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Original Research Article

Drug Properties, Chemical Reactivity and Docking Binding Energy of Cinnamon with Estrogen, Testosterone, Progesterone as Potential Drug: Theoretical Investigation

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ABSTRACT

Cinnamon is applied for diabetes and insulin resistance as a plant medicine. In this study, DFT calculations to consider the pregnancy function role of cinnamon compounds was done by B3LYP/6-311G. Thermodynamics properties, molecular electronics, docking of cinnamon compounds with estrogen, testosterone and progesterone and drug parameters calculated the results obtained among sexual hormones; progesterone acts with the chemical component of Cinnamon.

Keywords: DFT, Cinnamon, A Sexual Hormone, Plant Medicine

Introduction

For centuries, natural medicines derived from plants [1], fungi, bacteria, protozoans, insects and animals [2] have been known to be useful in the treatment of various diseases. Among natural products [3], active herbal ingredients [4,5] are particularly valued as a precious resource for the development of novel therapeutic agents due to their broad structural diversity as well as the wide range of pharmacological activities and comparatively low side effects. Noteworthy, already in 2000, it was estimated that approximately one-third of the top-selling drugs in the world had been derived from medicinal herbs. The finding obtained the evidence-backed by hard research on why Cinnamon [6–10] may be the solution for blood sugar control, weight loss, alertness, creating natural disinfectants

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and cancer prevention. Cinnamon [11,12] is a powerful antibacterial [13–16]. Cinnamon is famous because of its aromatic structure and good behaviour. It has understood to be extremely helpful in treatment on diabetes and insulin resistance. The report on cinnamon's effect on hormones [17,18] don't publish up to now. Traditional medical experience showed that the warm tasty spices affected on sexual hormones [8,19–22]. On the present work, sexual hormones such as estrogen, progesterone and testosterone has been selected to consider for investigating chemical interactions with cinnamon as a potential drug. Theoretical calculations [23–26] have been done by Gaussian software, and the molecular properties and structural parameters to recognize chemical interactions have been calculated in this study. Docking analysis has been done to find binding energy.

Theoretical method

All geometry optimizations and quantum chemical calculations were performed through Gaussian 09 software [26] using density functional theory (DFT) with B3LYP quantum level and 6-311g basis set. The B3LYP (Becke's hybrid 3-parameter functional with Lee-Yang-Parr correlation) functional was selected for the calculations. From the optimized structures, the molecular geometry along with thermodynamical parameters was analyzed. In order to estimate the stability of the complexes, the interaction energies (Eint) were calculated B3LYP had been introduced as one of the most accurate methods for energy calculation. Structure parameters have been calculated by optimizing type jobs in the Gaussian package. For thermodynamic properties (ΔG), the frequency type job at the Gaussian package has been done with the same method. The molecular electrostatic potential was performed to examine the donor-acceptor and the charge transfers between them. The molecular electrostatic potential energy surface was calculated to describe the overall molecular charge distribution.

The Electrostatics potential (ESP) map was calculated as well. DFT-based chemical reactivity and stability descriptors which are electronic chemical potential (μ), chemical hardness (η), chemical softness (S) and electrophilicity (ω), were calculated as defined in Eqs. (1– (4) according to the Koopmans theorem:

$$\mu = -\chi \quad (1)$$

$$\eta = ((I-A)/2) \quad (2)$$

$$S = 1/\eta \quad (3)$$

$$\omega = \mu 2/2\eta \quad (4)$$

Where μ is chemical potential, η is chemical hardness, S is global softness, and ω is electrophilicity index. Docking binding energy calculated by Autodock4.2.

Result and Discussion

The level of sexual hormones affects pregnancy and other sexual behavior in humans and animals. In recent years all scientists considerably studied the interaction of them with different drugs to help men who do not have a child and cannot be pregnant. Industrial and synthesized drugs have lots of side effects on non-target parts of the body. The researchers have tried to obtain away or compound to reduce this side effect. Therefore, one of these ways is to use medicinal plants instead of chemical synthesis drugs compound. One kind of plant which used as a drug is Cinnamon for pregnancy and sexual behavior. The essential oil or extract part of a plant has various chemical compounds could behave interact with the hormones; some of the chemical compounds that identified in Cinnamon, the compound in Fig 1 and 2 selected to be considered for investigating the interactions with sexual hormones.

The structure of compound and sexual hormones (Fig 1 and Fig 2) has been optimized by B3LYP/6-311g level to compute thermodynamically and structural parameters. The optimized structures are in table 1.

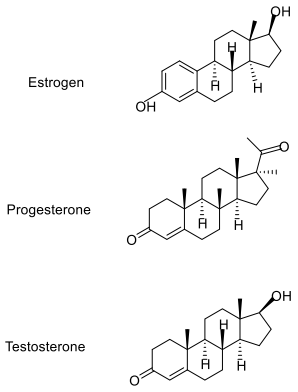


Fig 1. structure of sexual hormones

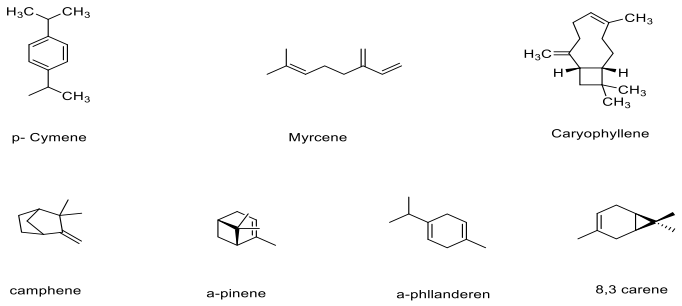
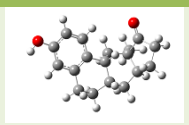
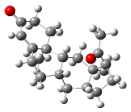
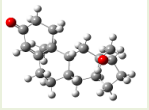
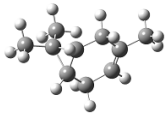
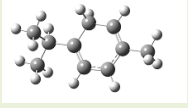
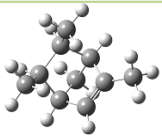
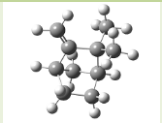
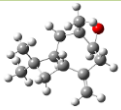
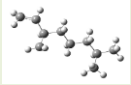
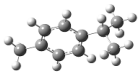


Fig 2. Selected compound on Cinnamon

Table 1. Optimized structure of chemical compounds

Compound	Structure
Estrogen	
Progesterone	
Testosterone	
8,3 Carene	
α- Phllanderen	
α - Pinene	
Camphene	
Caryophyllene	
Myrcene	
p- Cymene	

In fact, for evaluating to predict the accuracy of binding ability between ligands and target hormones, the binding free energies (ΔG) for the docking models and the crystal structures were calculated. The lower binding energy value specifies the binding strength of the ligands and docking model. Therefore, to calculate the binding strength, the complexes docked were analyzed based on minimum binding energy values and interaction (hydrogen/hydrophobic) pattern. Docking results reported in table 2 recognized that hormones had good interaction with ligands and indicated a biological manner in the solvent.

Table 2. The binding energy of hormones with cinnamon compounds

The binding energy of estrogen with cinnamon compounds	
Cinnamon compound	Binding energy(cal)
a-phllanderen	-1.77×10^{-16}
a-pinene	-1.43×10^{-16}
camphene	-1.73×10^{-16}
caryophyllene	-1.38×10^{-16}
myrcene	-1.77×10^{-16}
p-cymene	-1.88×10^{-16}
8,3 carene	-1.25×10^{-16}
The binding energy of progesterone with cinnamon compounds	
a-phllanderen	-1.95×10^{-16}
a-pinene	-1.95×10^{-16}
camphene	-1.25×10^{-16}
caryophyllene	-1.61×10^{-16}
myrcene	-2.06×10^{-16}
p-cymene	-1.95×10^{-16}
8,3 carene	-1.94×10^{-16}
The binding energy of testosterone with cinnamon compounds	
a-phllanderen	-1.84×10^{-16}
a-pinene	-1.83×10^{-16}
camphene	-1.84×10^{-16}
caryophyllene	-1.56×10^{-16}
myrcene	-1.84×10^{-16}
p-cymene	-1.95×10^{-16}
8,3 carene	-1.84×10^{-16}

In the physical sciences, a partition coefficient (P) or distribution coefficient (D) is the ratio of concentrations of a compound in a mixture of two immiscible solvents at equilibrium. This ratio is, therefore, a comparison of the solubilities of the solute in these two liquids. The partition coefficient generally refers to the concentration ratio of un-ionized species of compound. In contrast, the distribution coefficient refers to the concentration ratio of all compound species (ionized plus un-ionized). In the chemical and pharmaceutical sciences, both phases usually are solvents. One of the solvents is water, while the second is hydrophobic, such as 1-octanol. Hence the partition coefficient measures how hydrophilic ("water-loving") or hydrophobic ("water-fearing") a chemical substance is.

Partition coefficients are useful in estimating the distribution of drugs within the body. Hydrophobic drugs with high octanol-water partition coefficients are mainly distributed to hydrophobic areas such as lipid bilayers of cells. Conversely, hydrophilic drugs (low octanol/water partition coefficients) are found primarily in aqueous regions such as blood serum. According to data in table 3, drug parameters of cinnamon compounds reported, logp=4.93 obtained for caryophyllene has the best pharmaceutics behavior.

Table 3. Drug properties of cinnamon compounds

Properties / Name	Surface area ($Å^2$)	Volume ($Å^3$)	Hydration energy (kcal/mol)	Log P	Refractivity ($Å^3$)	Polarizability ($Å^3$)
p-Cymene	388.76	614.21	2.08	4.09	32.88	21.44
Myrcene	403.82	567.32	0.55	4.10	25.57	18.55
caryophyllene	303.74	663.56	2.68	4.93	55.82	26.46
Camphene	293.74	529.85	1.84	3.17	36.51	17.38
a-pinene	293.75	529.77	1.84	3.17	36.51	17.38
a-phllanderen	345.79	540.98	2.56	3.48	31.14	17.97
8,3 carene	314.75	523.32	2.58	3.09	36.52	17.38

Hydration energy (also hydration enthalpy) is the amount of energy released when one mole of ions undergoes hydration. Hydration energy is one component in the quantitative analysis of solvation. It is a particular special case of water. The value of hydration energies is one of the most challenging aspects of structural prediction. Upon dissolving a salt in water, the cations and anions interact with the positive and negative dipoles of the water. The trade-off of these interactions' vs those within the crystalline solid comprises the hydration energy. Molar refractivity, is a measure of the total polarizability of a mole of a substance and is dependent on the temperature, the index of refraction, and the pressure. Table 4 reached the stability energy of three sexual hormones. The results reached using 6-311g level can be the best and save time quantum level for computing the other parameters.

Table 4. Stability energy of sexual hormones

Compound	Stability Energy(kJ)	Stability Energy(eV)
Estrogen	-2.23×10^{4}	-1.39×10^{20}
progesterone	-2.54×10^{4}	-1.58×10^{20}
Testosterone	-2.34×10^{4}	-1.46×10^{20}

Data in table 4 illustrated that progesterone has minimum negative energy of formation -2.5×104 kJ, which is stable molecule than the other hormones. In this case, can resulted in progesterone may act better than the other hormones. Table 5 shows the calculated molecular parameters. The energy of LUMO describes the electron-accepting ability of a molecule, and thus, the lower the value of ELUMO, the more probable the molecule would accept electrons. The energy gap between the HOMO

and LUMO energy levels of a molecule is an important parameter because it is a function reactivity. The energy of HOMO indicates the ability of molecules to donate electrons, and thus, the higher value of EHOMO, the more probable the molecule would donate electrons. Ionization potential is a basic description of the chemical reactivity of atoms and molecules; high IP pertains to towering stability. A hard molecule has a large energy gap, and a soft molecule is more reactive than hard one because it could easily offer electrons to an acceptor. The ability of the molecules to accept electrons may be described by the electrophilicity index.

Thermodynamic data in table 5 have demonstrated that progesterone has a minimum of ΔH and ΔG. therefore, it is stable to firm action in chemical and biochemical media. ΔS of progesterone also shows it is stable in environment temperature. Dipole momentum of sexual hormone illustrated that all of them are polar and can be reacted in polar media, and can act as polarity compounds between chemical compositions. If each of the hormones has been done in reaction with cinnamon, the reaction may be spontaneously reaction Because of negative reaction energy. Bandgap energy of hormones obtained in progesterone has more reactivity than the other one because of at least the value of bandgap energy. The other molecular electronics parameters show the same result for determining the reactivity of hormones.

Cinnamon has chemical components such as a-phllanderen, a-pinene, camphene,caryophyhhene, myrcene, p-cymene and 8,3 carene. In this study, molecular electronics parameters of all components were calculated to determine the reactivity of the sexual hormones. According to data table 4, progesterone has more reactivity. Some researchers recognize that cinnamon, may help to be pregnant. Therefore, for recognizing the interaction of sexual hormones and cinnamon, molecular parameters of Cinnamon were calculated. Thermodynamics data illustrated that caryophyllene has minimum formation energy and is more stable in chemical and biochemical media. ΔS also showed this matter. However according to electronics data, we can recognize the reactivity of molecules. The bandgap of myrcene with at least value 0.059 eV showed this component may be more reactive than the other ones. The softness of all compound obtained myrcene with high of value is the most active than the other ones.

Table 5. Molecular parameters of all compounds

molecule	HOMO	LUMO	ΔE=energy gap	IP(eV)	EA(eV)	ΔH(kJ)	ΔS(cal)	ΔG(kJ)	μ (deby)	ω(eV)	η(eV)	χ(eV)	σ(eV)
Estrogen	-0.3288	-0.17469	0.15411	0.3288	0.17469	-849.082	129.65	-849.20	6.48	0.0024	0.077	0.251	12.9
Progesterone	-0.35803	-0.20527	0.15276	0.35803	0.20527	-967.71	148.14	-967.84	8.56	0.0030	0.076	0.281	13.1
Testosterone	-0.36018	-0.20527	0.15491	0.36018	0.20527	-890.36	137.50	-890.49	8.03	0.0030	0.077	0.282	12.9

a-phllanderen	-0.25585	-0.16368	0.09217	0.25585	0.16368	-389.58	102.90	-389.67	0.65	0.0010	0.046	0.209	21.6
a-pinene	-0.35097	-0.15656	0.19441	0.35097	0.15656	-390.161	92.96	-390.251	3.96	0.0031	0.097	0.253	10.2
camphene	-0.37039	-0.16231	0.20808	0.37039	0.16231	-390.166	91.48	-390.253	0.47	0.0036	0.104	0.266	9.6
caryophyllene	-0.35544	-0.16091	0.19453	0.35544	0.16091	-581.88	111.42	-581.98	0.92	0.0032	0.097	0.258	10.2
myrcene	-0.28063	-0.22106	0.05957	0.28063	0.22106	-391.34	75.12	-391.35	1.29	0.0009	0.029	0.251	33.5
p-cymene	-0.35566	-0.17762	0.17807	0.35566	0.17762	-389.05	102.53	-389.15	0.04	0.0031	0.089	0.266	11.2
8,3 carene	-0.23232	0.02743	-0.25975	0.23232	-0.02743	-390.16	97.15	-390.24	1.12	0.040	0.129	0.102	7.6

Corresponding data determined progesterone may act with myrcene in chemical media. Myrcene acts as a donor, and progesterone act as an acceptor in chemical and biochemical conditions. The electrostatic potential (ESP) is used to analyze the positively and negatively charged regions of a molecule. In atomic units, it is defined as the interaction energy of the molecule with an infinitesimal positive point charge, per unit charge. Fig 3 shows the docking pose of cinnamon compounds by each structure of estrogen, progesterone and testosterone.

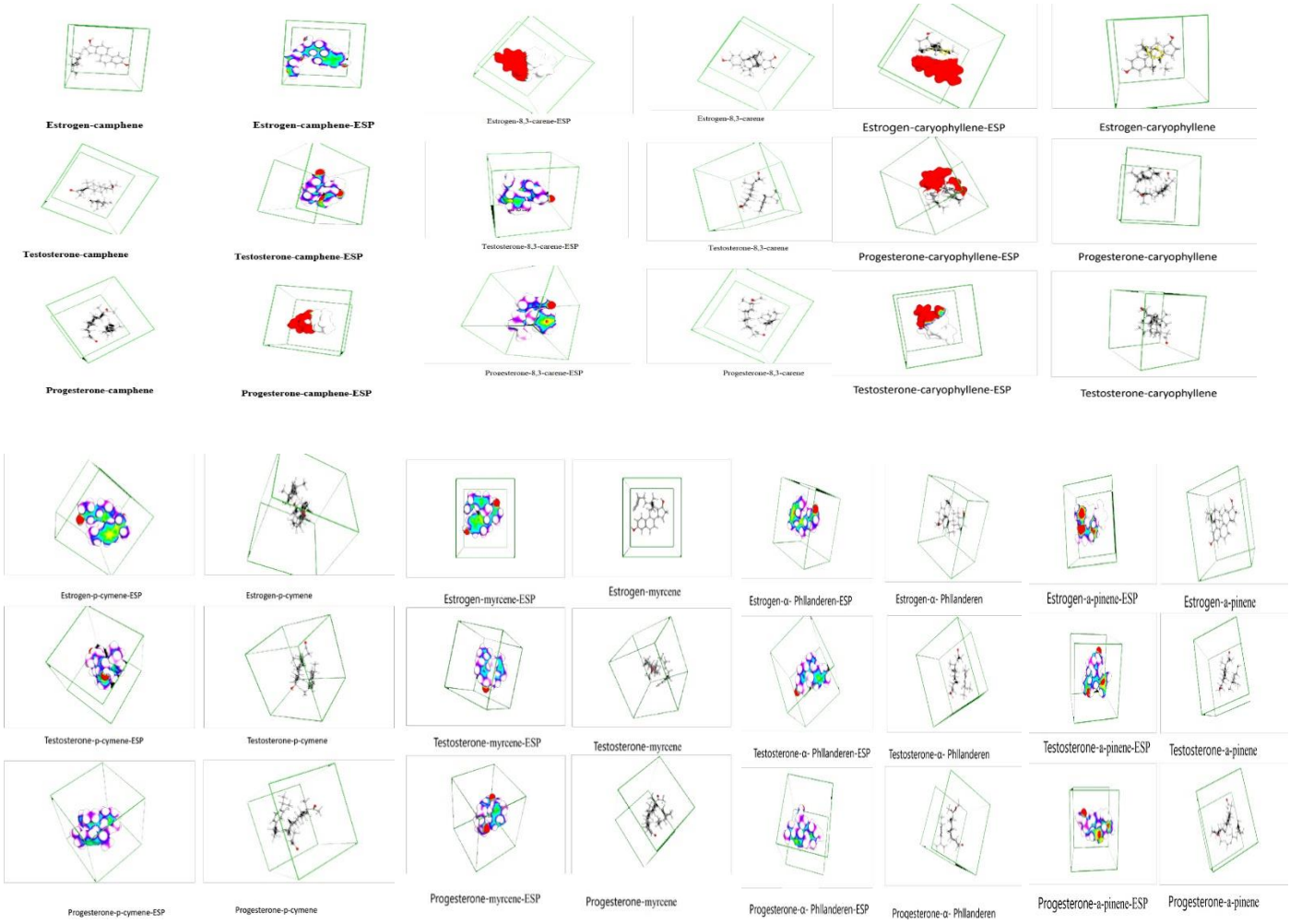


Fig 3. Electrostatic potential of docked structures

Typically, hard acids/electrophiles attack a molecule where the electrostatic potential is most negative, and the hard bases/nucleophiles attack a molecule where it is mostly positive. The value of the

electrostatic potential at a nucleus is often interesting, because it shows how the energy changes when the atomic number of the nucleus changes (to first order). Therefore, it is relevant for alchemical changes as an atom change to an adjacent atom in the periodic table.

Conclusion

Cinnamon as a drug for pregnancy has been used in plant medicine. In order to recognize the chemical effect of sex hormones with cinnamon, molecular electronics parameters have been calculated. Among of hormones, progesterone has reactivity, and among chemical components of cinnamon, myrcene has reactivity. Therefore, in chemical and biochemical conditions, interaction of myrcene and progesterone for pregnancy should be considered.

Declarations

There is no conflict of interest in this manuscript. I am Corresponding Author, declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. I would like to draw the attention of the Editor to the following publications of one or more of us that refer to aspects of the manuscript presently being submitted.

I can confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. I further confirm that the order of authors listed in the manuscript has been approved by all of us. I understand that the Corresponding Author is the sole contact for the Editorial process and is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. I confirm that the data are original, and the software that I applied, is mentioned in the method.

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