Research Square

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

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Research Article

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Abstract

Cinnamon is applying for diabetes and insulin resistance as plant medicine. In this study DFT calculation to consider pregnancy function role of cinnamon compounds were 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 of sexual hormones ,progesterone has act with chemical component of cinnamon.

Introduction

Since 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), herbal active ingredients(4,5) are particularly valued as a precious resource for a 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 have been derived from medicinal herbs. The finding obtained the evidence backed with hard research on why Cinnamon(6–10) maybe the solution for blood sugar control, weight loss, alertness, creating natural disinfectants, cancer prevention. Cinnamon(11,12) is a powerful antibacterial(13–16). Cinnamon is famous because of its aromatic structure and good behavior. It has understood to be extremely helpful in treatment of diabetes and insulin resistance. The report of cinnamon effect on hormone's(17,18) don't publish up to now. In traditional medical experience showed that the warm tasty spices affected on sexual hormones(8,19–22). In present work sexual hormone's such as estrogen, progesterone and testosterone has been selected to consider for investigating chemical interactions with cinnamon as potential drug. Theoretical calculations(23–25) 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 were analyzed. In order to estimate the stability of the complexes the interaction energies (E_{int}) were calculated B3LYP has been introduced as one of the most accurate methods for energy calculation. Structure parameters have been calculated by optimize type job in Gaussian package. For thermodynamic properties (ΔG), frequency type job at Gaussian package has been done with the same method. The molecular electrostatic potential was performed to examine the donor-acceptor and the charge transfers taking place between them. The molecular electrostatic potential energy surface were calculated to describe overall molecular charge distribution. 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 Koopmans theorem:

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

$$\eta = \left(\frac{I-A}{2}\right) \quad (2)$$

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

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

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 affected on pregnancy and other sexual behavior in humans and animals. In recent years all scientific considerably study the interaction of them with different drugs to help mans who don't have child and can't be pregnant. The industrial and synthesized drugs have lots of side effect on non-target some parts of the body. The researchers have been tried to obtain a way or compound to reduce this side effect. Therefor one of these ways is to use medicinal plants instead of chemical synthesis drugs compound. One kind of plant which used as drug is cinnamon for pregnancy and sexual behavior. The essential oil or extract part of plant has various chemical compound could be have interaction with the hormones some among of chemical compound that identified on cinnamon, the compound in Fig 1 and 2 selected to be consider for investigating the interactions with sexual hormones.

The structure of each compounds and sexual hormones (see 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.

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 specify 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 by ligands and indicated biological manner in solvent.

Table 2 binding energy of hormones with cinnamon compounds

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}
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}
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, whereas the distribution coefficient refers to the concentration ratio of all species of the compound (ionized plus un-ionized). In the chemical and pharmaceutical sciences, both phases usually are solvents. Most commonly, 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 {\displaystyle A}, 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 -2.5×10^{4} kJ which is stable molecule than the other hormones. In this case can resulted progesterone may act better than the other hormones.

Table 5 showed 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 of the molecule reactivity. The energy of HOMO indicates the ability of a molecule 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 ones because they 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 progesterone has minimum of ΔH and ΔG. therefore it is stable to form action in chemical and biochemical media. ΔS of progesterone also shows that 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 compound between chemical compositions. If each of hormones has been done on reaction with cinnamom, the reaction may be spontaneously reaction Because of negative reaction energy.

Band gap energy of hormones obtained progesterone has more reactivity than the other one because of at least value of band gap energy. The other molecular electronics parameters show the same result for determining reactivity of hormones.

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

Corresponding data determined progesterone may act with myrcene in chemical media. Myrcene acts as donor and progesterone acts as 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 showed the docking pose of cinnamon compounds by each structure of estrogen, progesterone and testosterone. 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 most 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 changes to an adjacent atom in the periodic table.

Table 5 molecular parameters of all compounds.

molecule	HOMO	LUMO	ΔE=energy gap	IP(eV)	EA(eV)	ΔH(kJ)	ΔS(cal)	ΔG(kJ)	μ(debye)	ω(eV)	η(eV)	χ(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
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
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
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
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
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
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
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
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
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

Conclusion

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

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Tables

Table 1 is available in the Supplemental Files section.

Figures

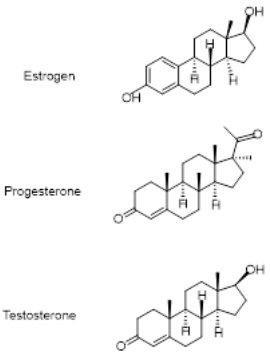

Figure 1

structure of sexual hormones

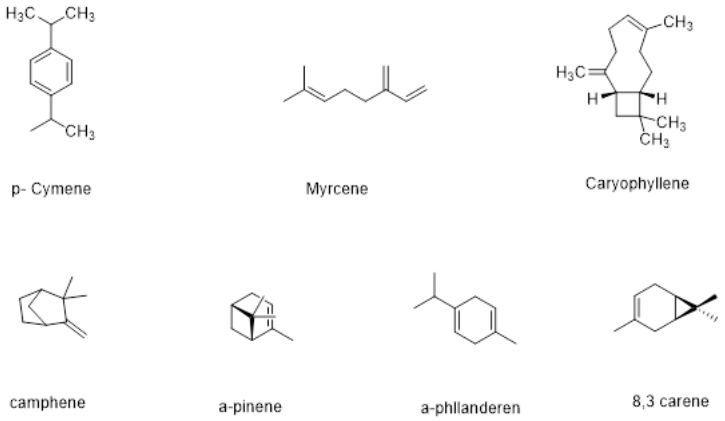

Figure 2

selected compound on cinnamon

Figure 3

Electrostatic potential of docked structures

Supplementary Files

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- Table1optimizedstructuredofchemicalcompounds.docx