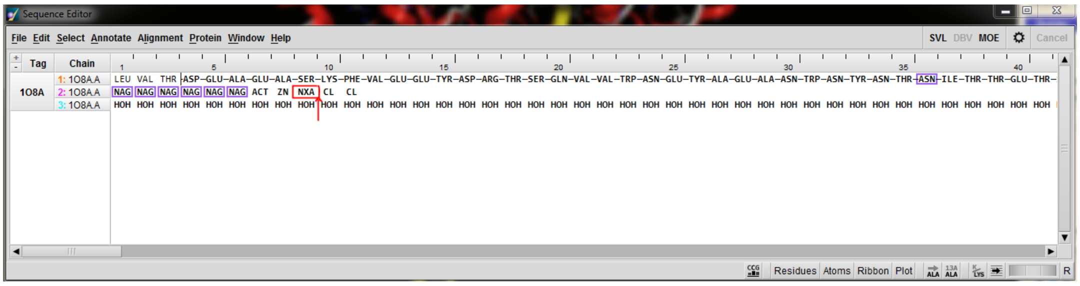

Fig. 2. The NXA reference ligand (personal figure)

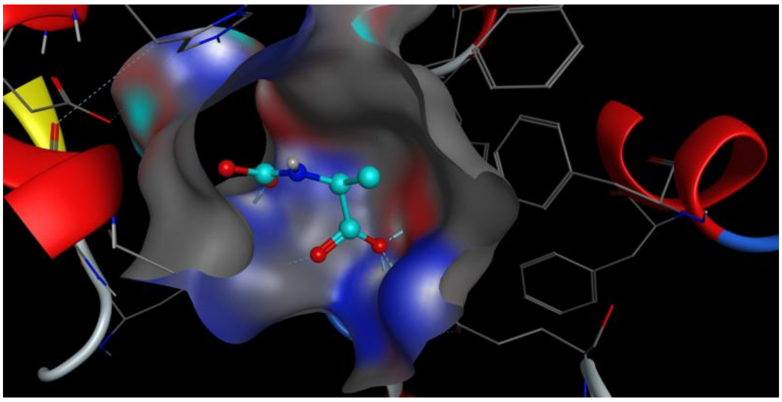

Fig. 3. The active site of the 1O8A enzyme

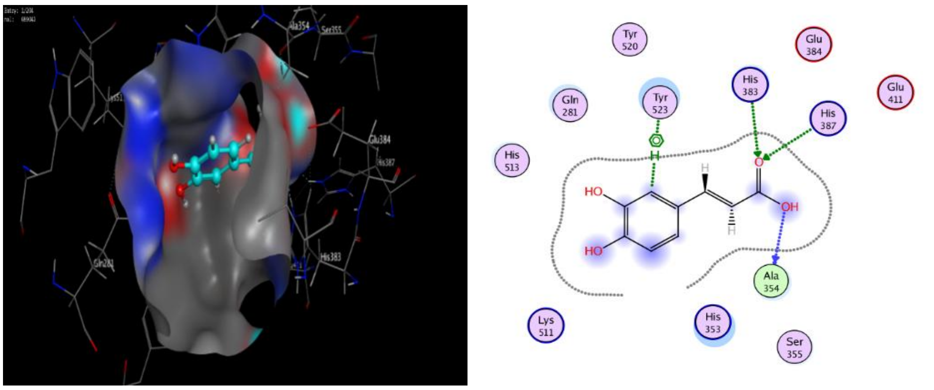

Fig. 4. 2D and 3D interaction between Caffeic acid and ACE (PDB ID 1O8A)

Table 1. The Docking results of the reference ligand

Poses	Compound ID (CID)	Score (Kcal/mol)	RMSD
1	5362119	-4,9633	0,4969
2	5362119	-4,2767	1,5556
3	5362119	-4,0448	3,3434
4	5362119	-3,8217	3,3414
5	5362119	-3,7858	3,7342
6	5362119	-3,7754	1,5957
7	5362119	-3,6140	3,7892
8	5362119	-3,5569	3,5242
9	5362119	-3,3906	2,9709

Table 2. Energy of the complexes formed (enzyme-ligands) for Hawthorn plant

Ligand	Compounds	CID	Score (Kcal/mol)
Reference	Ligand reference	5362119	-4,9633
1	Caffeic acid	689043	**-5,4179**
2	Crategolic acid	73659	-3,5647
3	Oleanolic acid	10494	1,7284
4	Ursolic acid	64945	-4,0350
5	Hyperoside	5281643	**-7,2448**
6	Proanthocyanidins	108065	**-7,2818**
7	Procyanidin B1	11250133	**-7,9996**
8	Quercetin	5280343	**-6,0254**
9	Rutin	5280805	**-9,7356**
10	Sterol	1107	**-5,8395**
11	Tyramine	5610	-4,4642
12	Vitexin-4'rhamnoside	5488886	**-9,0614**

Table 3. Energy of the complexes formed (enzyme-ligands) for the Rosemary plant

Ligand	Compounds	CID	Score (Kcal/mol)
Reference	Ligand reference	5362119	-4,9633
1	Caffeic acid	689043	**-5 ,4238**
2	Carnosic acid	65126	**-6,2413**
3	Chlorogenic acid	1794427	**-6,9464**
4	Oleanolic acid	10494	1,7265
5	Rosmarinic acid	5281792	**-7,0495**
6	Ursolic acid	64945	-4,0365
7	Alpha-pinene	6654	-4,3390
8	Camphor	2537	-4,4508
9	Carnosol	442009	**-6,3811**
10	Eucalyptol	2758	-4,2944
11	Eugenol	3314	**-4,9898**
12	Luteolin	5280445	**-6,0562**
13	Rosmadial	15801061	**-6,2426**
14	Rosmanol	13966122	**-6,0417**
15	Rosmaquinone B	46883407	**-6,5417**
16	Rosmaquinone	14314745	**-6,7913**

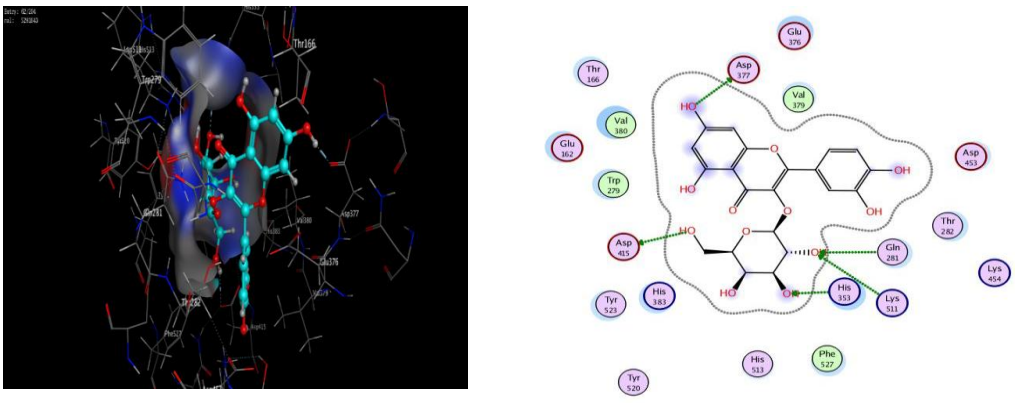

Fig. 5. 2D and 3D interactions between Hyperoside and ACE (PDB ID 1O8A)

Proanthocyanidins give a score of -7.2818 Kcal/mol. As shown in Fig. 6, two H-donor interactions to Glutamic acid (376) with a distance of 3.18 Å and energy equal to -1.5 kcal/mol, and a distance of 3.32 Å and energy equal to -0.6 kcal/mol are possible as well as an

H-donor interaction to Glutamic acid (384) with a distance of 2.62 Å and energy equal to -6.2 kcal/mol.

Procyanidin B1 gives a score of -7.9996 Kcal/mol. In Fig. 7, two H-donor interactions to Glutamic acid (384) and Glutamic acid (376) with a distance of 2.61 Å and energy of -3.4 kcal/mol, and distance of 2.83 Å and energy of -1.0 kcal/mol are observed respectively. One H-donor interaction to Glutamic acid (162) is also observed with a distance of 2.95 Å and energy of -4.5 kcal/mol.

Quercetin gives a score about -6.0254 Kcal/mol. Fig. 8 shows an H-donor interactions to Glutamic acid (384) with a distance of 2.84 Å and an energy of -1.5 kcal/mol, and another H-donor interaction to the Glutamic acid (376) with a distance of 3.30 Å and energy equal to -0.8 kcal/mol.

Rutin gives the best score which is equal to -9.7356 Kcal/mol. Fig. 9 shows two H-donor interactions to Glutamic acid (384) and Histidine (383) with a distance of 2.84 Å and energy of -1.1 kcal/mol, and a distance of 2.94 Å and energy about -1.7 kcal/mol respectively. An H-acceptor interaction to Histidine (387) with a distance of 2.68 Å and energy of -1.1 kcal/mol is also observed.

Sterol gives a score equivalent to -5.8395 Kcal/mol. According to Fig. 10, a single H-acceptor interaction is observed to Histidine (353) with a distance of 2.82 Å and energy of -4.9 kcal/mol.

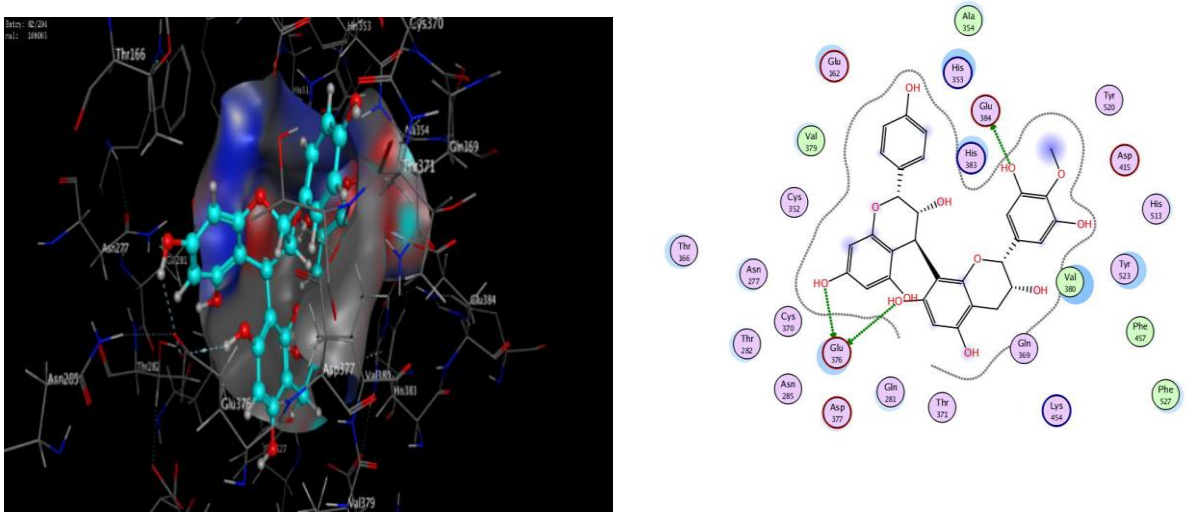

Fig. 6. 2D and 3D interactions between Proanthocyanidins and ACE (PDB ID 1O8A)

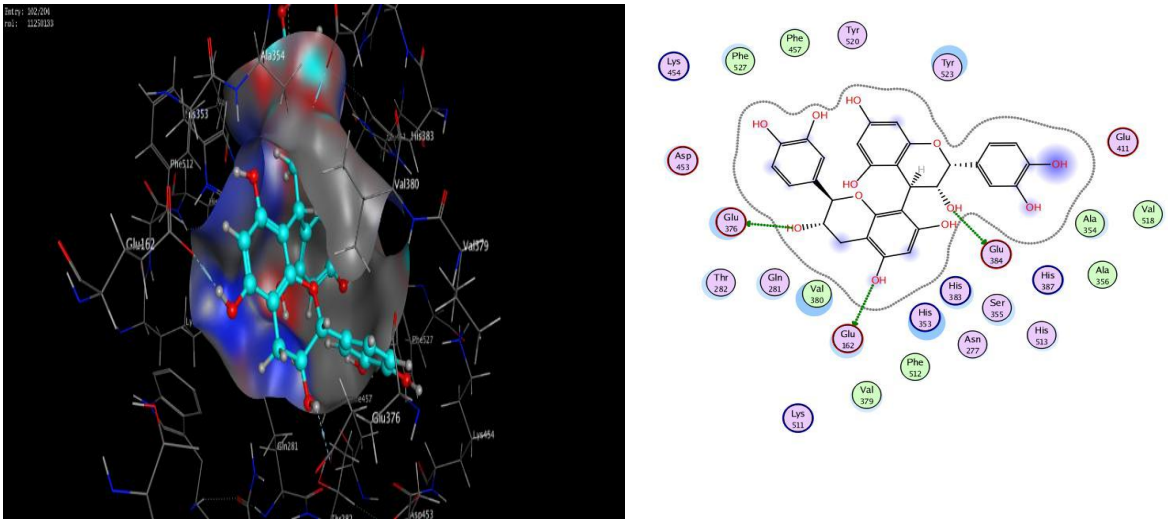

Fig. 7. 2D and 3D Interactions between Procyanidin B1 and ACE (PDB ID 1O8A)

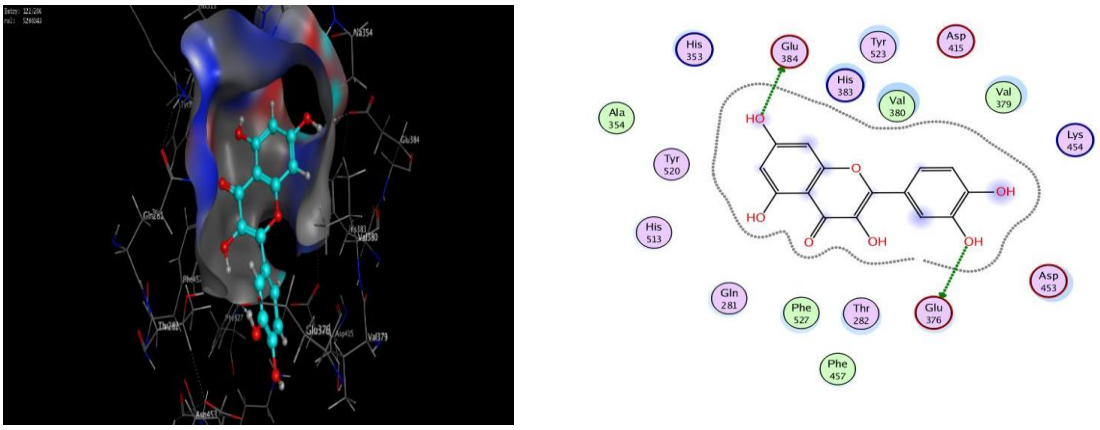

Fig. 8. 2D and 3D Interactions between Quercetin and ACE (PDB ID 1O8A)

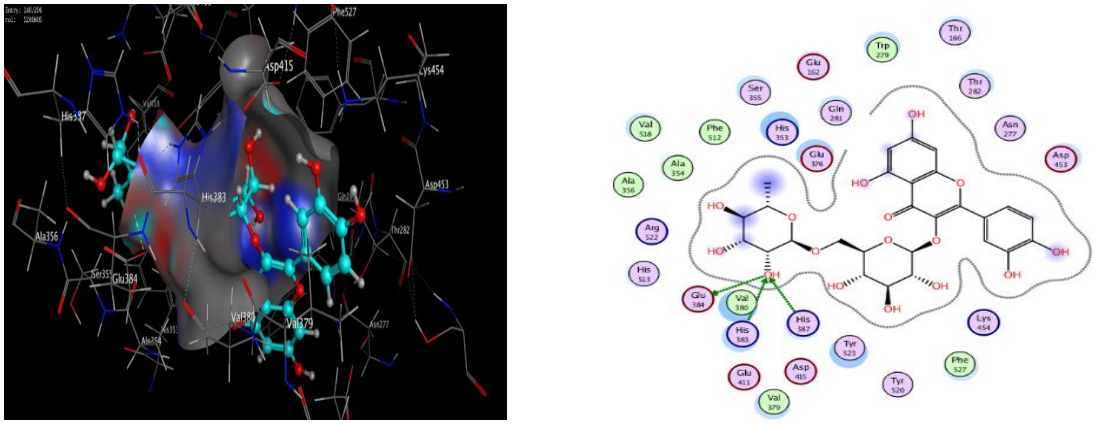

Fig. 9. 2D and 3D Interactions between Rutin and ACE (PDB ID 1O8A)

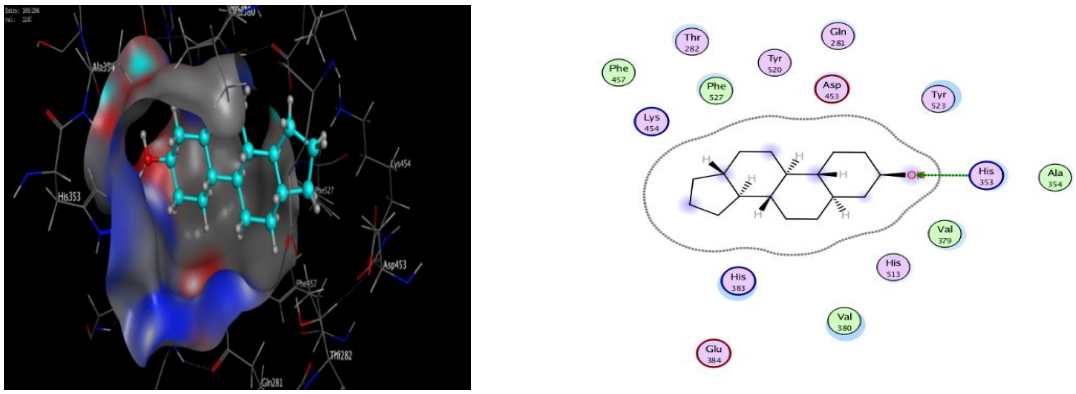

Fig. 10. 2D and 3D Interactions between Sterol and ACE (PDB ID 1O8A)

Vitexin-4′rhamnoside gives a significant score equal to -9.0614 Kcal/mol. According to Fig. 11 three H-donor interactions to Glutamic acid (162), Glutamic acid (411), and Glutamic acid (376) are observed with a distance of 2.87 Å, 3.00 Å and 2.68 Å and energy of -1.4 of kcal/mol, -3.4 kcal/mol, and -3.4 kcal/mol, respectively. Also, two H-acceptor interactions to Asparagine (277) and Alanine (354) are observed with a distance of 2.98 Å, 3.02 Å and energy of -0.1 kcal/mol, -2.3 kcal/mol respectively. H-π interaction to Histidine (383) with a distance of 4.13 Å and energy of -1.9 kcal/mol is also detected.

3.2 Description of the Interactions between Rosemary's Compounds and ACE Enzyme (PDB ID 1O8A)

Caffeic acid gives a score of about -5.4238 Kcal/mol. According to Fig. 12, H-donor interaction to Alanine (354) with a distance of 2.99 Å and energy equal to -3.6 kcal/mol, and H-acceptor interaction to Histidine (383) with a distance of 2.98 Å and energy equal to -4.8 kcal/mol are observed. H-acceptor interaction to Histidine (387) with a distance of 3.07 Å and energy equal to -3.9 kcal/mol is also observed. H-π interaction to Tyrosine (523) with a distance of 4.54 Å and energy equal to -0.7 kcal/mol is also noticed.

Carnosic acid gives a score of -6.2413 Kcal/mol. As shown in Fig. 13, H-donor interaction to Glutamic acid (376) with a distance of 3.23 Å and energy of -0.6 kcal/mol is observed. Another H-acceptor interaction to Glutamine (281) with a distance of 3.13 Å and energy of -1.0 kcal/mol is noticed. H-π interaction to Histidine (383) with a distance of 3.84 Å and energy equal to -1.2 kcal/mol is also observed.

Chlorogenic acid gives a score of -6.9464 Kcal/mol. As shown in Fig. 14 there is only one H-donor interaction to the Glutamic Acid (384) with a distance of 3.48 Å and energy of -0.7 kcal/mol.

Rosmarinic acid gives a score equal to -7.0495 Kcal/mol. Fig. 15 shows two H-donor interactions to Glutamic acid (384); the first with a distance of 3.32 Å and energy of -1.6 kcal/mol, and the second with a distance of 3.42 Å and energy equal to -0.7 kcal/mol. H-acceptor interaction to Lysine (511) with a distance of 3.11 Å and energy of -5.1 kcal/mol is also observed.

Carnosol gives a score of -6.3811 Kcal/mol. As shown in Fig. 16 no interactions made by Carnosol can be observed, only electrostatic interaction may be perceptible.

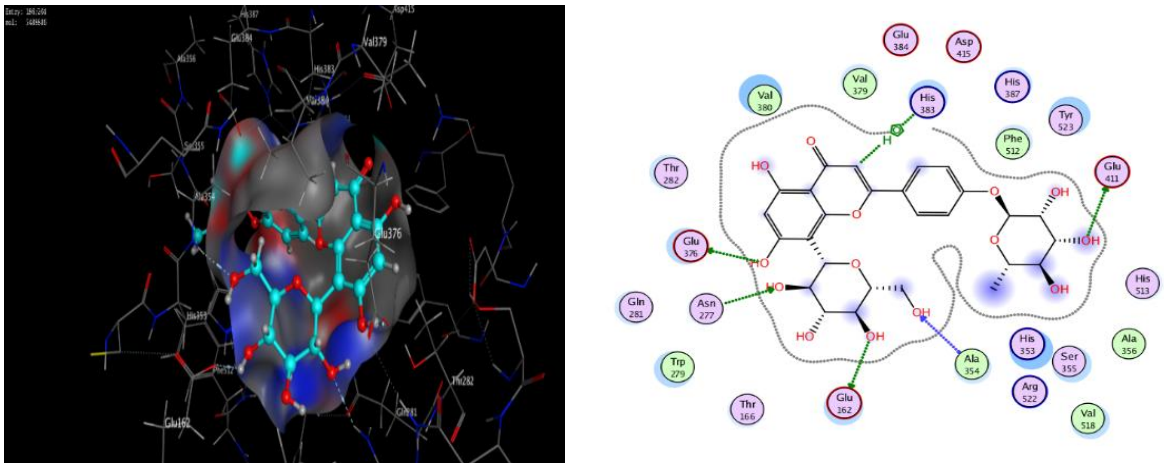

Fig. 11. 2D and 3D Interactions between Vitexin-4'rhamnoside and ACE (PDB ID 1O8A)

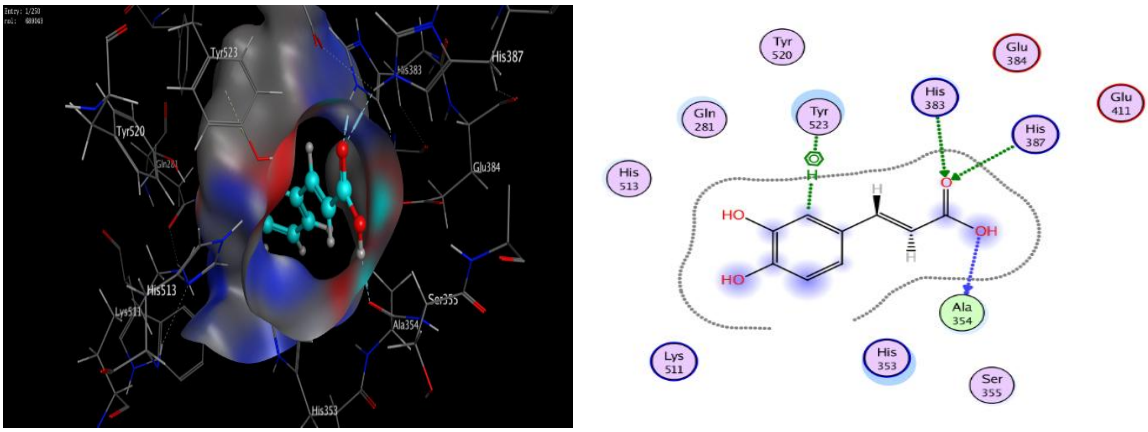

Fig. 12. 2D and 3D Interactions between Caffeic acid and ACE (PDB ID 1O8A)

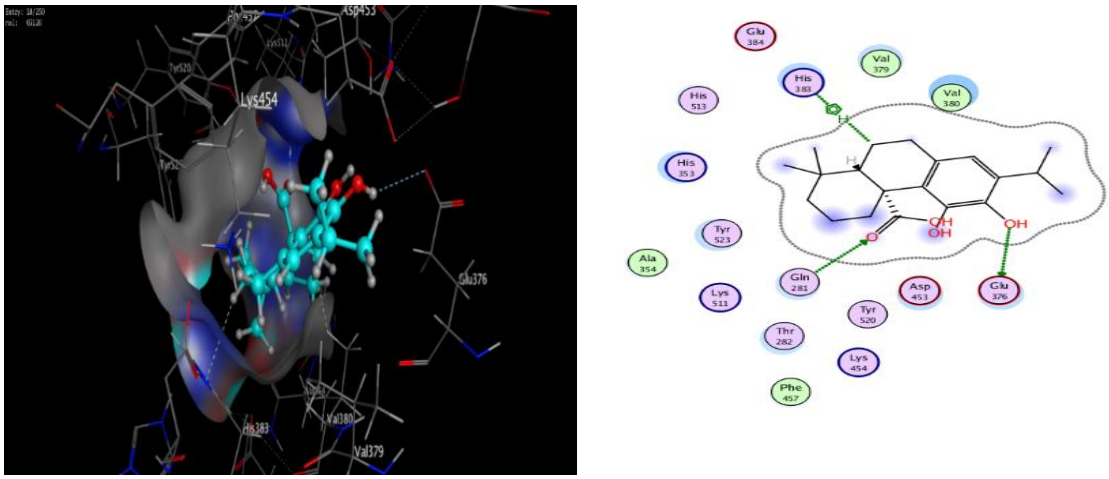

Fig. 13. 2D and 3D Interactions between Carnosic acid and ACE (PDB ID 1O8A)

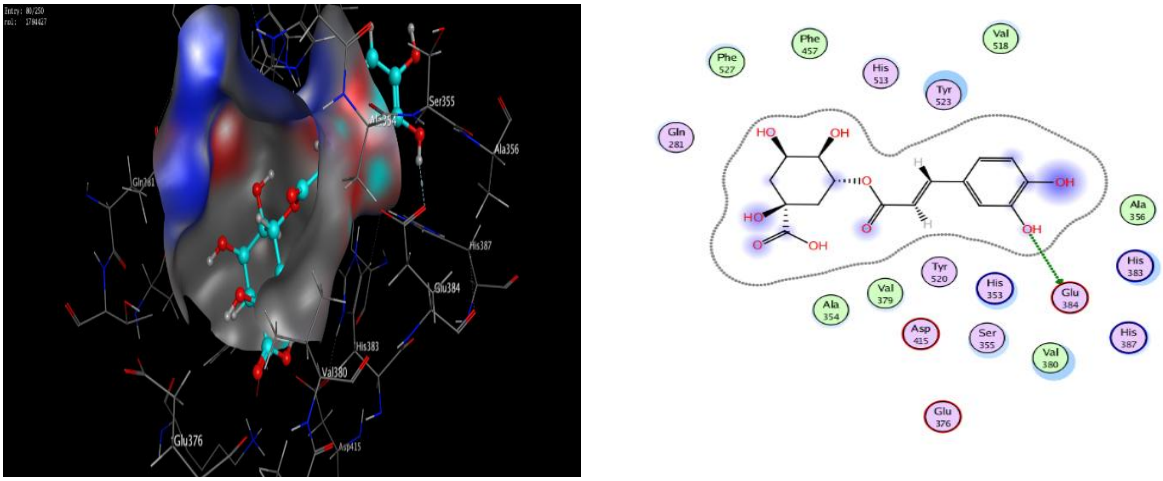

Fig. 14. 2D and 3D Interactions between Chlorogenic acid and ACE (PDB ID 1O8A)

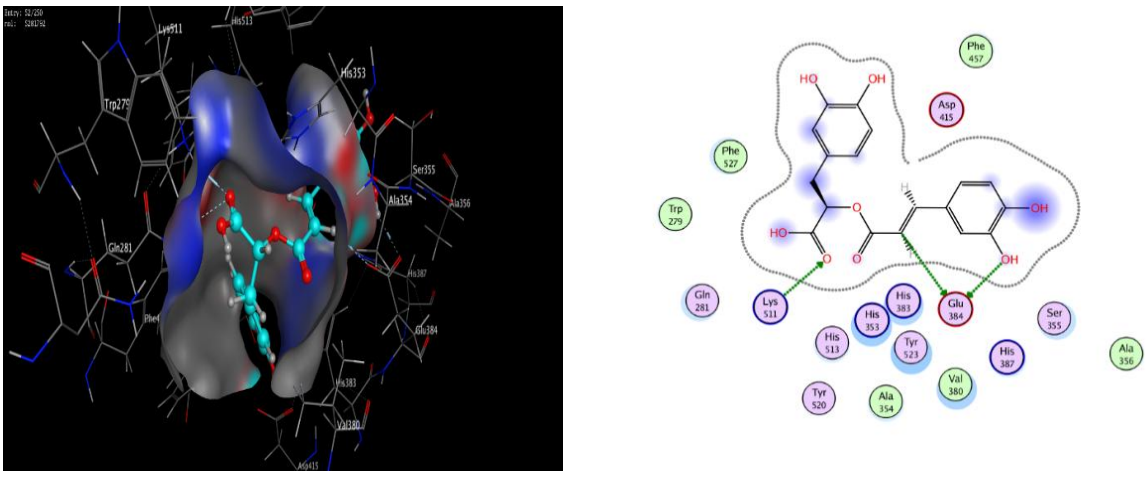

Fig. 15. 2D and 3D Interactions between Rosmarinic acid and ACE (PDB ID 1O8A)

Eugenol gives a score of -4.9898 Kcal/mol without any significant interactions as shown in Fig. 17, but the high score may be accorded to electrostatic interactions (Van der Waals).

Luteolin gives an important score of -6.0562 Kcal/mol. As shown in Fig. 18, H-donor interaction to the Glutamic acid (384) with a distance of 3.48 Å and energy of -0.8 kcal/mol is

observed. Cation-π interaction to Histidine (353) with a distance of 3.38 Å and energy equal to -1.7 kcal/mol is also observed.

Rosmadial gives a score of -6.2426 kcal/mol. According to figure 19, H-donor interaction to the Glutamic acid (376) with a distance of 2.99 Å and energy of -0.7 kcal/mol is noticed. H-acceptor interaction to Glutamine (281) with a distance of 2.91 Å and energy equal to -1.2 kcal/mol is also observed.

Rosmanol gives a score equal to -6.0417 Kcal/mol. According to Fig. 20, no interactions made by Rosmanol are observed, only electrostatic interactions (Van der Waals) may be perceptible.

Rosmaquinone B gives a score of -6.5417 Kcal/mol. Fig. 21 doesn't show any interactions with Rosmaquinone B, but certainly electrostatic interactions are made (Van der Waals).

Rosmaquinone gives a score equal to -6.7913 Kcal / mol. As shown in Fig. 22, only one H-acceptor interaction to glutamine (281) with a distance of 2.95 Å and energy equal to -1.5 kcal / mol is perceptible.

3.3 Drug Likeness Study

Several definitions of Drug-Likeness have been proposed, suggested or inferred in the literature of ligands properties' as filters to consider a compliant molecule to be developed to a drug [35]. According to Dubois [36], some definitions which led to the implementation of new filters can be cited;

- Lipinski [37] describes drug-like molecules as compounds which possess ADME/T properties sufficiently acceptable for oral administration.
- Walters and Murcko in 2002 [38] define a drug-like compound as a molecule which contains functional groups and/or which has physicochemical properties consistent with the majority of known drugs. They review several computer techniques to identify drug-like molecules.
- Muegge [39] proposes that the drug-like criterion is a general descriptor which defines the potential of a small molecule to become a drug.
- Vieth et al [35] say that drug-like properties are seen as those which confer desirable pharmacokinetic and pharmacodynamic properties to the molecule regardless of the biological target.

In the present study, Lipinski's rule as a filter is considered because the use of the plants studied requires oral administration. In addition, Lipinski's "Rule of 5" [37] (for oral administration) is the most widely used. According to Lipinski, 4 parameters concerning the properties of a ligand should be established in order that a molecule can be orally administered;

- Molecular weight ≤ 500 g/mol.
- Hydrophobicity (log P) ≤ 5.
- Number of hydrogen bonds donor (H-Donor) ≤ 5.
- Number of hydrogen bonds acceptor (H-acceptor) ≤ 10.

Lipinski indicates that if at least two of these conditions are not met, the molecule may have low absorption or low permeability. In 2002, Veber and his colleagues [40] supplemented the rule of 5 with two new parameters;

- Topological polar surface area (TPSA) ≤ 140 Å².
- Number of rotatable bonds (RT) ≤ 10

According to Kadam and Roy [41], if a compound fails the Rule of Five, there is a high probability that problems with oral activity will be encountered. However, passing the rule of five is no guarantee that a compound looks like a drug. Solubility is one of the most important properties in drug discovery; low solubility in water can lead to poor absorption and oral bioavailability [42]. Solubility is expressed in log S and log S values superior to −4 are acceptable for a drug [43].

The SwissADME tool is an open access website for calculating physicochemical, pharmacokinetic, drug-like and other parameters related to the molecule intended to be developed to a drug [44].

To study a molecule via the SwissADME tool, a molecule is either drawn then converted into a SMILES code, otherwise, we add the SMILES code of the molecule directly from the PubChem database to the online software for calculating properties. The results obtained by SwissADME are listed in Table 4.

3.4 Discussion

According to table 4, it has been noticed that only 6 molecules passed the drug-likeness filter such

as Caffeic acid, Quercetin, Luteolin, Eugenol, Rosmaquinone, and Rosmaquinone B; although there are many other molecules with higher scores than those mentioned but they haven't compatible physicochemical (drug-likeness) properties to be considered for oral drug development. This observation doesn't prevent molecules that haven't passed the filter from being studied for another form of administration.

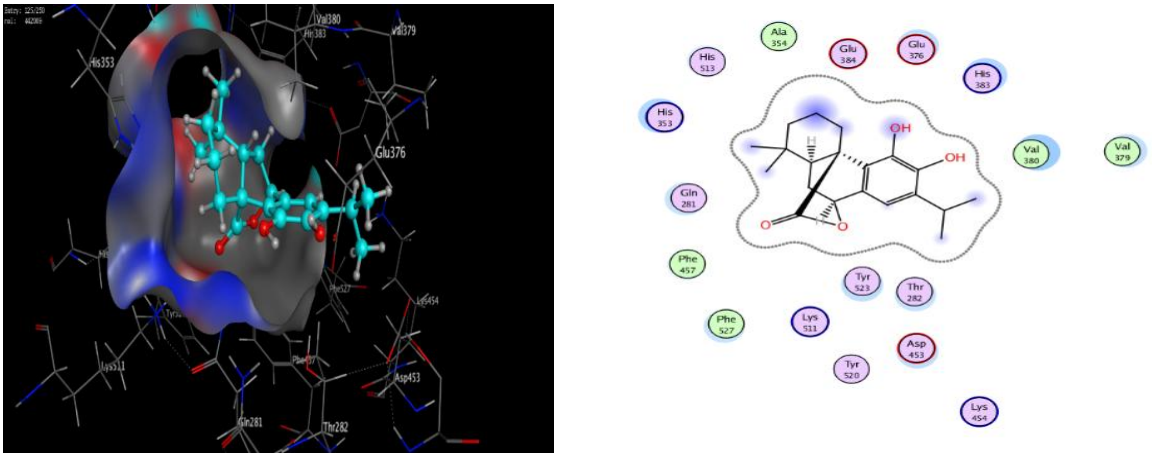

Fig. 16. 2D and 3D Interactions between Carnosol and ACE (PDB ID 1O8A)

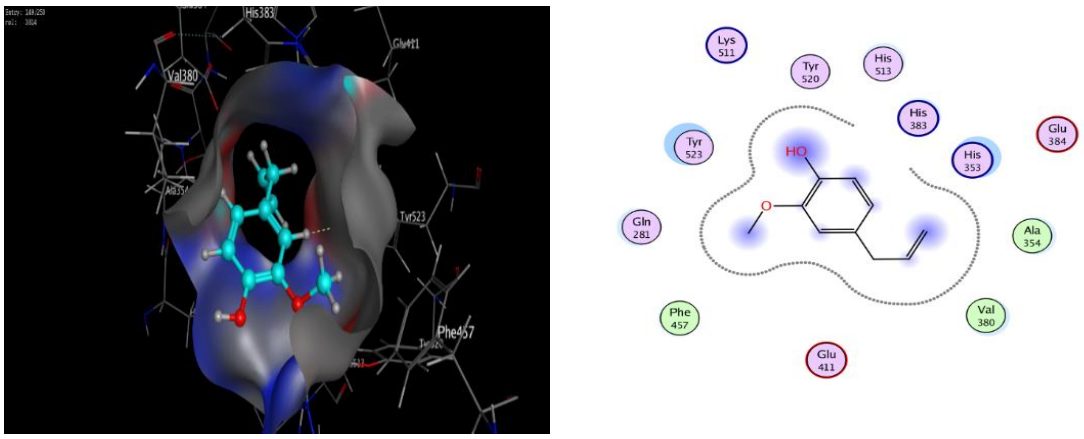

Fig. 17. 2D and 3D Interactions between Eugenol and ACE (PDB ID 1O8A)

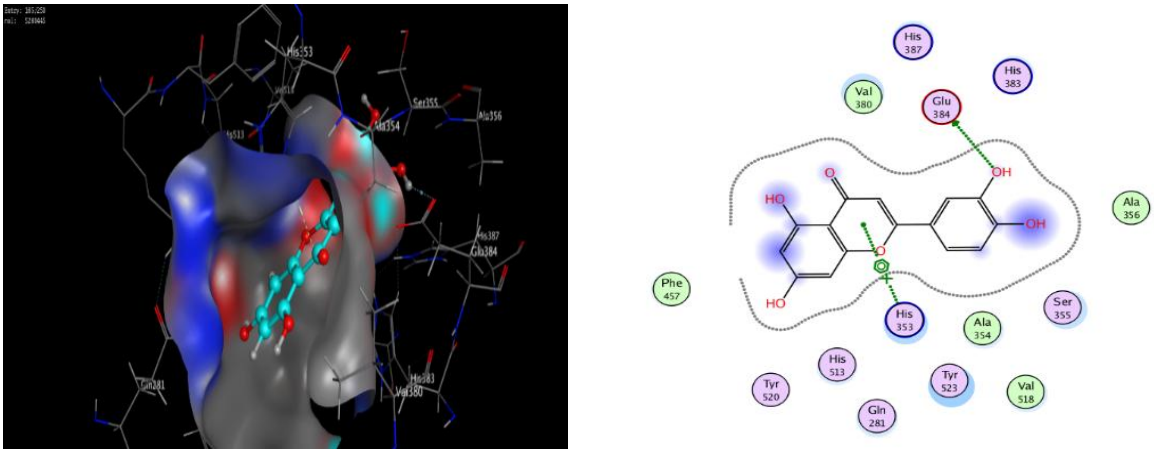

Fig. 18. 2D and 3D Interactions between Luteolin and ACE (PDB ID 1O8A)

Table 4. Physicochemical properties of ligands for drug-likenesses obtained by SwissADME

Properties / Molecules	MW g/mol	Log P	Log S	HBA	HBD	TPSA Å²	RB	MR
Caffeic acid	180,16	0,93	-1,89	4	3	77,76	2	47,16
Hyperoside	464,38	-0,25	-3,04	12	8	210,51	4	110,16
Proanthocyanidins	592,55	1,85	-5,36	12	9	209,76	4	151,18
Procyanidin B1	578,52	1,53	-5,14	12	10	220,76	3	146,71
Quercetin	302,24	1,23	-3,16	7	5	131,36	1	78,03
Rutin	610,52	-1,12	-3,30	16	10	269,43	6	141,38
Sterol	248,40	3,93	-4,60	1	1	20,23	0	76,54
Vitexin-4'rhamnoside	578,52	-0,97	-2,69	14	9	239,97	5	137,57
Carnosic acid	332,43	3,80	-5,03	4	3	77,76	2	95,43
Chlorogenic acid	354,31	-0,38	-1,62	9	6	164,75	5	83,50
Rosmarinic acid	360,31	1,52	-3,44	8	5	144,52	7	91,40
Luteolin	286,24	1,73	-3,71	6	4	111,13	1	76,01
Carnosol	330,42	3,72	-4,77	4	2	66,76	1	92,83
Eugenol	164,20	2,25	-2,46	2	1	29,46	3	49,06
Rosmadial	344,40	3,19	-4,04	5	1	80,67	3	94,14
Rosmanol	346,42	2,88	-4,25	5	3	86,99	1	93,99
Rosmaquinone B	358,43	2,78	-3,61	5	0	69,67	2	95,91
Rosmaquinone	344,40	2,25	-3,25	5	1	80,67	1	91,18

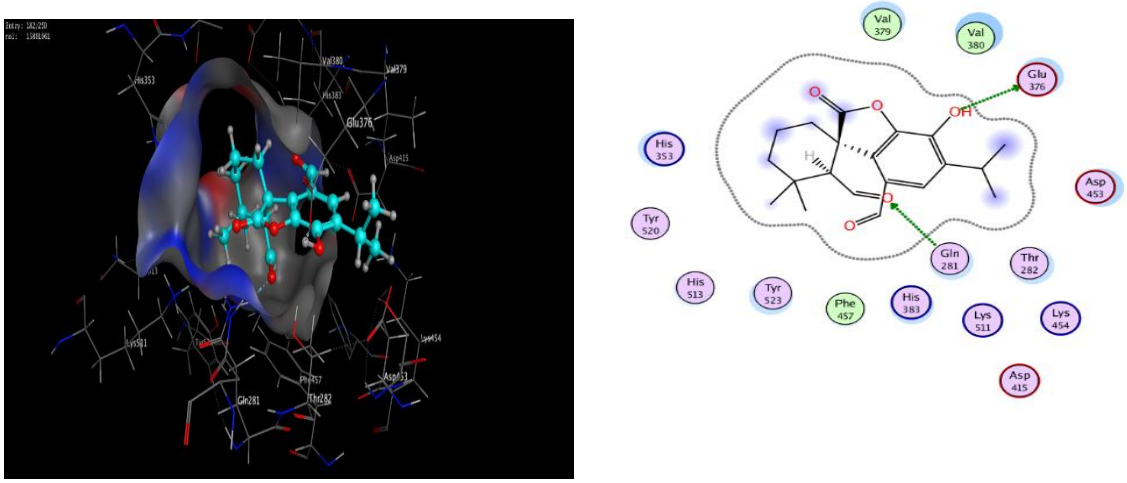

Fig. 19. 2D and 3D Interactions between Rosmadial and ACE (PDB ID 1O8A)

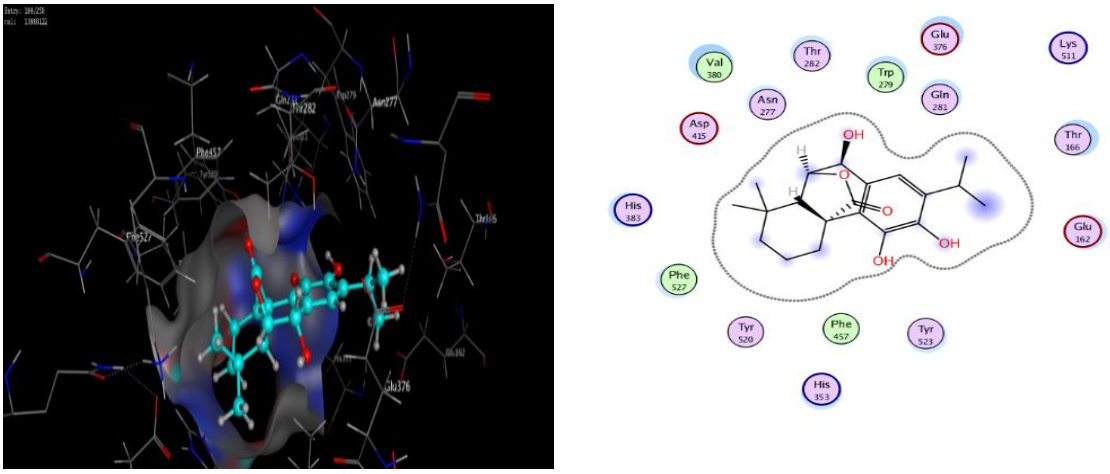

Fig. 20. 2D and 3D Interactions between Rosmanol and ACE (PDB ID 1O8A)

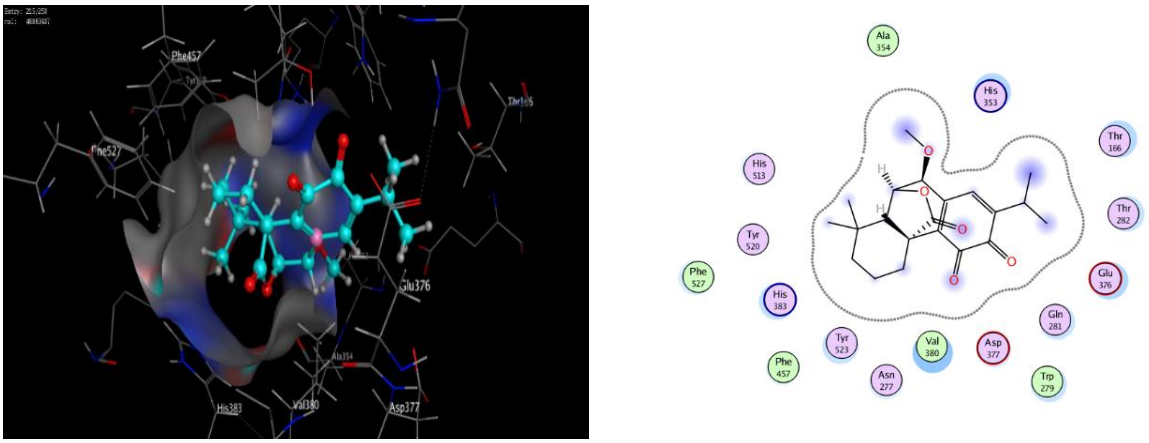

Fig. 21. 2D and 3D Interactions between Rosmaquinone B and ACE (PDB ID 1O8A)

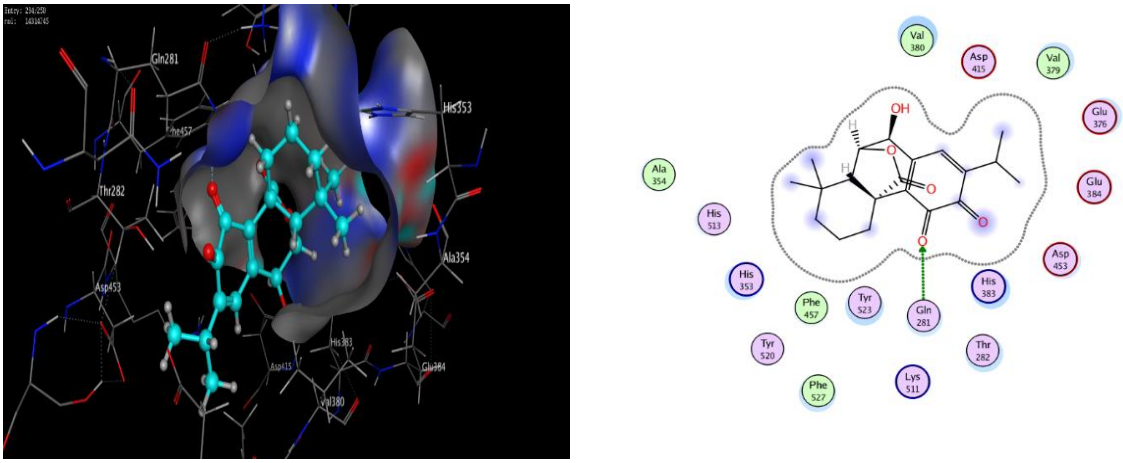

Fig. 22. 2D and 3D Interactions between Rosmaquinone and ACE (PDB ID 1O8A)

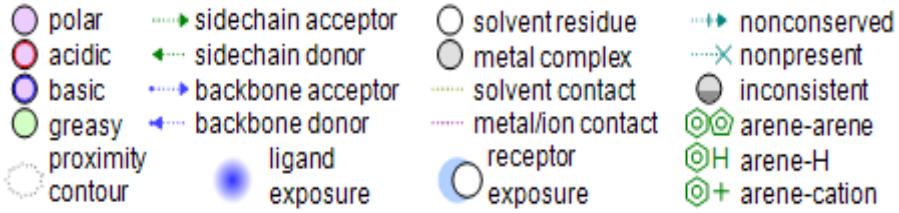

Fig. 23. 2D diagram legend

Enhancing the study with other scientific works to clarify and confirm the importance of these molecules in the treatment of arterial hypertension is important in order to match with our patient's needs as some are diabetic and leukemic and have other serious illnesses. This will allow the prevention of side effects of ~~the~~ synthetic medications.

To date, Caffeic acid has been reported as a potent antihypertensive agent [45], and a good inhibitor of the angiotensin-converting enzyme [46]. Quercetin shows its antihypertensive actions via modification of various factors controlling blood pressure, such as vascular compliance (reciprocal of elastance) and resistance, renin-angiotensin-system via anti-inflammatory, and anti-oxidative abilities [47]. Studies concerning Eugenol, show that it contributes to reducing systemic blood Pressure *in-vivo* via the activation of the TRPV4 (Transient receptor potential cation channel subfamily V member 4) channels in mesenteric artery endothelial cells, leading to vasorelaxation.

Eugenol may be therapeutically useful as an antihypertensive agent [48]. Luteolin has been shown to exhibit antihypertensive activity in many experiments [49]. Ichimura and coworkers [50] had reported that orally administered Luteolin (50 mg/kg), lowered significantly systolic blood pressure in SHRs (spontaneously hypertensive rats). Concerning Rosmaquinone and Rosmaquinone B molecules, no previous studies (main scientific databases) show their probable implication in blood pressure regulations, which make them promising components for hypertension treatment.

4. CONCLUSION

The present study aims to identify natural treatment for hypertension arterial disease using computational methods. Hypertension is known as the silent killer because it shows no symptoms and induces complications that can cause death. It is possible to reduce blood pressure damage in a safe way using natural molecules extracted from medicinal plants and herbs, such as rosemary and hawthorn plants. Via molecular docking approach and scoring function, ligands with higher scores than the referenced molecule were identified by creating a complex giving the lowest energy with enzyme involved in arterial hypertension. Obtained results showed that these molecules have a hypotensive effect. Therefore we proceeded to the oral administration filters using the SwissADME tool in order to determine the appropriate molecules to be developed into a drug orally administrated.

The investigation leads to conclude that these molecules have shown to be the suitable ones to be developed into oral administration drugs:

- The Caffeic acid from the hawthorn plant, with a score of -5, 4179 Kcal/mol, and also found in the rosemary plant, scored -5, 4238 Kcal/mol.
- The Quercetin from the hawthorn plant, with a score of -6, 0254 Kcal/mol.
- The Luteolin from the rosemary plant, with a score of -6, 0562 Kcal/mol.
- The Eugenol from the rosemary plant, with a score of -4, 9898 Kcal/mol.
- The Rosmaquinone from the rosemary plant, with a score of -6, 7913 Kcal/mol.
- The Rosmaquinone β from the rosemary plant, with a score of -6, 5417 Kcal/mol.

The Hawthorn and rosemary plants confirmed the existence of the antihypertension via contained molecules, which means that they can be considered as potential inhibitors of the angiotensin converting enzyme (ACE) to treat high blood pressure. It is highly recommended the benefit of these molecules in future studies for the treatment of hypertension and further *in-vitro* and *in-vivo* experiments.

NOTE

The study highlights the efficacy of "herbal medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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