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Molecular Docking Study on Tamoxifen and Toremifene's Effects on the Breast Cancer Receptors

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Abstract: Both toremifene (TOR) and tamoxifen (TAM), selective estrogen receptor modulators, are equally effective therapies for breast cancer (BrCa). In high-risk women, anti-estrogenic tamoxifen is frequently used for both (BrCa) treatment and prevention. Another anti-estrogen that is successful in the treatment of (BrCa) is toremifene. Anti-estrogens have emerged as one of the most widely utilized medicine classes among women because (BrCa) is the most frequent malignancy in this population. Consequently, we performed a docking study to assess the effects of tamoxifen and toremifene therapy on the (BrCa) receptor. Tamoxifen and toremifene's interactions with the (BrCa) receptor were examined by a computational study of the ligand's binding. These receptors are named (1jnx), (1n5o), (1oqa), (1t2u), (1t29), (4igk), (4jlu), and (4y2g). All the docking has been done by software named Molecular Operating Environment (MOE) which was used to evaluate the binding docking and docking score between the ligand (TAM or TOR) with the (BrCa) receptors.

Keywords: Docking, Breast cancer receptors, Tamoxifen, Toremifene

1. Introduction

As it recently overtook lung cancer as the most common disease diagnosed globally, breast cancer (BrCa) has long been a major social concern [1,2]. The World Health Organization (WHO) projected that there will be more than two million (BrCa) patients worldwide in 2021(3). The second most frequent form of cancer in women is (BrCa), which is characterized by the unchecked development of epithelial cells in the breast. Based on the mechanism and routes of carcinoma, (BrCa) has been categorized, and these classifications have produced the fundamental targets for the prognosis and treatment of the illness [4,5].

It has been demonstrated that toremifene (TOR) and tamoxifen (TAM) are equally effective for premenopausal and postmenopausal women with estrogen receptor-positive (BrCa) conditions [6]. Synthetic ligands have been used to modify estrogen functionality by binding to the estrogen receptor with a bioactive small molecule. Toremifene, a chlorinated derivative with similar site-specific activity, has been developed in response to concerns about (TAM)'s side effects, which include thromboembolic events, endometrial malignancies, and ocular damage. Tamoxifen inhibits the production of estrogen by acting as an ER antagonist and an aromatase inhibitor [7-9].

Estrogen receptors, which are found in both (BrCa) cells and reproductive organs, are inhibited by anti-estrogens. Anti-estrogen use can thus have a range of gynecological consequences. The use of anti-estrogens is linked to vasomotor symptoms, dryness, and irritation of the vagina, which may be symptoms and effects of hypo-estrogenism, according to research, most of which are cross-sectional. Anti-estrogens have an impact similar to oestrogens in the uterus, particularly in the endometrium, and (TAM) may be more effective than (TOR) in this regard, at least in animal studies.

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(TAM) and (TOR) use have been associated with an increased risk of endometrial polyps, and (TAM) may also raise the risk of endometrial cancer [10-14].

In the (TOR) vs. (TAM) Adjuvant Trial, more than 1800 perimenopausal or postmenopausal women with invasive (BrCa) who tested positive for the hormone receptor (HR) were administered (TOR) or (TAM). The two primary outcomes that were evaluated were overall survival (OS) and disease-free survival (DFS) [15]. Tamoxifen usage is a common therapy option for (BrCa) which has hormone receptors. In a trial, the effectiveness and safety of (TOR) and (TAM) were evaluated in the treatment of premenopausal women with operable hormone receptor-positive (BrCa) [16-17].

There are numerous instances of (BrCa) patients who underwent surgery and then received endocrine medication therapy. All patients were randomly assigned to (TOR) and (TAM) groups [18]. Hepatic cytochrome P450s (CYPs) may have the most bearing because of the structural differences between (TAM) and (TOR), which result in differences in pharmacokinetics and pharmacodynamics [19,20].

A selective estrogen receptor modulator, (TOR) is equally effective as (TAM) in treating (BrCa) in patients. So, contrasted the safety of (TAM) and (TOR) when used as adjuvant therapy for premenopausal (BrCa) [21]. Despite having comparable clinical effectiveness as palliative and postmenopausal adjuvant medicines, (TOR) and (TAM) are metabolized differently due to a single side chain chloride ion, giving (TOR) a more favorable toxicity profile [22].

Toremifene may reveal existing endometrial cancers rather than cause new ones, according to data on secondary endometrial cancer that indicated their incidence was lower with the drug than (TAM). Toremifene may carry a decreased risk of stroke, pulmonary embolism, and cataracts than (TAM) [23]. According to several earlier research, more than 40% of patients receiving TAM therapy developed fatty liver throughout (3-5) years of follow-up [24,25]. An essential component of postoperative comprehensive care for patients with (BrCa) is adjuvant endocrine therapy. Endocrine therapy has been demonstrated in numerous studies to have some effect on the serum lipids of (BrCa) patients, and alterations in lipid profiles (26) may result in several issues (27). Low-density lipoprotein cholesterol and serum triglyceride levels are both increased by TAM and are significant indicators of risk for cardiovascular (28). In comparison with TAM, which does so in vitro, TOR does not raise triglyceride concentrations intracellularly [29].

A computer program (software package) was used to analyze the molecular docking [30] binding between the ligand (such as medicine) and the proteins. For the analysis of drug-protein interactions, docking was used. To provide the best energy stability for the docking combinations, every medication was coupled with a protein [31]. The predicted compounds' physical and chemical characteristics were evaluated to choose the best form as the COVID-19 treatment candidate [32] or the Ebola virus [33].

The goal of molecular docking approaches is to forecast the most effective way for a ligand to bind to a macromolecular group, and A computational method called molecular dynamics (MD) models the dynamic behavior of molecules as a function of time [34]. Molecular docking and dynamic simulation techniques were used to investigate the molecular interactions between natural products and overexpressed receptors in (BrCa). The best ligand was then extracted from citrus-limetta and developed for nanoscale encapsulation using soy lecithin and a sonicator [35].

There was a significant interaction between (TOR) and the methyltransferase nonstructural protein (NSP), which may prevent viral replication by interfering with its active site. By preventing the spike protein of SARS-CoV-2, findings propose a possible therapeutic candidate [36,37] for COVID-19 by pointing to potential structural pathways for (TOR) [38]. Tamoxifen alone or in combination with ovarian suppressive methods makes up the majority of the endocrine adjuvant treatment for (BrCa) in premenopausal women. A chlorinated version of (TAM), (TOR) has a better risk-benefit ratio than its parent drug. intended to establish the function of (TOR) as an alternative to (TAM) for premenopausal patients with estrogen or progesterone receptor-positive breast cancer [39].

2. Computational Method

The RCSB Protein Data Bank was used to obtain the 3D structures of the protein targets identified as

(1jnx), (1n5o), (1oqa), (1t2u), (1t29), (4igk), (4jlu) and (4y2g) [40]. These files were sent to the (MOE) software and were modified to add polar hydrogen atoms and remove water molecules. Chem-Office 2D was used to create the 3D structure of the ligands (TAM and TOR) and convert it to the (MOE) software. The molecular docking analysis was carried out using the Molecular Operating Environment (MOE). To determine the binding energy between the ligands (medicines) and the (BrCa) receptor, the results were assessed. The (MOE) program was utilized to visualize the protein-ligand complexes. After characterizing the polar and hydrophobic interactions between the ligand and the target, 2D and 3D representations of these interactions were created.

3. Results and discussion

The influence of the ligand-protein complex's stability interacts with the bound docking outcome. The receptor 1t29 has the best docking score (-6.65281 kcal/mol) for toremifene out of all of them, followed by 1oqa (-5.83953 kcal/mol). Tamoxifen demonstrated the highest docking score with (1oqa) of -6.30418 kcal/mol), which was followed by (4y2g), which obtained a value of (-5.93631 kcal/mol.

The findings showed that polar H-bond and hydrophobic contacts were created by the drug's active core pocket's interactions with the target protein and amino acid residues. Figures (2-17) display the best-docked position view of TAM and TOR with BrCa receptors in three dimensions (3D). The docking map displays the interactions between the amino acid residues (Leu 1800) and (Glu 1829). The interaction involved TAM's connections with (Leu 1701) and several polar hydrogen and hydrophobic bonds with TOR

Table 1. The score values of two drugs docking with different breast cancer proteins

No.	Protein name	Tamoxifen		Toremifene	
		Score (kcal/mol)		Score (kcal/mol)	
		more stable	less stable	more stable	less stable
1	1jnx	-5.55416	-5.32851	-5.78573	-5.22148
2	1n5o	-5.49180	-5.29124	-5.78781	-5.33136
3	1oqa	-6.30418	-5.91453	-6.57282	-5.83953
4	1t2u	-5.21551	-5.10039	-5.39296	-5.18298
5	1t29	-5.75445	-5.52505	-6.65281	-5.57145
6	4igk	-5.90209	-5.57644	-6.05901	-5.67005
7	4jlu	-5.80364	-5.47576	-5.84705	-5.70310
8	4y2g	-5.93631	-5.63084	-6.13029	-5.52424

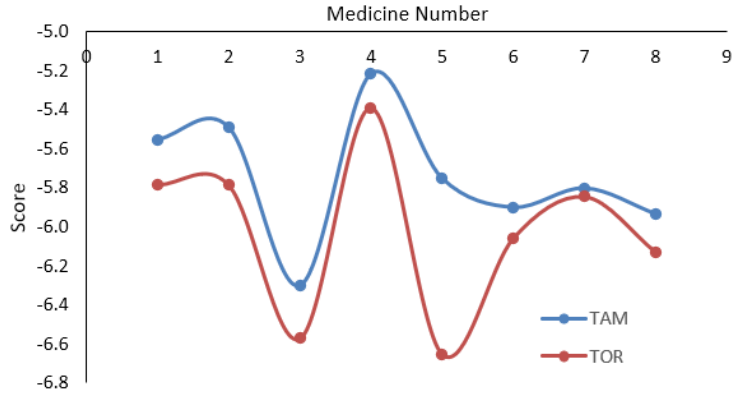

Figure 1. Comparison of (TAM and TOR) docking scores with various (BrCa) receptors in a more stable configuration

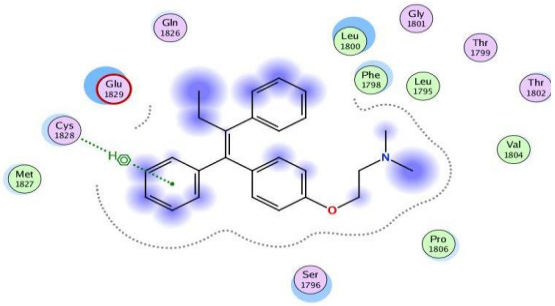

Figure 2. Tamoxifen with (1jnx)

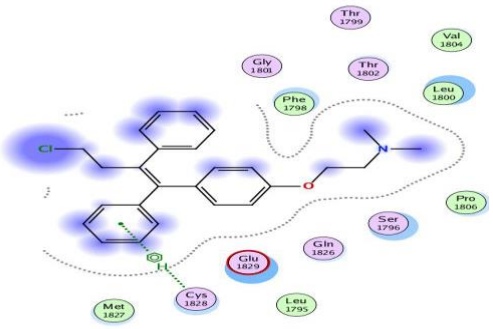

Figure 3. Toremifene with (1jnx)

According to ligand-protein (Drug-1jnx) interactions, the amino acids (Cyc 1828) actively participate in hydrophobic interactions with aromatic bonds by (TAM) and (TOR) respectively.

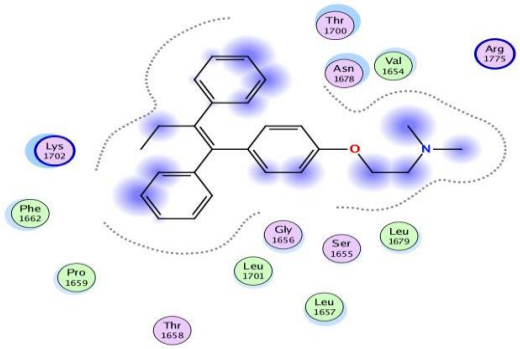

Figure 4. Tamoxifen with (1n5o)

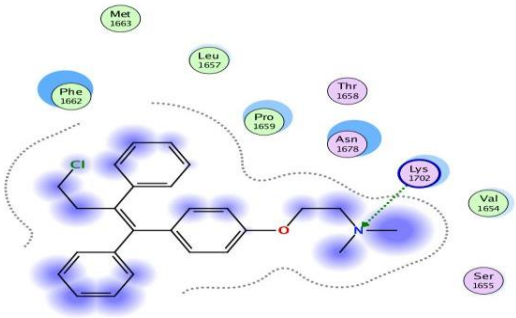

Figure 5. Toremifene with (1n5o)

TOR's hydrophobic interactions with proteins led to the production of amino acid residues (Lys1702).

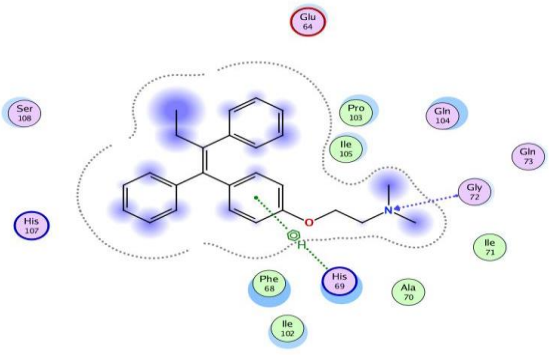

Figure 6. Tamoxifen with (1oqa)

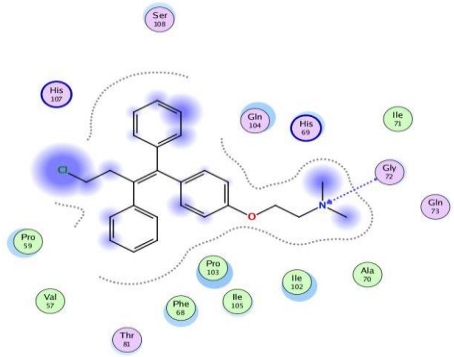

Figure 7. Toremifene with (1oqa)

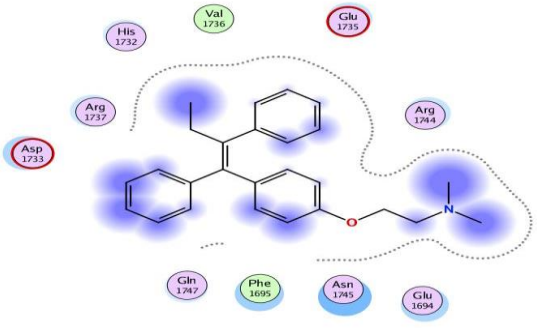

Figure 8. Tamoxifen with (1t2u)

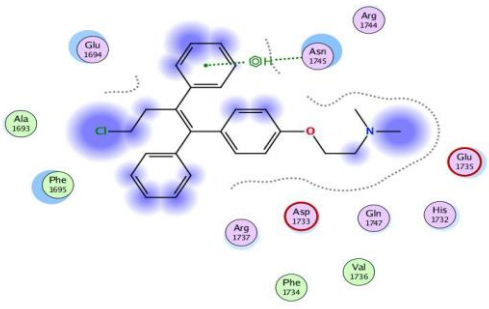

Figure 9. Toremifene with (1t2u)

Amino acid residue like (Asn 1745) was produced as a result of TOR's hydrophobic interactions with proteins.

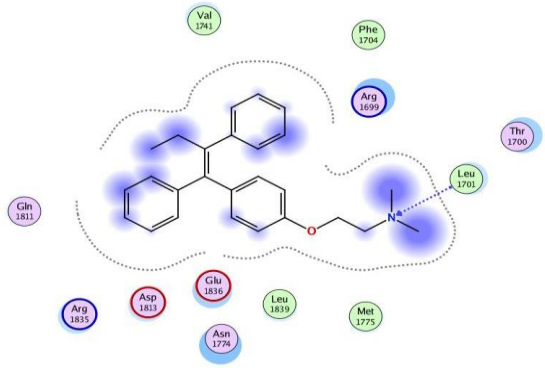

Figure 10. Tamoxifen with (1t29)

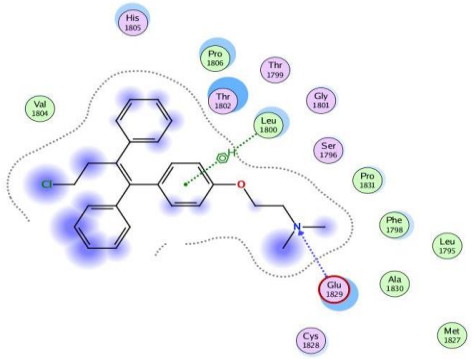

Figure 11. Toremifene with (1t29)

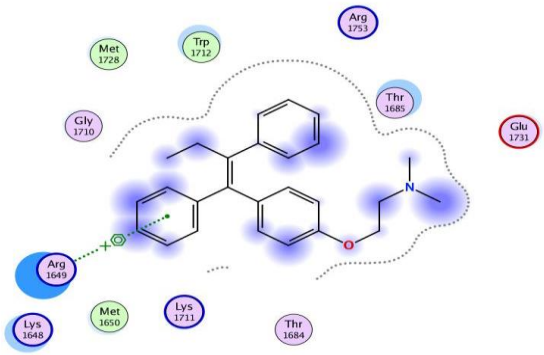

Figure 12. Tamoxifen with (4igk)

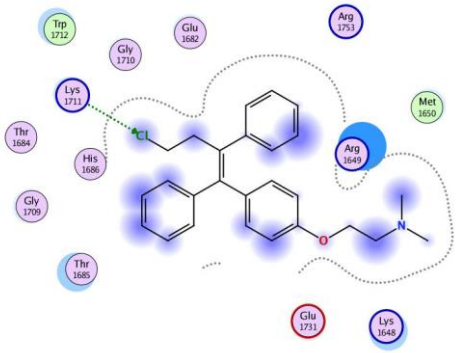

Figure 13. Toremifene with (4igk)

Through contact with (Arg1649), the Pi-aromatic's TAM in the binding site was performing activity. (Lys1711) with an active group identified as the protein binding site residues by chloride in TOR medicine.

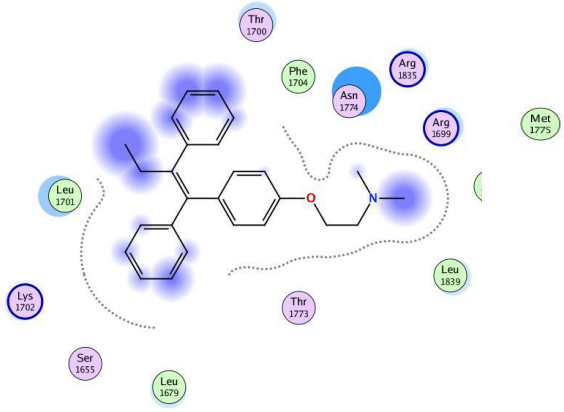

Figure 14. Tamoxifen with (4jlu)

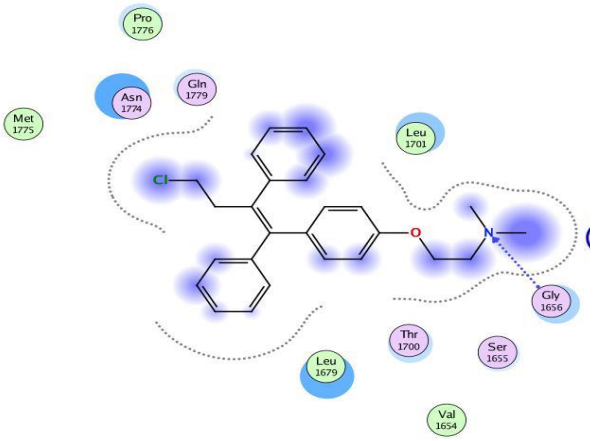

Figure 15. Toremifene with (4jlu)

The docking binding discovered that the receptor's ability to interact with TOR was represented by the amino acid (Gly1656). Nevertheless, this does not appear clearly in TAM medication. While Arg 1699 interacted with the hydroxy active group in the TAM medicine, Gln 1811 created a link with the Pi-

aromatic group. Leu 1701 interacted with the TOR medication's amino active group, whereas Arg 1835 formed a bond with the Pi-aromatic group.

4. Conclusions

This research primarily compares the medication efficacy of (TOR) and (TAM) through docking binding with several (BrCa) protein receptors. Although (TAM) is a commonly used medicine for treating (BrCa), there are questions and disagreements about its effectiveness because it can cause endometrial cancer and other side effects [41]. Rarer side effects include hepatotoxicity, visual issues, and an increased risk of colorectal cancer [42].

A lower binding energy typically indicates a more effective and stable interaction between the ligand and receptor. The best complex for binding, however, was the TOR complex because it was the most stable. These docking score data suggest that TOR is a more effective prospective cancer therapeutic agent than TAM.

Finally, the Tamoxifen (TAM) and Toremifene (TOR) drugs their results give the importance of using these drugs which act as inhibitors or modulators for treatments the patients with breast cancer [43,44].

CONFLICT OF INTEREST:

The authors declared that they had no conflicts of interest.

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