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In silico study of the active components (17α-ethinyl estradiol and segesterone acetate) of annovera as a novel vaginal contraceptive system by docking of their binding to estrogen and progesterone receptors

Mehdi Nabati*, Vida Bodaghi-Namileh

Synthesis and Molecular Simulation Laboratory, Chemistry Department, Pars Isotope Company, P.O. BOX 1437663181, Tehran, Iran

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Abstract

The main purpose of the present research article is the docking analysis of active substances of annovera (segesterone acetate and ethinyl estradiol) with progesterone and estrogen receptors (PR and ER), respectively. The first step of this study is optimizing the title compounds using B3LYP/6-311++G(d,p) basis set of theory at room temperature in the isolated form of Gaussian 03 software. The frontier molecular orbital (FMO) theory is used to understand the reactivity and stability of the said compounds. The global reactivity indices indicate that both molecules have similar electrophilicity. After the quantum mechanical (QM) study, the docking analyses of the compounds embedded in the active sites of the receptors (PR and ER) are done using Molegro Virtual Docker (MVD) software. The docking studies show that the steric interactions play the main role in ligands complex formation with the receptors.

Keywords: Annovera; estrogen receptor; ethinyl estradiol; molecular docking; progesterone receptor; segesterone acetate.

Introduction

Fertility control, commonly known as birth control or contraception has been utilized by women over the course of history. Through time, methods of birth control have been optimized to achieve safer and more effective means of contraception [1]. Althoughoral hormonal contraceptives are recognized as the most frequently used methods of contraception in modern medicine their effectiveness in practice leaves something to be desired [2]. This unsatisfactory observation stems mostly from the uneducated and inept use by women [3]. Therefore, in order to reduce errors, hormonal methods with longer lasting contraceptive effects for use in extended periods of time were investigated [4]. Mishell et al., were the first to signify vaginal application of contraceptives by designing and publishing a clinical study and analyzing a medroxyprogesterone acetate releasing vaginal ring [5].

Vaginal rings are designed in accordance to their desired function and vagina's anatomical capacity. The

*Corresponding author: Mehdi Nabati
Tel: +98 (21) 88337023, Fax: +98 (21) 88337024
E-mail: mnabati@ymail.com

elastomers used in the structure of vaginal rings have the ability to release these contraceptive hormones at a mostly constant rate. Furthermore, the vaginal epithelium cells have the capacity to swiftly absorb steroids and release them into circulation resulting in an improved bioavailability [6, 7].The two most important types of vaginal rings are 1) Rings constituted of solely progestin and 2) Combined progestin and estrogen rings [8].

Annovera is a combined vaginal ring which granted its FDA approval on August 10th of 2018 as the first and only contraceptive that renders an entire year of protection against unplanned pregnancy [9]. Annovera consists of 103 mg segesterone acetate (progestin) and 17.4 mg ethinyl estradiol (estrogen) and is designed to release an average of 150 mcg/day segesterone acetate and 13 mcg/day ethinyl estradiol. For each 28 days menstrual cycle, Annovera is vaginally administered for 21 consecutive days and removed for the remaining 7 [6]. Segesterone acetate is a steroidal progestin and an analog of the hormone progesterone. Despite the slight difference in their structure, SA and progesterone act in a similar manner. Same as progesterone, SA not only specifically binds to progesterone receptors, but also shows no affinity towards estrogen or androgen receptors [10]. Consequently, the side effects usually witnessed the following treatment with hormonal contraceptives are non-existent in SA. In addition, SA was observed to possess up to 100 times more potent progestational activity compared with progesterone. SA is marketed under the brand name of Nestorone and mediates contraception through inhibition of ovulation. Ethinyl estradiol is a semi-synthetic analog of the estrogen estradiol. It is mostly used in hormonal oral contraceptives as the estrogenic constituent [11]. The combined use of SA and EE results in a synergistic effect on the inhibition of ovulation in women [12].

Previous studies have evaluated that Annovera mostly regarded this drug's efficacy and safety in fertility regulation, with emphasis on the effect on progesterone and estrogen receptors (PR and ER) [13]. However, the exact sequential interaction of Annovera and its components with these receptors is yet to be discovered. Furthermore, the information about pharmacokinetics and biological attributes of this drug, specifically the effect on cytochrome P450 is still unclear. The present study was undertaken in order to provide a more comprehensive understanding of Annovera vaginal ring capacity to affect PR and ER and the exact structure and sequential mechanism of this interaction as well as the biological activities of the titled drug using molecular docking methods and computational chemistry [14-17].

Computational methods

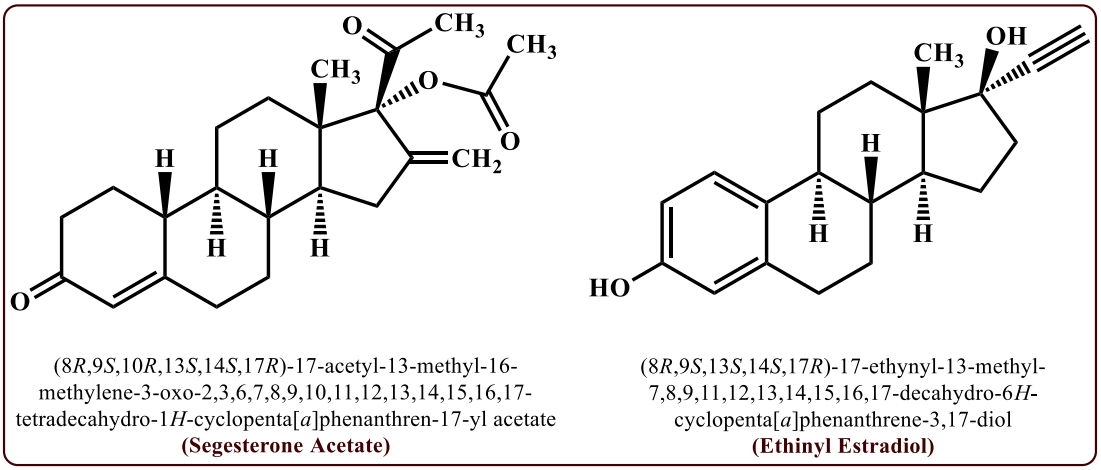
Theoretical chemistry is a branch of chemistry that explains the concept of chemical bonding, molecule activation, chemical reaction, orbital interaction, valence (the number of bonds formed by the atom of an element), molecular orbitals and the surface of potential energy[16-19].Molecular dynamics (MD) and Quantum mechanics (QM) are two main parts of the theoretical chemistry[20].Quantum chemistry describes the molecular properties including the interactions of the particles (protons, electrons and neutrons) with together. The results of the quantum mechanical studies are fundamental [18-20]. Thus, the rules of this science will be used to access the molecular properties of annovera substituents in the present study. Here,

the geometries of the molecules under study were optimized using Gaussian 03 software by the density functional theory method. All computations were done using B3LYP/6-311++G(d,p) basis set of theory. The frontier molecular orbital (FMO) theory has been used to know the stability and reactivity of the title compounds. On the other hand, the online website *www.swissadme.ch* was used to describe the biological activities of the annovera substituents. Also, the docking study of the compounds bindings to their receptors was carried out using molegro virtual docker (MVD) program.

Results and discussion

Structural properties study of annovera active compounds

Scheme 1 shows the molecular structures of annovera active substances (segesterone acetate and ethinyl estradiol). (*8R,9S,10R,13S,14S,17R*)-17-acetyl-13-methyl-16-methylene-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl acetate is the IUPAC name of segesterone acetate.Ethinyl acetate is preferred to its IUPAC name: (*8R,9S,13S,14S,17R*)-17-ethynyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H* cyclopenta[a]phenanthrene-3,17-diol. For our computational studies, the geometries of the title compounds were optimized using B3LYP/6-311++G(d,p) level of theory at room temperature by Gaussian 03 software. Figure 1 indicates the theoretical geometric structures of the compounds under study. We have used the comparison of empirical and theoretical bond length data of the optimized substances to validate our computational method. Figure 2 indicates the dependence between the theoretical and experimental bond lengths of the said molecules. This dependence for segesterone acetate and ethinyl estradiolare shown by the equations y=1.0239x-0.0315 and y=0.9898x+0.0046. The higher correlation coefficients ($R^2_{\text{segesterone acetate}}$=0.99809 and $R^2_{\text{ethinyl estradiol}}$=0.9714) for these equations show great convergences. So, the B3LYP/6-311++G(d,p) basis set of theory is a good method to compute the electronic properties of the title compounds.



Scheme 1. The molecular structures of annovera active compounds

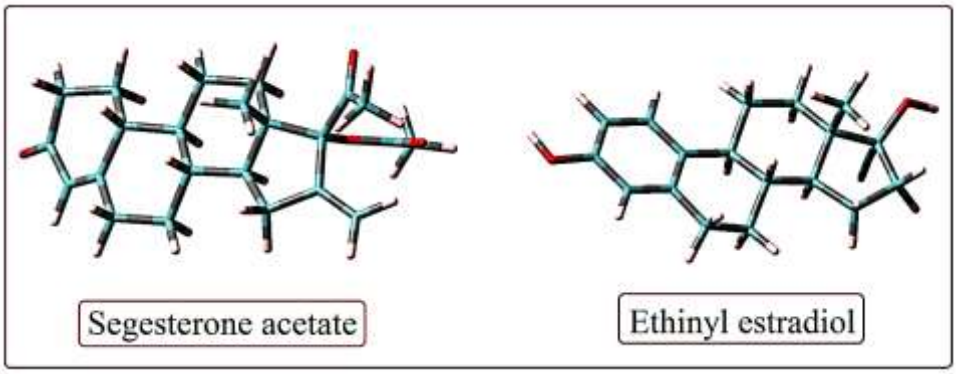


Figure 1. The theoretical geometric structures of annovera active compounds

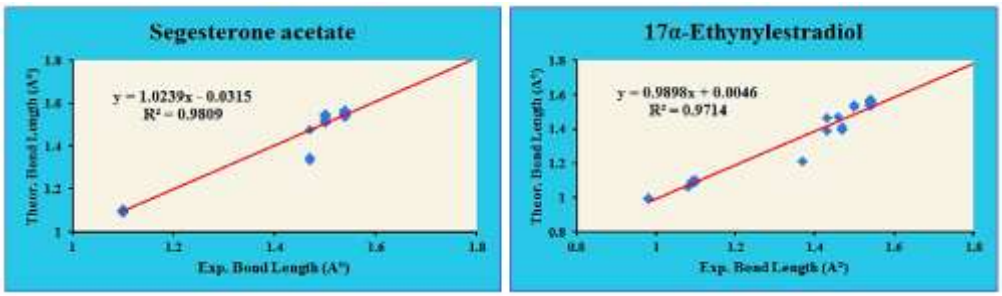


Figure 2. The experimental and theoretical bond length relationships of annovera active compounds

Stability and reactivity study of the active substances of annovera

The frontier molecular orbital (FMO) theory indicates the best available qualitative/semi quantitative treatment of chemistry in terms of quantum theory. These orbitals of a molecule are at the frontier of electron occupation. The highest energy occupied and lowest energy unoccupied molecular orbitals are called HOMO and LUMO, respectively. The HOMO and LUMO have nucleophilic and electrophilic properties, respectively. The stability and reactivity of a compound and a chemical reaction can be explained by the filled HOMO and empty LUMO interactions of one or more compound [19-23]. Figure 3 shows the frontier molecular orbitals (the filled HOMO and the empty LUMO) of the frontier molecular orbitals of annovera active substances. We can see that the HOMO and LUMO of segesterone acetate are in the cyclohexenone ring. Also, these frontier molecular orbitals are on the phenolic ring of ethinyl estradiol. So, it predicted that both nucleophilic and electrophilic reactions will be done by these rings when the active compounds of annovera interacted with estrogen and progesterone receptors.The stability and global reactivity indices of a chemical molecule can be gained using FMO theory [24]. The global reactivity descriptors like energy gap (Eg), ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical softness (S), electronegativity (χ), electronic chemical potential (μ) and electrophilicity index (ω) can be obtained from the energies of the frontier orbitals. These reactivity indices are achieved by following formulas [25]:

$$E_g = E_{LUMO} - E_{HOMO}$$

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$

$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$S = \frac{1}{\eta}$$

Table 1 has listed the global reactivity indices and frontier molecular orbitals energies of the said compounds segesterone acetate and ethinyl estradiol. As we know, the high amount of HOMO/LUMO energy gap shows the high stability of an organic compound. In comparison the HOMO and LUMO energy gap of segesterone acetate with ethinyl estradiol, we can see that both compounds are stable molecules but the stability of ethinyl acetate is more than segesterone acetate. Figure 4 indicates the density of states (DOS) graphs of the title compounds. It can be seen from these graphs that segesterone acetate has more frontier orbitals density than ethinyl acetate. So, it can be deduced that segesterone acetate has more reactivity. The low energy of the electron affinity (EA) and high energy of the ionization potential (IP) shows both substances have high electrophilic properties. On the other hand, segesterone acetate has more electronegativity and low chemical hardness in comparison with ethinyl acetate. So, it can be concluded this compound has more tendency than ethinyl estradiol to react with other agents. Also, both substances have similar electrophilicity index. It means both compounds show similar reactivity with electron rich reagents. The electrostatic potentials negative, zero and positive have been shown by red, green and blue colors in molecular electrostatic potential (MEP) graphs (Figure 5). It can be seen that all segments of both molecules except the nitrogen and oxygen elements have electrostatic potential zero. So, these substances prefer to react only with powerful nucleophile agents.

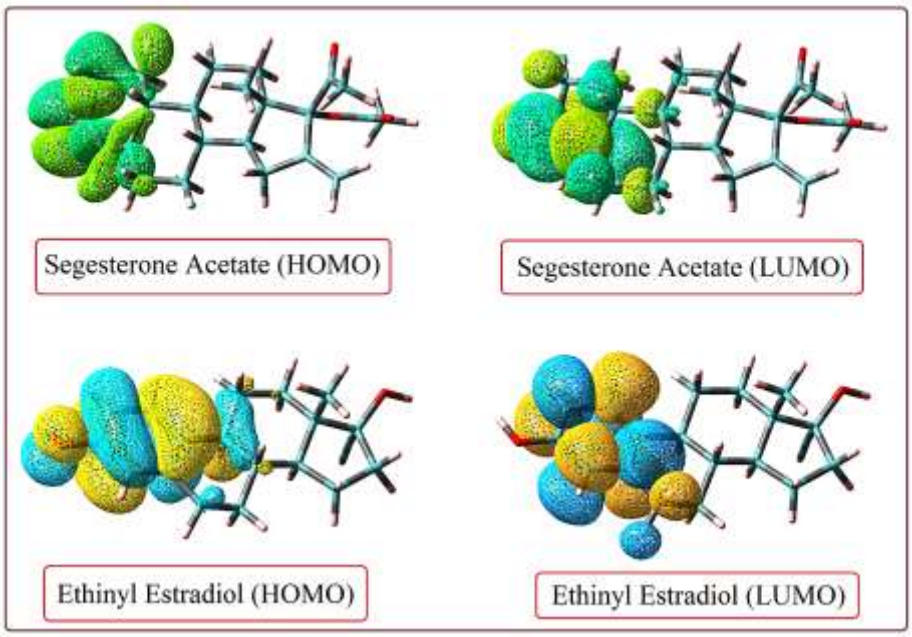


Figure 3. The frontier molecular orbitals of annovera active compounds

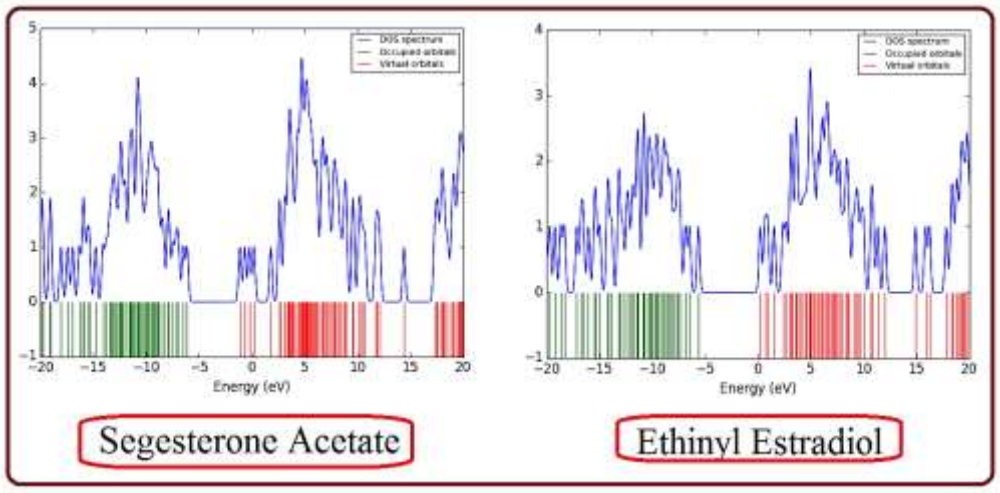


Figure 4. The density of states (DOS) graphs of annovera active compounds

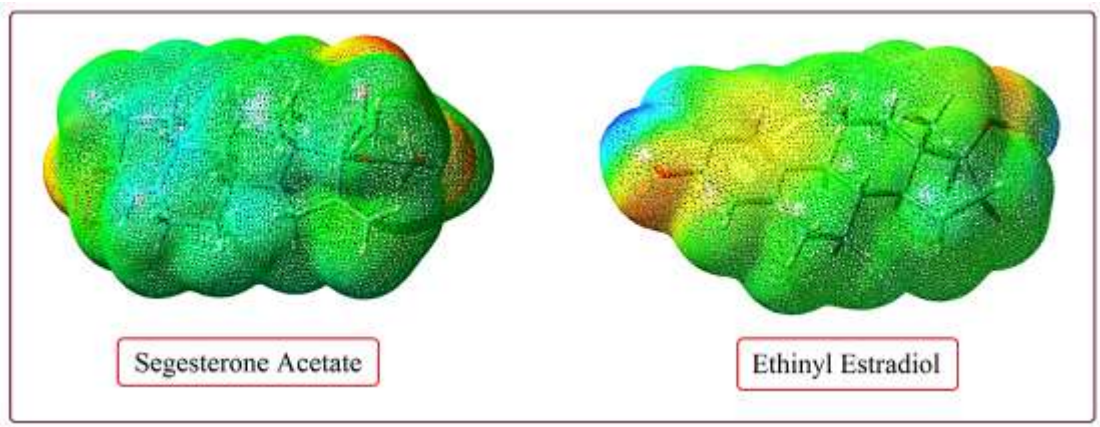


Figure 5. The molecular electrostatic potential (MEP) graphs of annovera active compounds

Table 1. Global reactivity indices of annovera active compounds

Parameter	Energy value (eV)	
	Segesterone Acetate	**Ethinyl Acetate**
HOMO	-6.12	-5.62
LUMO	-1.12	0.23
Ionization Potential (IP)	6.12	5.62
Electron Affinity (EA)	1.12	-0.23
Energy Gap (Eg)	5.00	5.85
Electronegativity (χ)	3.62	2.70
Chemical Potential (μ)	-3.62	-2.70
Chemical Hardness (η)	2.50	2.93
Chemical Softness (S)	0.40	0.34
Electrophilicity index (ω)	1.25	1.24

Physicochemical descriptors and ADME parameters of the active substances of annovera

The physicochemical descriptors computations and prediction of the ADME (absorption, distribution, metabolism, and excretion) parameters and pharmacokinetic properties of the molecular structures under study are done using a SwissADME web tool. Figure 6 shows the predicted physicochemical graphs of the title molecules. The colored zone shows the suitable physicochemical space for oral bioavailability. So, both active substances have suitable oral bioavailability. Segesterone acetate has 3 rotatable bonds and4 hydrogen bond acceptors. In contrast, ethinyl estradiol has 2 hydrogen bond acceptors and 2 hydrogen bond donors. Ethinyl acetate is a rigid molecule and has no rotatable bond. The molar refractivity for segesterone acetate and ethinyl estradiolare 104.73 and 88.84, respectively. The topological polar surface areas (TPSA) of these compoundsare 60.44 $Å^2$ (segesterone acetate) and 40.46 $Å^2$ (ethinyl estradiol). Also, the computations indicate 3.29 and 2.95 as a lipophilicity index ($LogP_{O/W}$ or iLogP) for segesterone acetate and ethinyl estradiol, respectively. On the other hand, Log S (ESOL) is a topological method for showing the water solubility of a chemical compound. The Log S scale is insoluble < -10 < poorly < -6 < moderately < -4 < soluble < -2 < very < 0 < highly. From the computational data, this index is -3.75 and -4.19 for the title compounds (segesterone acetate and ethinyl estradiol). So, both active substances are moderately soluble in water. The pharmacokinetic parameter predictions show these molecules have BBB permeability and higher gastrointestinal (GI) absorption. Also, segesterone acetate is a cytochrome P450 (CYP2C9) inhibitor. In contrast, ethinyl estradiol is a cytochrome P450 inhibitor (CYP2C9 and CYP2D6).The skin permeation index (Log Kp) of these molecules (segesterone acetate and ethinyl estradiol) is -6.52 cm/s and -5.50 cm/s, respectively. Generally, the bioavailability scorefor these active subtances is 0.55 due to their obeying from Lipinski rules (a: MW ≤ 500, b: MLOGP ≤ 4.15, c: N or O ≤ 10, d: NH or OH ≤ 5) [26].

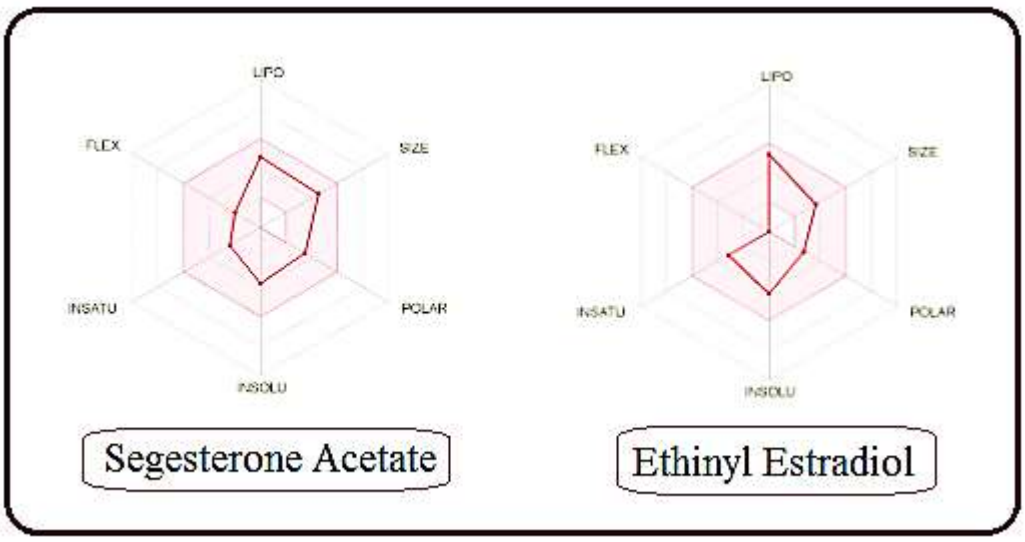


Figure 6. The physicochemical properties graphs of the active substances of annovera

Charge distribution and molecular docking

The Mulliken charge distribution on atoms of the active substances of annovera is shown in Figure 7. In this graph, the red, black and green colors relate to the negative, zero and positive charges, respectively. In these molecular structures, the centers with negative charges like to interact with the residues of receptors containing positive charges or electron poor groups. In contrast, the centers of these molecules containing positive charges like to interact with electron rich residues or groups. On the other hand, Figure 8 indicates the two-dimensional electron-localization graphs of segesterone acetate and ethinyl estradiol. These graphs indicate that the main charge localization is around the rings of the title compounds. So, these rings of the said compounds can be participated in steric interactions with the residues of the receptors (PR and ER).

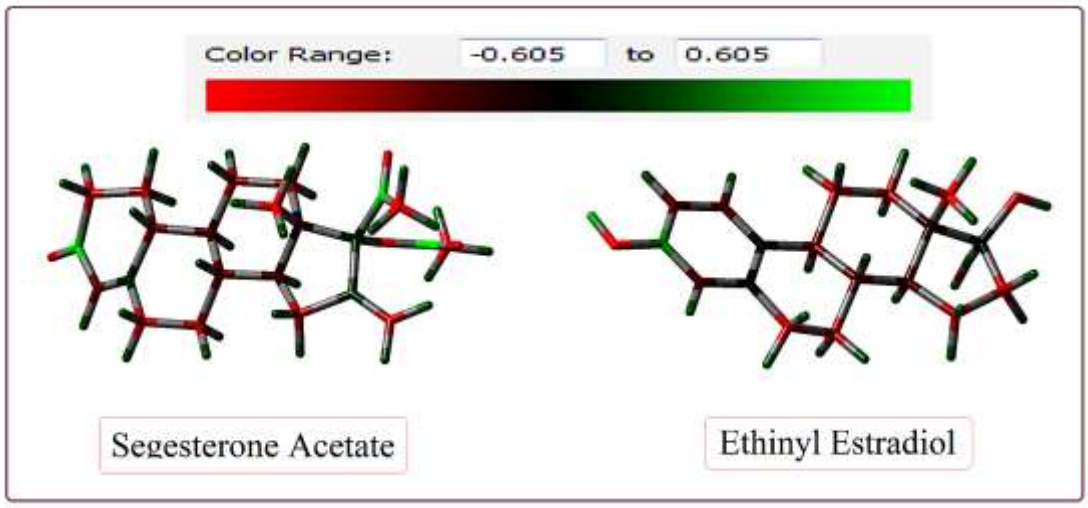


Figure 7. The charge distribution of the active substances of annovera

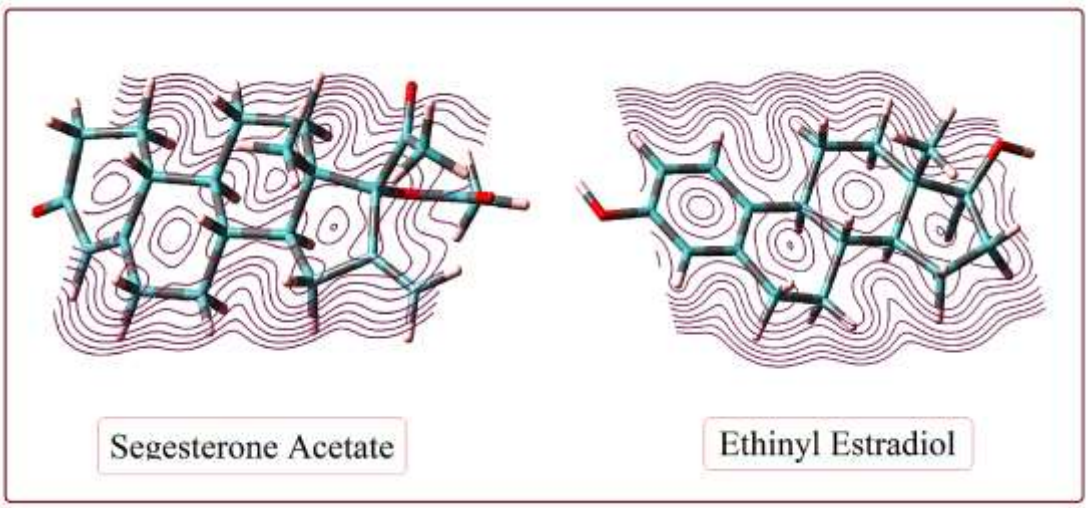


Figure 8. The two-dimensional electron localization graphs of the active substances of annovera

Literature review clearly shows that the active molecules of annovera have high affinities to form complexes with progesterone and estrogen receptors (PR and ER) [27]. Thus, interactions of segesterone acetate and ethinyl estradiol with PR and ER will be analyzed using docking studies. The three dimensional crystal structures of the title receptors (PR and ER) were obtained from protein data bank (PDB) and the docking analyses were carried out using Molegro Virtual Docker (MVD) program. Figure 9 collects the graphs of the title compounds embedded in the active site of the progesterone and estrogen receptors. We can see that ethinyl estradiol can make a complex with a second chain of estrogen receptor. In contrast, segesterone acetate interacts with first chain of progesterone receptor. It can be seen from the data of the Table 2 that the formation of ethinyl estradiol-estrogen receptor complex is mainly done by steric interactions with moldock score -115.420. The total energy score for the binding of this molecule to the ER is -108.221. On the other hand, this score is -122.005 for the segesterone acetate-progesterone receptor complex formation (Table 3). The steric interactions between segestrone acetate and progesterone with moldock score -142.701 is the main interaction in ligand binding to PR. Also, the hydrogen bond interactions do not play an important role in complex formation of both compounds with related receptors (PR and ER). It can be deduced that the segesterone acetate-progesterone receptor interaction is stronger than the ethinyl estradiol-estrogen receptor. Figure 10 shows the hydrogen bond and steric interactions of title substances embedded in the active site of the estrogen and progesterone receptors (ER and PR). It can be seen from the data of the Table 4 that the ER residues containing Phe [B] 404, Leu [B] 346, Leu [B] 387, Leu [B] 391, His [B] 524, Met [B] 421, Met [B] 388, and Leu [B] 525 play the main role in the estrogen receptor complex formation with ethinyl estradiol. In contrast, the PR-segesterone acetate complex formation is mainly done by the residues Phe [A] 778, Met [A] 759, Leu [A] 718, Tyr [A] 890, Leu [A] 887, Cys [A] 891, Leu [A] 763, Met [A] 756, Leu [A] 797, Val [A] 760, and Gln [A] 725 (Table 5).

Figure 9. The ligands (ethinyl estradiol and segesterone acetate) embedded in the active sites of receptors (ER and PR)

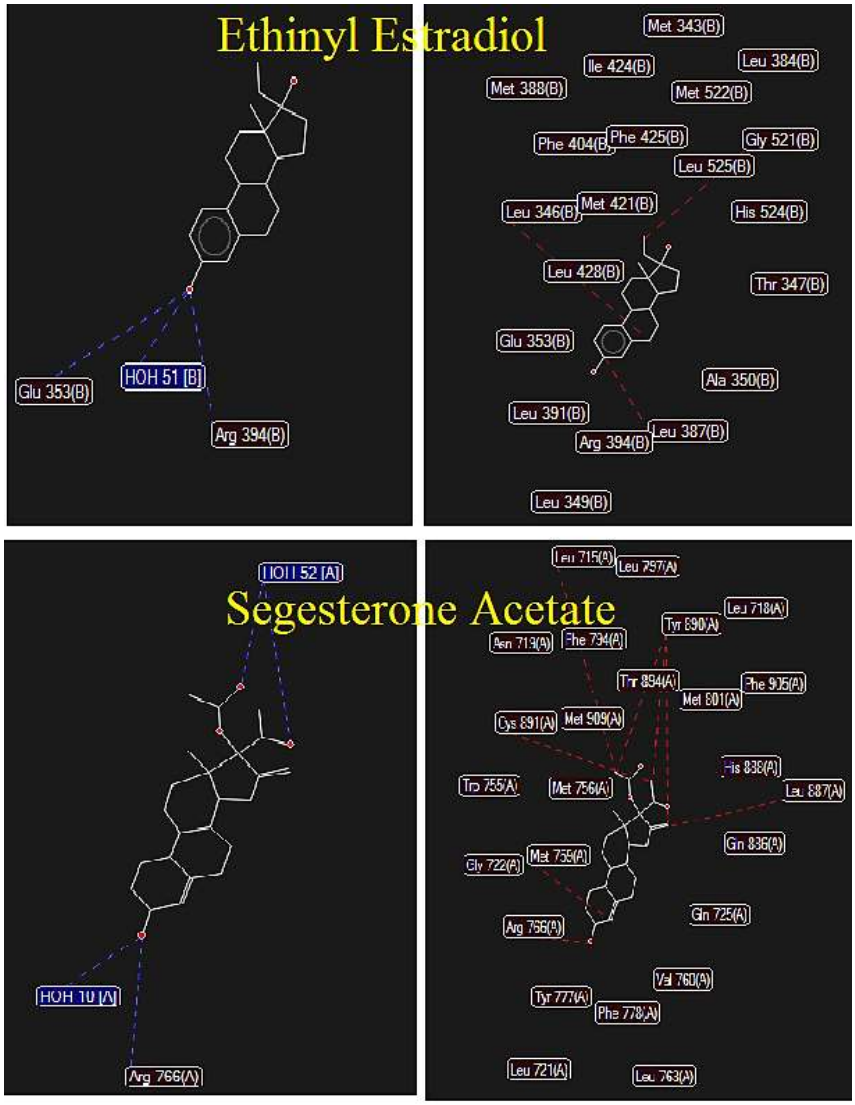


Figure 10. H-bond and steric interactions of theligands (ethinyl estradiol and segesterone acetate) embedded in the active sites of receptors (ER and PR)

Table 2. The ethinyl estradiol-estrogen interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-115.420
	Steric (by LJ12-6)	-43.049
	Hydrogen bonds	-0.398
	Hydrogen bonds (no directionality)	-4.938
Water-Ligand Interactions		-3.816
Internal Ligand Interactions	Torsional strain	0.061
	Steric (by PLP)	11.352
	Steric (by LJ12-6)	67.796
External and Internal Ligand Interactions	Total Energy	-108.221

Table 3. The segesterone acetate-progesterone interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-142.701
	Steric (by LJ12-6)	-26.049
	Hydrogen bonds	1.269
	Hydrogen bonds (no directionality)	1.269
Water-Ligand Interactions		-8.721
Internal Ligand Interactions	Torsional strain	2.263
	Steric (by PLP)	25.885
	Steric (by LJ12-6)	120.291
External and Internal Ligand Interactions	Total Energy	-122.005

Table 4. The participated estrogenresidues in ligand-receptor interactions

Residue/HOH	Total energy score
Phe [B] 404	-16.3062
Leu [B] 346	-13.6793
Leu [B] 387	-11.8512
Leu [B] 391	-10.1359
His [B] 524	-9.15281
Met [B] 421	-7.25498
Met [B] 388	-7.15192
Leu [B] 525	-5.22364
Glu [B] 353	-4.85910
Ile [B] 424	-4.36218
Leu [B] 384	-3.91519
Water HOH 51 [B] 19	-3.81577
Ala [B] 350	-3.77754
Leu [B] 349	-3.02071
Met [B] 343	-2.43165
Arg [B] 394	-2.39712
Gly [B] 521	-1.80154
Thr [B] 347	-1.45193
Leu [B] 428	-1.24748
Phe [B] 425	-0.740808
Met [B] 522	-0.498374

Table 5. The participated progesterone residues in ligand-receptor interactions

Residue/HOH	Total energy score
Phe [A] 778	-15.0425
Met [A] 759	-13.6566
Leu [A] 718	-12.7654
Tyr [A] 890	-11.4556
Leu [A] 887	-10.9634
Cys [A] 891	-9.32749
Leu [A] 763	-8.99099
Met [A] 756	-8.57350
Leu [A] 797	-6.55324
Val [A] 760	-6.45227
Gln [A] 725	-5.93413
Water HOH 52 [A] 227	-5.73393
Met [A] 801	-4.75887
Asn [A] 719	-4.20168

Leu [A] 721	-4.16223
Phe [A] 794	-2.88695
Water HOH 10 [A] 1	-2.88661
Thr [A] 894	-2.48152
Met [A] 909	-1.73100
Gly [A] 722	-1.64284
Phe [A] 905	-1.14158
Leu [A] 715	-0.940143
Arg [A] 766	-0.873874
Trp [A] 755	-0.863352
Tyr [A] 777	-0.436699
His [A] 888	-0.425940
Gln [A] 886	-0.411805

Conclusion

The present study is related to the docking analysis of active substances of annovera (segesterone acetate and ethinyl estradiol) with progesterone and estrogen receptors (PR and ER), respectively. The Gaussian 03 and Molegro Virtual Docker (MVD) software were used to optimize the molecular structures and their binding to the said receptors. The computations show that the steric interactions play the main role in the ligand-receptor complex formation. The ERresidues containing Phe [B] 404, Leu [B] 346, Leu [B] 387, Leu [B] 391, His [B] 524, Met [B] 421, Met [B] 388, and Leu [B] 525 play the main role in the estrogen receptor complex formation with ethinyl estradiol. In contrast, the PR-segesterone acetate complex formation is mainly done by the residues Phe [A] 778, Met [A] 759, Leu [A] 718, Tyr [A] 890, Leu [A] 887, Cys [A] 891, Leu [A] 763, Met [A] 756, Leu [A] 797, Val [A] 760, and Gln [A] 725.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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