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In-Silico investigation of drug delivery efficacy, Chemical Reactivity Properties and Bioactivity Scores in the Treatment of Arterial Hypertension

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Abstract

In the present work carried out a comparative study of the anti-hypertensive properties of five natural molecules: S-Allycysteine (contained in garlic), Capsaicin (contained in chilli pepper), Gingerol (contained in ginger), Piperidine and Geraniol (contained in bay leaves). By using quantum chemical approaches as density functional theory (DFT) and molecular docking strategies through ADMET analysis, drug-like properties predictions have been provided and characterized. Ananalysis of the various results obtained leads to the following conclusions that all of these molecules can be used in clinical trials because they are pharmacologically very active. Overall, all of the five compounds studied had a strong inhibitory effect on the angiotensin II receptor type (ATR1), as protein responsible for arterial hypertension. The complexes formed between each of the molecules and ATR1 were stabilised by Van der Waals (VdW) forces and the hydrogen bonds have been established between the inhibitors and the amino acids sites. Moreover, Piperidine, Geraniol and S-Allycysteine stand out the most biologically active. They have the best antihypertensive properties of the five molecules. Definitively, garlic and bay leaves appears to be the best choice for treating high blood pressure.

Keywords: Arterial Hypertension, B3LYP, ATR1, ADMET, Molecular Docking.

Introduction

Arterial hypertension is a crucial public health problem that has been on the rise for the last few decades[1]. It is generally defined as the force exerted by the blood flow on the artery walls. For a standardised clinical blood pressure, arterial hypertension is defined as 140/90mm Hg and above, while for patients with diabetes it is defined as 130/80 mm Hg and above[2]. According to the World Health Organisation (WHO), of the 57 million deaths worldwide in 2008, 63% were caused by non-communicable diseases[3]. Projections indicate that the annual number of deaths attributable to cardiovascular disease, for example, is set to rise from 17 million in 2008 to 25 million in 2030. In reality, behavioural risk factors, such as smoking, physical inactivity, poor diet and alcohol abuse, are responsible for around 80% of coronary heart disease and cerebrovascular disease[4]. In Africa, particular attention is paid to infectious diseases, while arterial hypertension deserves more sustained attention. In several African countries, almost half the adult population suffers from this condition[5]. Unrecognised or poorly treated, it can cause serious damage to the arteries of the brain, heart and kidneys, leading to serious complications such as stroke, myocardial infarction or heart attack, heart failure and kidney failure. In many cases, these complications lead to death or early disability[6]. However, several epidemiological and clinical studies confirm the undeniable role of regular consumption of fruit, spices and vegetables in reducing the risk of cancer and chronic diseases such as cardiovascular disease and hypertension. This finding seems all the more important given that the prevention of these pathologies has become an extremely interesting strategy. These foods play a crucial role in the pharmaceutical industry and in a variety of everyday uses, as they possess virtues that are attributed, among other things, to the nutrients or phytonutrients that make them up, including garlic, chilli, ginger and bay leaves[7,8]. Their protective effect is due to their ability to neutralise free radicals[9]. In fact, the chilli pepper belongs to the Capsicum genus and is one of the most widely consumed vegetables in the world[10]. It contains a large number of phytochemical compounds that may contribute to its antioxidant and antihypertensive activity[11,12]. It is a rich source of phenolic compounds, capsaicinoids, carotenoids, chlorophylls and vitamins (A, B1, B2, B3, C and E)[13,14]. Studies of the phytochemical sreening of ginger (rhizome Zingiber offcinale), published in the literature, have shown the presence of polyphenols (gingerol, paradol, shogoal, zingerone), terpenes (zingiberene, geranial, curcumene, neral), as well as flavonoids and phenolic acids[15]. Numerous studies (*in vitro* and *in vivo*) have confirmed thebeneficial effects of ginger as an anti-nauseant, anti-inflammatory, antioxidant, antimicrobial, anticancer, antidiabetic, antihypertensive and respiratory agent[16].

Experimental studies published in the literature have shown that garlic has a varied chemical composition. It contains special molecules: sulphur compounds such as thiosulfinates, the most important of which are allicin, ajoenes, vinyldithiins and sulphides. They give garlic its characteristic smell and flavour. It also contains many other substances, in particular fructosans. It is also rich in vitamins and minerals. It is to these that garlic owes its anti-cancer, anti-diabetic and anti-hypertensive properties[17].

Phytochemical screening of bay leaves revealed that they contain cineol, piperidine, eugenol, geraniol and terpineol. These molecules are thought to have anti-inflammatory, antioxidant, antimicrobial, anticancer, antihypertensive and antidiabetic properties[18].

It should be noted that, to our knowledge, no theoretical or experimental work has compared the anti-hypertensive powers of S-Allycysteine (found in garlic), Capsaicin (found in chilli peppers), Gingerol (found in ginger), Piperidine and Geraniol (found in bay leaves) (seen in Figure 1).

The aim of the present work is to determine the best antihypertensive of these compounds using theoretical chemistry methods. The reactivities of the various compounds will be compared with each other, in order to deduce which of the three substances is most active against arterial hypertension.

To achieve this objective, electronic parameters, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties and interaction energies between the Angiotensive II type 1 receptor and the various compounds were calculated. The results were used to rank the anti-hypertensive properties of each compound.

The chemical systems studied were: S-Allycysteine, Capsaicin, Gingerol, Piperidine, Geraniol and Receptor type 1 (ATR1).

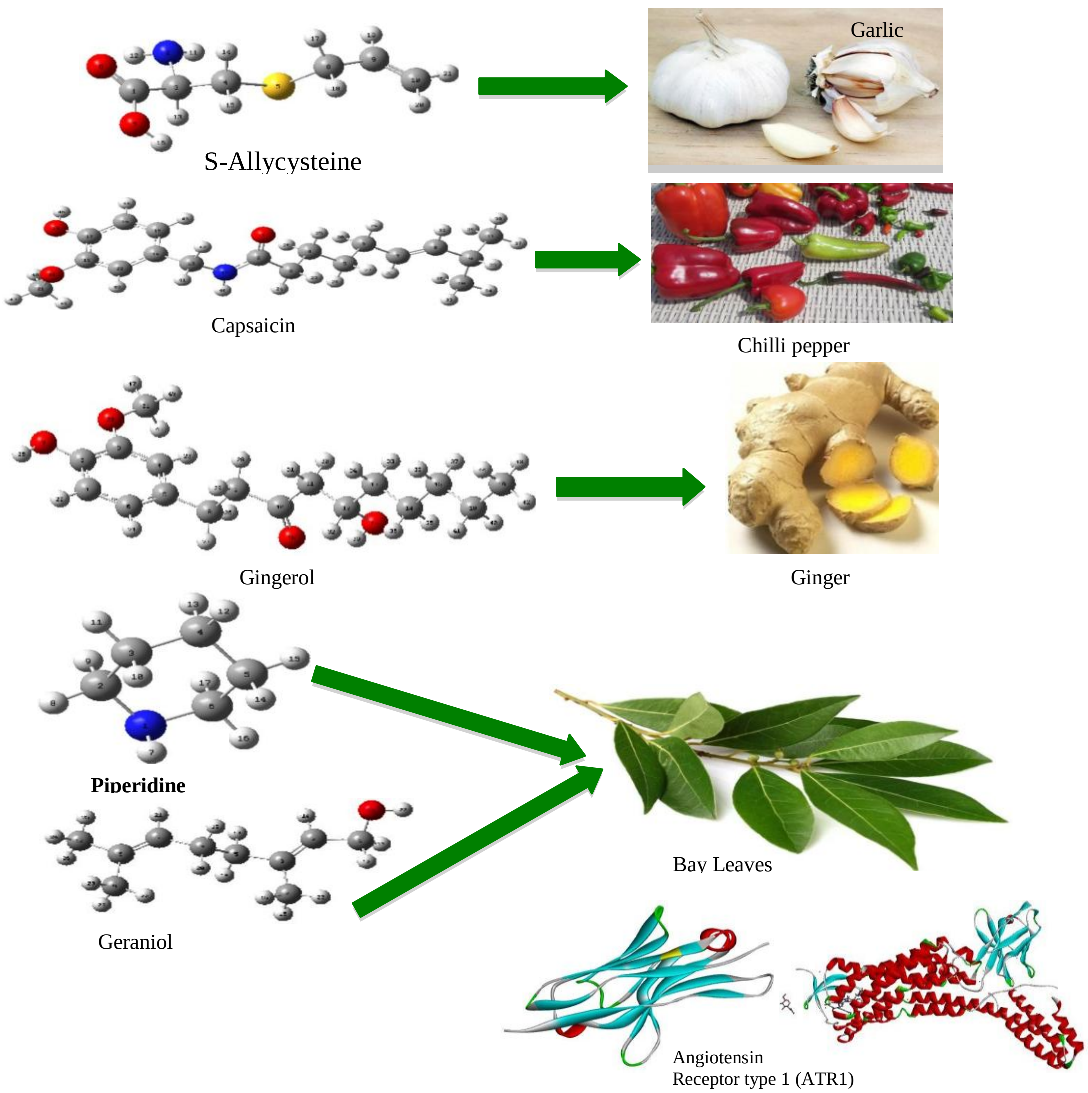

Figure-1: Anti-hypertensives molecules with receptor type 1.

Materials and Methods

The Quantum chemical methods have been demonstrated as predicting tool for examining inhibition of anti-hypertensives molecules. For S-Allycysteine, Capsaicin, Gingerol, Piperidine, Geraniol and Angiotensin II receptor type 1 (ATR1), the parameters calculated were:

Electronic parameters: i. the Energy gap$\Delta Gap = E_{LUMO} - E_{HOMO}$, which is lower than the higher antihypertensive power of the molecule. ii. the Dipole moment (D), which reflects the greater or lesser polarity of a molecule. iii. the Hardness (η), which expresses a molecule's resistance to changes in its electronnumber or to charge transfer[18]. The greater the hardness, the less reactive the molecule:$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$ iv. the Chemical potential (μ), which measures the tendency of a chemical species toattract electrons[19]: $\mu = \frac{1}{2(E_{LUMO} + E_{HOMO})}$ v. the Electrophilic index (ω), which is the stabilization energy of a molecule saturated by electrons from its surroundings[20]: $\omega = \frac{\chi^2}{2\eta}$ vi. the Charge transfer index (ΔNmax). A positive value of ΔNmax indicatesthat our system is acting as an electron acceptor, whereas a negative value indicates that the charge comes from the system or that our system is acting as an electron donor[21]: $\Delta N_{max} = -\frac{\mu}{\eta}$

All the geometric parameters calculations are carried out under the wheel of Gaussian09W software package[22]. The structure visualization were done with Gauss View. 5.0.8 package, with density functional theory (DFT), B3LYP under the quantum chemical basis set 6-311G (d,P)[23-26]. Parameters of pharmacokinetic properties (Absorption, Distribution, Metabolism and Excretion) and physico-chemical characteristics those are essential in the identification of new treatments. The Swiss ADME online tool was used to examine the weights, molar refractive index, solubility, bioavailability and bioavailability radar maps of selected bioactive substances[27]. Docking was used to predict ligand-protein (target) interactions. The values obtained for interaction energies, docking score, PLP Score and H-bond Score were obtained using the Gold program[28].

Results and Discussion

Molecular Electronic Properties of Anti-hypertensive Compounds: In this section, Tables-1 and 2 show the calculated values of some electronic parameters of S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol, in the gas phase and in water respectively.

Table-1: Calculated values (in eV) of some electronic parameters in gas phase at B3LYP/6-311G(d,P) level of theory.

Indices	Target Molecules				
	S-Allycysteine	Capsaicin	Gingerol	Piperidine	Geraniol
E_{LUMO}	-0.019	-0.010	-0.033	0.038	0.008
E_{HOMO}	-0.239	-0.221	-0.210	-0.215	-0.231
Gap	0.220	0.211	0.177	0.253	0.239
η	-0.110	-0.105	-0.88	-0.126	-0.118
μ	-3.87	-4.54	-4.13	-5.68	-6.66
ω	93.68	58.05	70.48	295.70	183.30
ΔNmax	-41.22	-34.23	-34.13	-64.54	-88.80
D	2.80	1.10	1.67	5.77	3.62

Table-2: Calculated values (in eV) of some electronic parameters in the aqueous phase at B3LYP/6-311G(d,P) level of theory.

Indices	Target Molecules				
	S-Allycysteine	Capsaicin	Gingerol	Piperidine	Geraniol
E_{LUMO}	-0.018	-0.014	-0.031	0.043	0.005
E_{HOMO}	-0.238	-0.226	-0.213	-0.220	-0.236
Gap	0.220	0.212	0.182	0.263	0.231
η	-0.128	-0.120	-0.122	-0.131	-0.115
μ	-3.90	-4.16	-4.09	-3.81	-4.34
ω	72.10	59.41	54.40	81.89	68.55
ΔNmax	-34.66	-29.08	-30.42	-37.73	-46.33
D	3.75	1.48	2.21	4.97	4.79

Based on these series of results, we can make the following observations: i. The values calculated at approximation level B3LYP/6-311G (d,p) rank in order: *Gap Piperidine > Gap Geraniol > Gap S-Allycysteine> Gap Capsaicin> Gap Gingerol*. The highest Gap values (HOMO-LUMO) were obtained for Piperidine, Geraniol and S-Allycysteine respectively. These results indicate that Piperidine followed by Geraniol and S-Allycysteine are the most reactive of the five molecules. ii. The hardness values (η) ranked in the order *η Gingerol > η Capsaicin > η S- Allycysteine> η Geraniol > η Piperidin*. These results indicate that Piperidin, Geraniol and S-Allycysteine have the lowest hardness values. As a result, Piperidine is the softest of the five molecules, followed by Geraniol and S-Allycysteine. Their electron density could therefore be easily modified by that of Gingerol and Capsaicin. We deduce that Piperidine followed by Geraniol and S-Allycysteine are the most reactive of the five molecules. iii. Calculations of the electrophilic index (ω) gave Piperidine followed by Geraniol and S-Allycysteine as the most electrophilic and therefore having the highest reactivities. iv. The negative values of the charge transfer index ΔN_{max}, indicate that S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol are all electron donor molecules. The lowest values for this index were obtained by Piperidine, Geraniol and S-Allycysteine respectively. These three molecules act as the strongest electron donors of the five. v. The highest dipole moment was obtained for Piperidine, Geraniol and S-Allycysteine, which appear to be the most polar, and therefore the most conductive and the most reactive of the five molecules. vi. The solvent water has no influence on the electronic properties of the molecules.

Finally, from all the results presented in Table-1, Piperidine, Geraniol and S-Allycysteine stand out as the most reactive. They therefore have the best antihypertensive properties of the five molecules.

ADMET properties of the targets molecules: The ADME (Absorption, Distribution, Metabolism and Excretion) properties of each compound (S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol) were determined in-silico using the Suissadme programme[29,30]. In order to analyse the medicinal properties of each of these molecules, the relevant physicochemical descriptors and pharmaceutical properties of the molecules were evaluated (Table-3).

Analysis of the results in Table-3 shows that: i. All the molecules showed good partition coefficient values (M log P) (-1.93 to 4.25), which are essential for drug absorption and distribution. ii. The stimulated number of hydrogen bonds that would be given by the solute to the water molecules in an aqueous solution of the compounds is between 1 and 2. ii. The estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution of the compounds is between 1 and 4. iii. The number of violations of Lipinski's rule of five is 0.

From these results, we can say that the molecules can be used in clinical trials because of their good ADME properties. This means that there is a strong tendency for all these molecules to be pharmacologically very active.

Bioavailabilities radars of the target molecules: Bioavailability radars were used for a rapid assessment of the similarity of each of the five molecules to a drug, in which six physicochemical properties were taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation. The maps representing the oral bioavailability radars of S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol are shown in Figure-2. Analysis of these bioavailability radars shows that the colored areas are the best physicochemical areas for oral bioavailability[31,32]. We can therefore deduce that the S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol studied confirm their drug-like properties. It could be said that these molecules are orally bioavailable.

Table-3: Bioactivity analysis of S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol.

Molecules	Lipinski's Ruleof Five					
	Molecular weight (g/mol)	Lipophilicity (MLog P)	Hydrogen Bond Donors	Hydrogen Bond Acceptors	No. of Rule Violations	Drug-Likeness
	Less than 500 Dalton	Less than 5	Less than 5	Less than 10	Less than 2 Violations	Lipinski's Rule Follows
S-Allycysteine	161.22	-1.93	02	03	No; 1 violation:	yes
Capsaicin	305.41	2.69	02	03	No; 2 violations:	yes
Gingerol	294.39	2.14	02	04	No; 1violation:	yes
Piperidine	85.15	0.76	01	01	No; 1 violation:	Yes
Geraniol	154.25	2.59	01	01	No; 2 violations:	yes

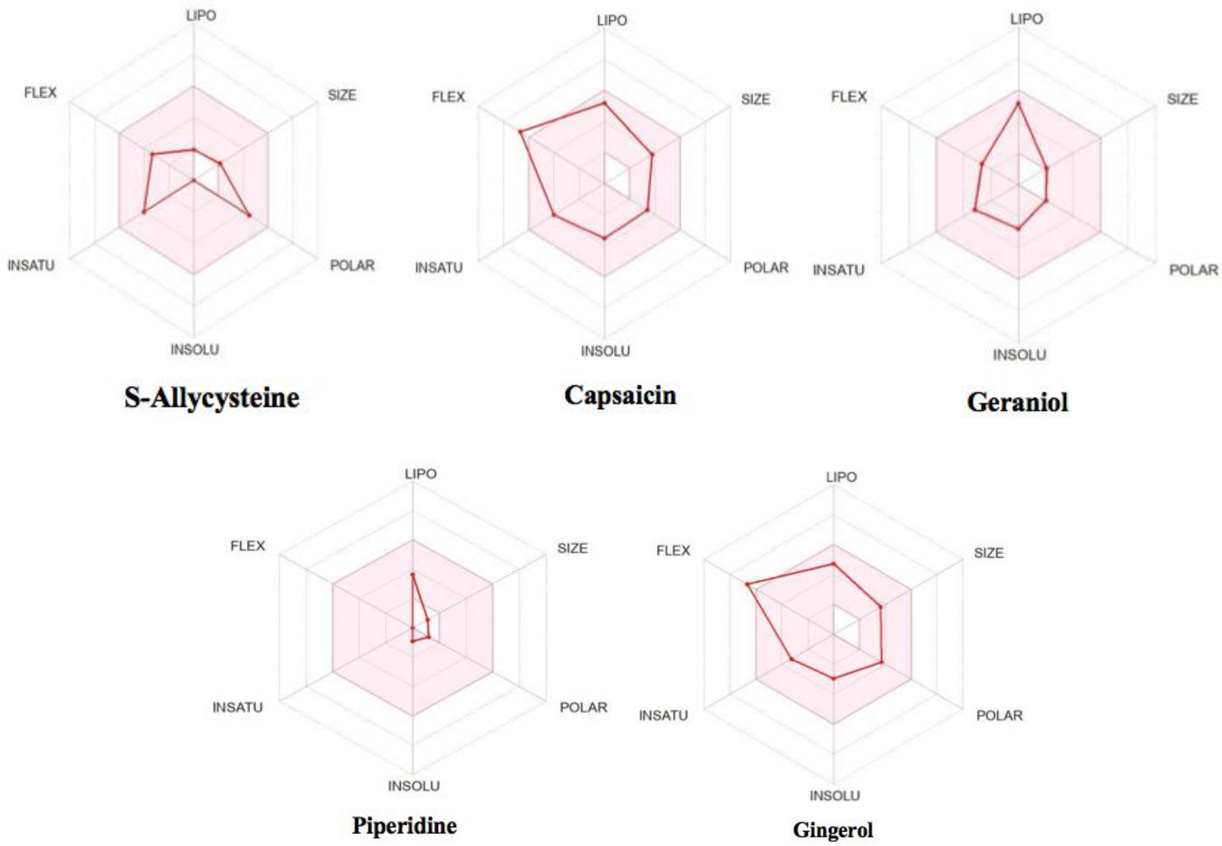

Figure-2: B ioavailability radar maps for S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol.

Interaction between Angiotensive II and the target molecules: The interaction between a protein and its substrate is the first step in most of the biological reactions. In the next stage of the work, a molecular docking study between the type 1 receptor for angiotensive II and each of the molecules will be carried out in order to further identify the most reactive molecules.

Table-4 shows the values obtained in kcal/mol for the interaction energies, docking score; PLP score and H bond score for S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol.

Analysis of the results in Table-4 shows that: i. Overall, all the compounds studied had a significant binding affinity for Angiotensive II ATR1; ii. The highest interaction energies with ATR1 of Angiotensive II were observed for S-Allycysteine and Piperidine (Table-4), due to their affinity in the active site of the enzyme studied; these molecules could have the highest potential for antihypertensive treatment; iii. The highest docking and PLP scores were obtained by S-Allycysteine and Piperidine. This result indicates that the complexes obtained from Angiotensive II ATR1 and each of these two molecules are much more stable than the other five molecules; iv. The highest values for hydrogen bond interaction energy (H bond Score) were obtained by S-Allycysteine and Piperidine respectively. These two molecules therefore have the strongest hydrogen bonds;

From these series of analyses, we can conclude that there is a strong affinity between the type 1 receptor (ATR1) of Angiotensive II, S-Allycysteine and Piperidine. These molecules therefore have the strongest antihypertensive activities of the five.

2D/3D interactions of S-Allycysteine and Piperidine in Angiotensive II ATR1: 3D (three-dimensional) diagrams representing the characteristics of the hydrogen bond donors and acceptors of the amino acid residues (Figure-3 and Figure-4) and 2-D (two-dimensional) diagrams (Figure-3 and Figure-4) showing several interactions between S-Allycysteine and Piperidine in the active site of angiotensin II were shown.

Visualisation of the 2D and 3D interactions of Piperidine and S-Allycysteine in the active site of ATR1 of Angiotensive II, shows overall good positioning of this inhibitor in the binding site of ATR1 of Angiotensive II. The complexes formed are stabilized by Van der Waals (VdW) forces and the hydrogen bonds established between the inhibitors and the amino acids.

Table-4: Values obtained (in Kcal/mol) for interaction energies, docking score, PLP Score, (hydrogen bond interaction energies) H bond Score for S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol.

Parameters	Target Molecules				
	S-Allycysteine	Capsaicin	Gingerol	Piperidine	Geraniol
Docking Score	61.22	60.28	53.39	61,18	61,18
PLP Score	-56.01	-53.70	-51.01	-57,97	-57,97
H bond Score	-2.91	-2.58	-0.98	-3,45	-3,45
Interaction energy	-4.85	-4.83	-4.48	-4.84	-4.84

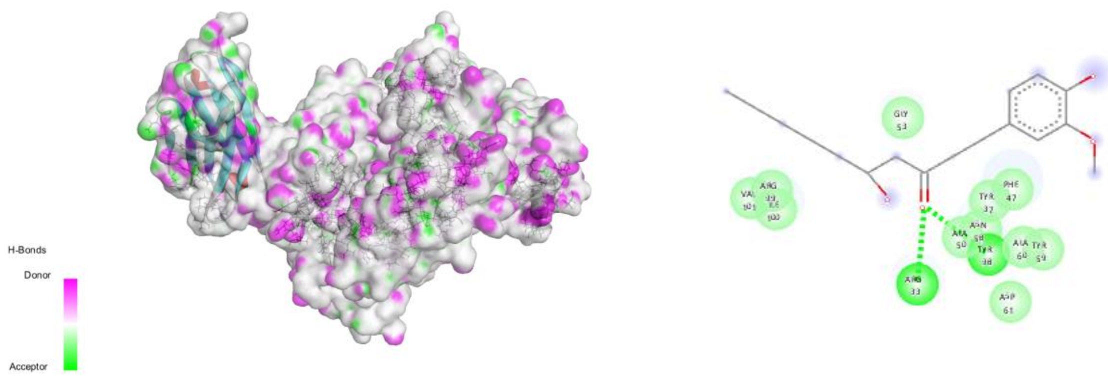

Figure-3: 2D (left) and 3D (right) visualization of interaction between Piperidine amino acid residues and angiotensin II.

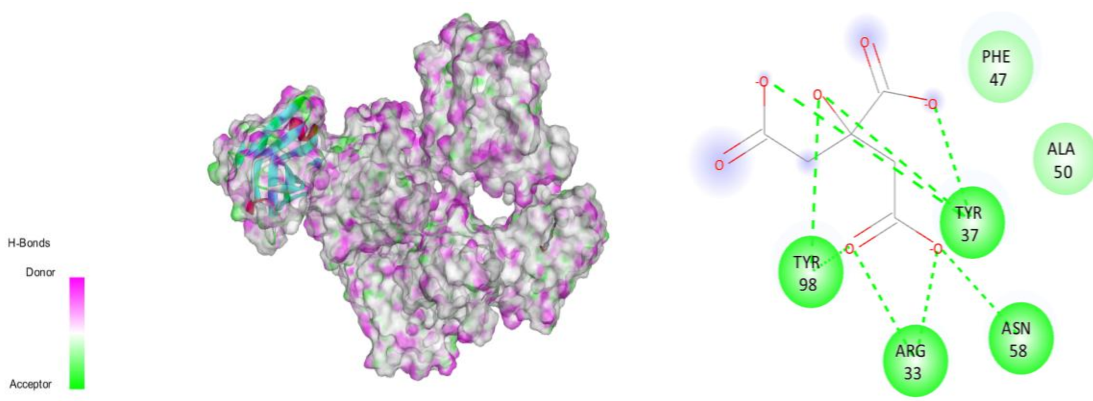

Figure-4: The 2D (left) and 3D (right) visualization of interaction between S-Allycysteine amino acid residues and angiotensin II.

Ramachandra curves and 2D Interactions of S-Allycysteine and Piperidine: The statistical distributions of amino acids in the protein crystal structure were studied using the Ramachandra curve (Figure-5). Analysis of the results showed that most of the amino acids are located in the authorized region of the crystal structure. This shows that the protein crystal structures are stable in nature. The allowed regions of the protein residues are shown in Figure-5. Moreover, these results were confirmed by the curves in Figure-5, which represent the hydrogen bond interaction energy surfaces (H bond plot), and the residues of S-Allycysteine and Piperidine in the ATR1 site of Angiotensive II. Analysis of each of these curves shows that there is a strong correlation between the hydrogen bonds on the one hand and between the amino acid residues of each of the molecules studied on the other.

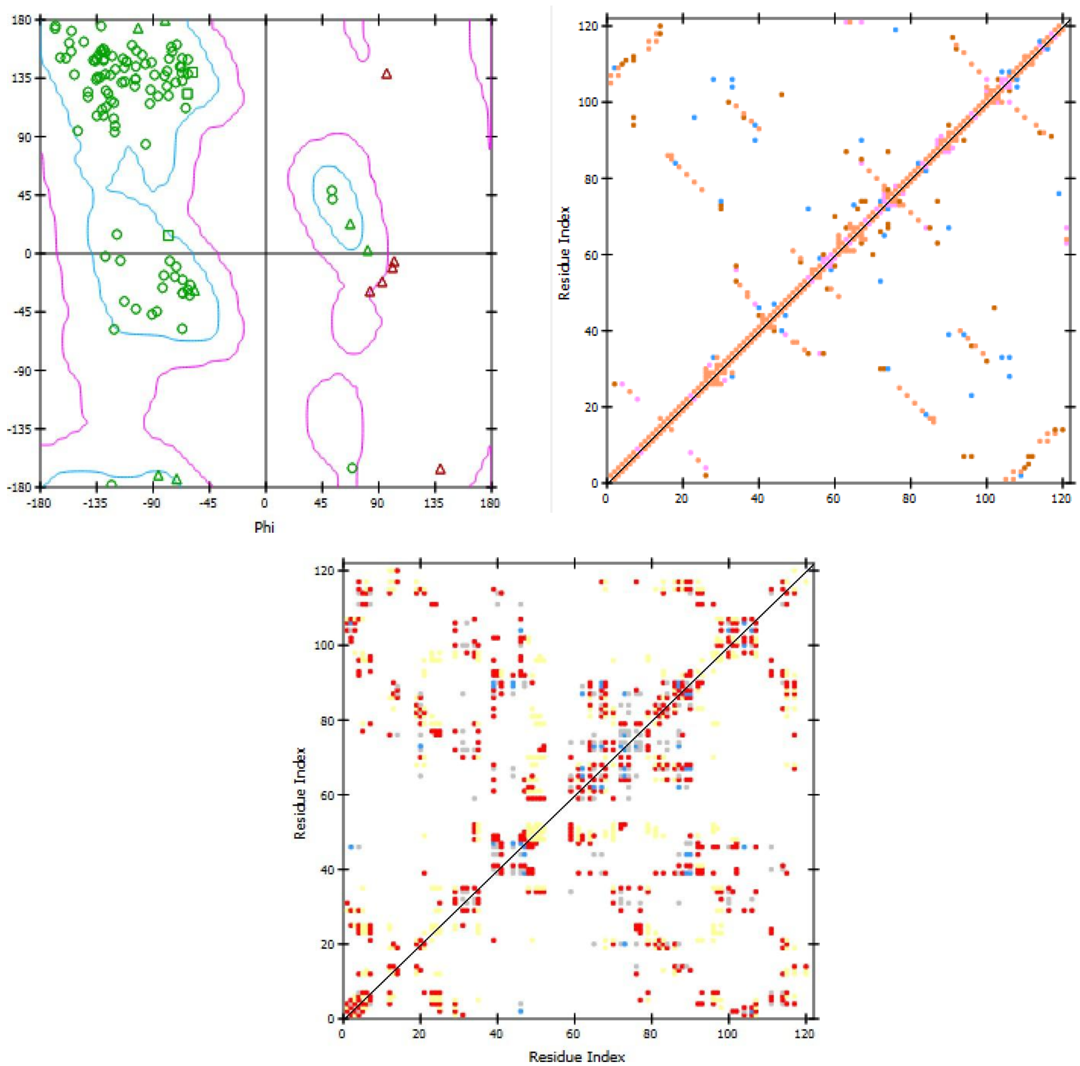

Figure-5: Ramachandra 2D curve, Hbond plot and Residue plot for the interaction between Piperidine and ATR1 of Angiotensive II.

Conclusion

This work reports the comparative study of the antihypertensive properties of five natural molecules: S-Allycysteine, Capsaicin, Gingerol, Piperidine and Geraniol were carried out by using quantum chemical approaches. The study consisted of calculating electronic parameters, properties and finally studying the interactions between Angiotensive II and each of the molecules. The analysis of the various results obtained leads that each of these molecules can be used in clinical trials because of their good ADMET properties and are pharmacologically very active. Overall, all five compounds studied have a significant binding affinity with Angiotensive II. Therefore, they have a strong inhibitory effect on ATR1, which is responsible for arterial hypertension. The complexes formed are stabilised by Van der Waals (VdW) forces and the hydrogen bonds established between the inhibitors and the amino acids of the targets molecules. Piperidine, Geraniol and S-Allycysteine stand out as the most reactive. They have the best antihypertensive properties of the five molecules.

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