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Chlorpheniramine Maleate against the antigenic peptide of Follicle-Stimulating Hormone Receptor (FSHR) using Insilico techniques.

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ABSTRACT

Background: To use insilico techniques to examine the potential effectiveness of an anti-allergy medication against the Polycystic Ovary Syndrome (PCOS) Antigenic peptide (Model Archive: https://modelarchive.org/doi/10.5452/ma-9vhj6). Our present work's main objective is to dock the modeled FSHR peptide with an anti-allergy medication. The effectiveness of Chlorpheniramine Maleate against the FSHR peptide was predicted using drug docking studies. **Materials and procedures**: The genomic sequence of FSHR-Peptide was obtained from the UniProt database. It was then docked using the CBDOCK server with Chlorpheniramine Maleate, an anti-allergy drug currently in use. **Results and Discussion:** This investigation shows that the reference drug, Chlorpheniramine Maleate, interact effectively with FSHR-peptide. The compound's effectiveness against the PCOS-causing protein was evaluated using the docking score. **Conclusion:** The study's conclusion is that PCOS drugs effectively block the FSHR protein that is impacted. The field of endocrinology informatics research is significantly impacted by the findings of this study.

Keywords: Model Archive, CBDOCK, Discovery Studio, Estrogen Receptor 1 (FSHR), and Chlorpheniramine Maleate.

1. INTRODUCTION

The primary cause of anovulatory infertility in females of reproductive age is polycystic ovarian syndrome (PCOS), a complicated endocrine condition [1, 2]. Between 6 and 26% of people globally have PCOS [3]. In addition to obesity, insulin resistance, and elevated LH levels [5, 6], PCOS is characterized by chronic anovulation, hyperandrogenism, and irregular menstruation [4]. According to the Rotterdam criteria from 2003, PCOS is diagnosed based on two out of three characteristics: Oligo/anovulation, a biochemical or clinical indication of hyperandrogenism, and the presence of polycystic ovaries on ultrasonography should all be present [7]. It's becoming clear that PCOS can strike a woman at any time. It may begin when she is still in the womb, manifest clinically in adolescence, and persist for the duration of her reproductive years. Furthermore, PCOS women have a higher risk of developing metabolic disorders such as diabetes, hypertension, and cardiovascular disease even after menopause [8].

Although the exact cause of PCOS is still unknown, it has been proposed that the condition is caused by a combination of environmental and genetic factors [9]. Gonadotropins such prolactin,

luteinizing hormone (LH), and follicle-stimulating hormone (FSH) have elevated amounts in PCOS. Women with hyperandrogenic PCOS have low FSH and an elevated LH pulse frequency as a result of continuous high-frequency GnRH stimulation [10]. Follicular development arrest brought on by lower FSH levels contributes to PCOS-related ovulatory failure. Numerous studies support these changes in gonadotropin production (LH and FSH) in PCOS, which may also be influenced by genetic variations of gonadotropic-related genes including FSHR (FSH receptor) and LHCGR (LH/choriogonadotropin receptor) [11].The FSHR, which has ten exons and nine introns, is found on chromosome 2 at positions p21–p16. The first nine exons of the receptor encode its extracellular domain. On the other hand, exon 10 encodes the intracellular domain, the whole transmembrane domain, and the C-terminal end of the extracellular domain of the FSHR. Graffian follicle formation, granulosa cell proliferation, and estrogen synthesis are all regulated by FSHR, which is expressed in granulosa cells in females [12]. Numerous intracellular signaling pathways are triggered when FSH interacts to its receptor, FSHR, and exon 10 is essential for signal transduction [13, 14].

Mutations in FSHR, particularly in exon 10, can cause follicle development to stop at various stages of growth and have a variety of phenotypic implications, including varied development of secondary sex traits, primary amenorrhea, hypoplastic ovaries, and elevated FSH serum levels [15, 16]. The two polymorphisms found in exon 10 of FSHR, Ser680Asn (rs6166) and Ala307Thr (rs6165), are well documented to impact the FSHR receptor's effectiveness toward its ligand (FSH) and raise FSH levels in a compensatory manner.This raises FSHR resistance, which lowers estrogen and inhibin B, which create the pituitary gland's inhibitory feedback loop. This leads to hyperandrogenism, which may stop the formation of follicles [17]. These polymorphisms may impact the menstrual cycle, ovarian hyperstimulation, and the development of PCOS, according to many research [18, 19]. The genetic relationship of these SNPs has been the subject of numerous investigations worldwide, although the findings have been inconsistent. Meta-analysis has been a well-known technique for resolving disagreements in genetic association research.

In particular, it improves statistical strength and impact estimation accuracy by incorporating results from multiple studies on the same topic [20]. There are some more articles on FSHR polymorphisms [24, 25], despite the fact that a meta-analysis has previously been conducted on both variations [21–23]. Moreover, only Asian studies are included in a recent meta-analysis by [23]. Therefore, we carried out a comprehensive and updated meta-analysis to determine the association between these polymorphisms and PCOS susceptibility in the global population.

In this study, we concentrate on Chlorpheniramine maleate , an NSAID (Nonsteroidal Anti-Inflammatory Drug), which suppresses the putative antigenic peptide FSHR by insilico procedures. Cyclophosphamide, an existing chemotherapy medication, was contrasted with Chlorpheniramine maleate . This helps us understand how an anti-inflammatory medication can help with cancer research.

2. MATERIALS AND METHODS

Ligand selection: Molecular docking study focused on chemical compounds with NSAID (Nonsteroidal Anti-Inflammatory Drug) characteristics, such as Chlorpheniramine maleate For the selected chemical, PubChem (https://pubchem.ncbi.nlm.nih.gov/) supplied the simplified molecular input line entry system (SMILES) format [18]. The canonical SMILES (Simplified Molecular Input Line Entry System) of the three chemical compounds were sent to the Online SMILES Translator (https://cactus.nci.nih.gov/translate/) in order to retrieve the PDB structure. The 3D antigenic Polycystic ovary syndrome (PCOS) peptide was downloaded from the PDB-Model archive (https://modelarchive.org/doi/10.5452/ma-9vhj6) in order to perform pharmacological docking investigations.

One of the most widely used insilico drug discovery methods is molecular drug docking, which examines the optimal conformations of small molecules during interactions with target molecules. Two chemical compounds and FSHR were subjected to docking analyzes. PDB files for the ligand and receptor 3D structures were uploaded to the CBDOCK website [19] (http://hdock.phys.hust.edu.cn/) in order to forecast the interaction between receptor and ligand molecules. The CBDOCK study also revealed information on the surface residues of the ligand and receptor. 3D visualization of macromolecules: Molecular drug docking studies employing FSHR were conducted on two compounds: Chlorpheniramine maleate . The three-dimensional structures of the compounds were visualized using a molecular visualization tool called Discovery Studio.

3. RESULTS AND DISCUSSION

To evaluate the binding efficacy, compounds such as the test chemical Chlorpheniramine maleate and the control medication was docked with the modelled FSHR as shown in Table 1. The binding model with the greatest docking score, as shown in Table 1, was chosen from the top 10 binding models generated by the CBDOCK server because it had a higher binding affinity for the receptor. With a docking value of -5.4 kcal/mol, the Chlorpheniramine maleate molecule has a higher binding score.

The score represents the possible energy change that might arise from the ligand-protein interaction. Thus, a very negative score indicates a strong link, while a less negative or positive value indicates a weak or absent bond. Using CBDOCK, a cutting-edge web server for template-based modeling and free docking, Chlorpheniramine maleate were docked with the modeled Estrogen Receptor 1 (FSHR) Peptide in this study. The drug binding affinities of the ligand and receptor are displayed in Table 1.

The three-dimensional (3D) structure of the ligand and receptor was analyzed using the molecular visualization software Discovery Studio after the docking analysis, as seen in Figures 2 and 3 for Chlorpheniramine maleate and (FSHR) and Figures 5 and 6 for (FSHR). The effectiveness of the CBDOCK server has been demonstrated by earlier research.

Table 1: Summary of docking scores of ligand and receptor

TABLE: 1 MOLECULAR DRUG DOCKING SUMMARY

	Drug (Test)
Target	Chlorpheniramine maleate
Follicle-Stimulating Hormone Receptor (FSHR)	-5.4 kcal/mol

Note: Chlorpheniramine maleate most effectively suppresses the growth of Polycystic ovary syndrome (PCOS) protein cells for FSHR, according to the docking score above. The control medication, cyclophosphamide, is the most effective treatment for Polycystic ovary syndrome (PCOS) .

Protein and drug complex: A drug is essentially a highly specialized, custom-made key or a pair of molecular shackles sent into the metropolis. The drug and the corresponding protein work well together. This combination structure is known as the drug-protein complex. Drug and receptor electrostatic force: A strong, non-covalent attraction occurs when a positively charged region on a drug molecule lines up with a negatively charged region on a receptor protein in an electrostatic interaction between a protein and a ligand (also known as the electrostatic force between a receptor and a drug). Imagine your medicine molecule as the matching key and your receptor protein as a safe electronic door lock. Electrostatic forces act as natural magnets that pull the drug-key toward the keyhole from a distance, even though some parts of the key must match the geometry of the lock. On the other hand, an intelligent drug designer will give the drug molecule a consistent positive charge at the exact spot if your target protein contains a section of amino acids that carry a negative charge (like Glu or Asp). These magnetic forces provide an extensive attraction when the drug passes through the crowded cellular environment. They create a stable drug-protein complex that either deactivates or activates the target by inserting the drug straight into the binding site and securing it firmly.

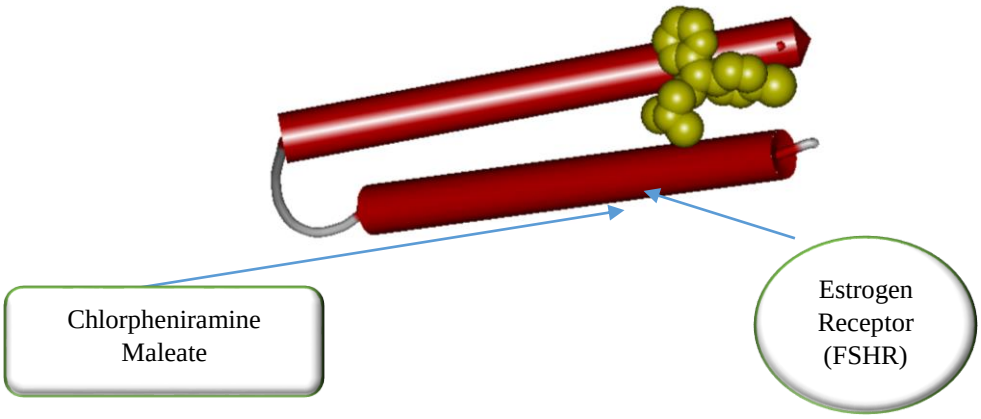

Figure 1 shows a tube model of the Follicle-Stimulating Hormone Receptor (FSHR) with Chlorpheniramine maleate using the visualization program Discovery Studio.

The docking study enables the evaluation, screening, and prediction of the computational electrostatics of the ligand-receptor complex [21], according to Sahoo et al. [20]. According to Mohapatra et al., this inquiry typically comprises of two separate steps [22]. Initially, the active site of the protein is used to sample ligand conformations. Second, a scoring system is used to rank conformations. Dash et al. [23] state that sampling algorithms should theoretically replicate experimental binding modes and that a scoring system should be used to assess confirmations [24]. According to Sahoo et al. [25] and Pramanik et al. [26], the dry lab approach has a major benefit over in vivo lab investigations in terms of resource and time commitment. According to Nanda et al. [27], this method forecasts the orientation of the ligand in a complex that the ligand forms with proteins or enzymes. Additionally, the interaction is quantified by the geometry and electrostatic interaction of the docked complex.

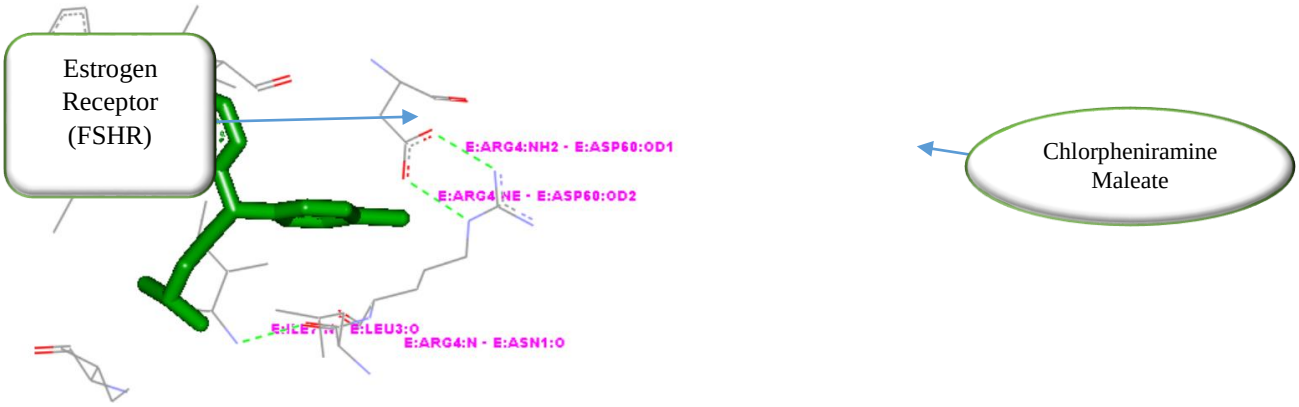

Figure 2: Using the visualization tool Discovery Studio, the H-Bond interactions model view of Chlorpheniramine maleate and the Follicle-Stimulating Hormone Receptor (FSHR).

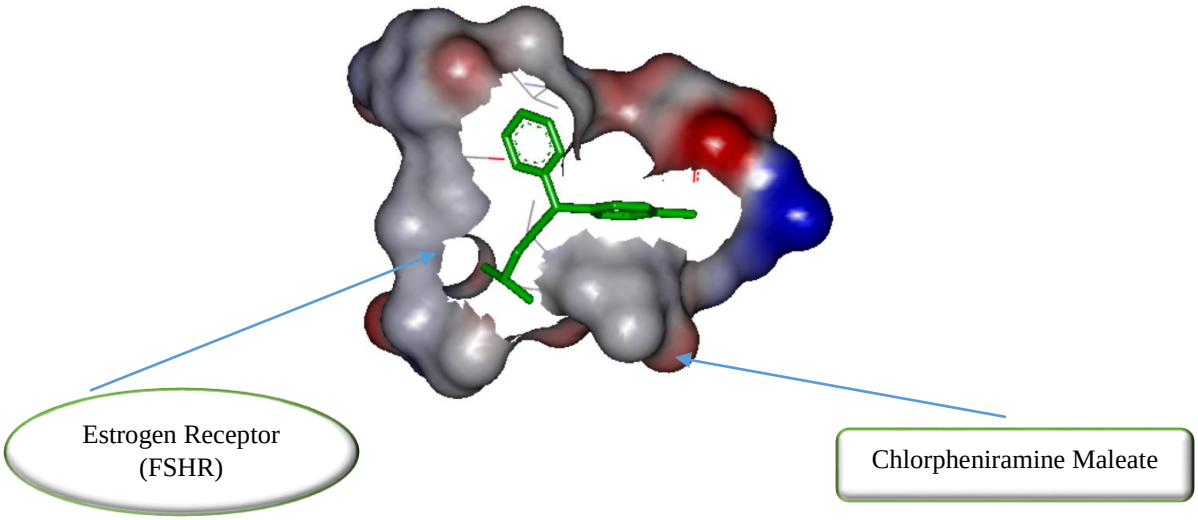

Figure 3 shows the Van der Waals interactions model view of the follicle-stimulating hormone receptor (FSHR) and Chlorpheniramine maleate using Discovery studio .

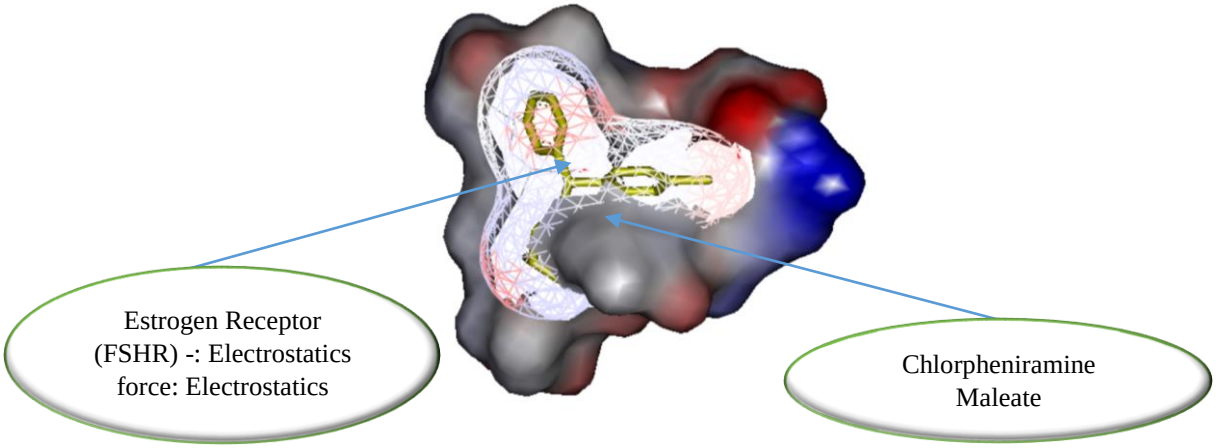

Figure 4 shows an electrostatic force model image of the follicle-stimulating hormone receptor (FSHR) with Chlorpheniramine maleate using the visualization program Discovery Studio.

Drug-receptor Van der Waals interaction: Van der Waals forces are weak, short-range electrostatic attractions that occur when the electron clouds of two neutral atoms get closer to one another. As a result, the atoms are softly pulled together by transitory dipoles. Van der Waals forces are comparable to molecular The magnets (electrostatic forces) can draw the key to the lock from a distance, but the key must precisely fit the internal geometry of the lock to turn it. At this time, van der Waals forces become important. A swarm of electrons in motion surrounds every atom.

Drug docking mechanisms: FSHR mutations alone do not fully account for endocrine resistance in MBC. About 50% of cases of endocrine resistance are associated with an FSHR mutation; additional, increasingly identified causes include alterations in the PI3K-AKT-mTORC1, RAS-MAPK, and CDK4/6-RB-E2F pathways as well as FSHR deletion, amplification, and translocation [26]. Additionally, FSHR mutations frequently occur with other concurrent genetic alterations, which together lead to a poorer prognosis globally [27, 28].

This study used virtual screening and molecular docking simulations to assess the binding kinetics of the common anti-inflammatory drug Chlorpheniramine maleate and the Follicle-Stimulating Hormone Receptor (FSHR) inhibitor. A synthetic alkylamine derivative, Chlorpheniramine maleate is used as an antihistamine for allergic responses, hay fever, rhinitis, urticaria, and asthma. Maleate exhibits anticholinergic and mild sedative properties in addition to acting as a competitive histamine H1 receptor antagonist.

Its competitive docking score was -5.4 kcal/mol. The continuous interaction characteristics of Chlorpheniramine maleate indicate a robust steric compatibility with the hydrophobic and electrostatic residues in the target protein's functional region. The amino acids ARG:4, ASN:1,ASP:60,ILE:4, LEU:3 engage with the H-Bond against the FSHR modeling peptide.

The combined thermodynamic data suggest that these compounds bind to the critical functional areas of the modeled Follicle-Stimulating Hormone Receptor (FSHR) transporter. It is evident from the docking experiments that Chlorpheniramine maleate is present in the membrane areas' binding site [29, 30].

4. CONCLUSION

Anovulation, infertility, obesity, insulin resistance, and polycystic ovaries are common symptoms of PCOS, a complicated endocrine and metabolic condition. The overall results clearly show that the drug (Chlorpheniramine maleate) may inhibit the hydrophobic portions of the distinct expected structure of the Follicle-Stimulating Hormone Receptor (FSHR) of PCOS. The docking data and the modelled structures have been submitted to the Model Archive (https://modelarchive.org/doi/10.5452/ma-9vhj6). This study suggests that Chlorpheniramine maleate , an anti-inflammatory drug (NSAID), binds to the estrogen receptor (FSHR) efficiently. The results of this study are essential to the field of modern Endocrinology research.

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6. CONFLICT OF INTEREST

No conflicts of interest are disclosed by the writers.

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