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IN SILICO MOLECULAR DOCKING, ADMET AND MOLECULAR DYNAMICS STUDIES ON AN EFFICIENT MONOMER FOR ANTI BREAST CANCER ACTIVITY

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ABSTRACT

Breast cancer in woman is the most prevalent cancer and in 2018 there were about 2 million new cases reported. The highest prevalence of breast cancer is registered in Belgium followed by Luxembourg. Mammary gland is a major organ in sperm that can secrete, synthesise and supply milk to children for nutrition, enhancement and defence. In ordinary and diseased conditions, oestrogen receptors (ER) are essential for improving the relevant treatment strategies. Estrogen is the key factor of the prognosis of breast cancer and plays a large part in improving breast cancer. Molecular docking and linking, free energy experiments investigated potent monomer binding mode, residue interaction patterns, and docking energy. Molecular dynamics research tracked the lead compounds and the diverse molecular stability and dynamic behaviour. The ADMET study was expected to demonstrate the drug like properties of monomer M4.

Keywords: Breast Cancer, Molecular Docking, ADMET, Molecular dynamics, monomer
INTRODUCTION

Breast cancer is the second most widespread cancer among women worldwide. Triple negative breast cancer is an extremely HER2

(estrogenic, progesterone, and human epidermal receptor) condition marked by a loss of expression. TNBC is typically violent

and can constitute up to 24 percent of all newly diagnosed cases associated with a bad prognosis [1]. Chemotherapy is the only available treatment choice because of no meaningful clinical purpose for TNBC [2]. In comparison, the recurrence risk of this breast cancer subtype is greater than that of other cancers and its survival is much lower. While many effective and innovative cancer detection and treatment methods have been developed, we are still handicapped in advanced metastatic cancer treatment. Breast cancer research found that 90% of deaths due to cancer were metastatic, not primary, tumour [3].

The aim of the study is to classify most possible estrogen receptor protein inhibitors to obtain new lead compounds to restrict the prognosis of breast cancer and understand its linkage to the establishment of drug molecules as opposed to the medication currently used.

METHODOLOGY

In our present study, *in silico* molecular docking and ADMET toxicity and Molecular Dynamic Simulation studies were carried out using AutoDock Vina, GROMACS 2020 and Biovia Discovery studio (DS) Visualizer 2020 software.

Ligand Preparation

In this *in silico* studies, we have analysis our previously synthesized (Z)-2-hydroxy-5-(5-((4-hydroxybenzylidene)amino)-4H-1,2,4-triazol-3-yl)benzaldehyde (M4)). The Anastrozole drug used as a standard for comparison study. The Anastrozole is used to treat breast cancer in women after menopause. Some breast cancers are made to grow faster by a natural hormone called estrogen. Anastrozole decreases the amount of estrogen the body makes and helps to slow or reverse the growth of these breast cancers. The molecule structure were drawn in Chemdraw software and the energy of the all the molecules were minimized and saved in SDF file format for further docking studies.

Protein Structure Preparation

In this analysis it was obtained from the protein Data Bank, RCSB, the structure of the estrogen receptor protein (PDB ID – 3ERT) and the structure of the PDB has different lack of detailed details on connectivity, along with structured shift and bond orders. The protein structure is imported by the protein preparation wizard from PDB into Maestro. The hydrogen polar display is only possible with the protein preparation wizard. These alternative reveals only polar atoms of hydrogen.

Molecular Docking

CDOCKER was recruited with the DS, which was primarily focused on the CHARMM force field, to examine the binding affinities between protein and ligand. Consequently, a spontaneous rigid body rotation has been generalized to different conformations. The generation of 10 conformers was allowed for each ligand, holding all of the other parameters as default. The results of the docking were read through the -CDOCKER energy interaction [3, 4], which means the energy of the non-connected interaction between ligand and protein. Higher energy exchange values also mean that the protein and ligand have a more desirable binding [5,6]. 4 ligand molecules and 4 FDA licensed breast cancer medications (anastrozole) were performed to detect the ability of the latest medicines in Docking. For the introduction of the docking protocol, the prepared protein and ligands were imported on DS. The results based on the ---CDOCKER interaction energy, interaction between the hydrogen bonds and the binding mode patterns were evaluated.

ADMET analysis

In this method, a variety of compound data bases can be used to minimize the time to scan for possible lead compounds for potential hits [7]. The estimation of the

ADMET profile for drug candidates and environmental chemicals is a significant factor in drug production and environmental risk assessment. The ADMET properties of the compounds were predicted using DS software in order to classify the potential adverse effects of these compounds in humans. Solubility, Absorption, BBB, HIA, and ADMET parameters are included. Risks and toxicity. 95% and 99% confidence ellipses in the ADMET PSA 2D, ADMET AlogP98 aircraft are described by the absorption levels of the HIA model [8].

Molecular Dynamic Simulation

The selective molecules with higher binding interaction in 3ERT receptor was applied to molecular dynamic Simulation (MD) analysis. The MD, analysis the temperature difference and stability of the 3ERT with selective molecules. The protocol for standard dynamic cascade and minimization analysis were clearly prescribed previously [9].

RESULTS AND DISCUSSION

Molecular Docking

The analyses of the drying against the oestrogen protein of breast cancer by simulated screening techniques have been carried out *in silico* n. In the expectation that efficient and selective inhibitors will constitute the latest class of cancer

therapeutics and other proliferative diseases, the discovery of compounds that could inhibit the activity of tyrosine kinase was carried out by pharmaceutical companies and university laboratories. 3ERT inhibitors can also be properly used as a new form of therapy for cancer. Recent silicon analysis has been carried out in order to identify active anti-breast cancer compounds. For their binding interaction in 3ERT active site, the four M4 and normal medicine Anastrozole were also evaluated. The simulated hits reported in this analysis can be used as an alternate target for breast cancer after testing by in-vitro experiments. The crystal structures have been refined by removing water molecules and repeated coordinates. Hydrogen atoms have been added and charges have been transferred to protein atoms. The secondary structure of the active-site sphere target protein (radius 9) is shown in **Figure 1**.

The binding analysis indicates that the Human Estrogen Receptor was successfully docked with the molecule. From the molecular docking results, the molecule M4 shows higher binding energy (CDOCKER Energy $-26.3475 \text{ Kcal/mole}^{-1}$) in 3ERT receptor compared to other molecules and Anastrozole drug. Mainly, the M4 molecules forms strong three hydrogen

bonds with Gly223 (bond distance is $2\text{\AA}$), Tyr383 ($1.9 \text{ \AA}$) and His274 ($1.9 \text{ \AA}$) respectively (**Figure 2**). The two aromatic benzene group of M4 molecules are shows Pi-anion interaction with Asp385 and Pi-Sulphur interaction with Met225. Additionally, most of the amino acids in active site 3ERT receptor formed weak van der Waals interaction with molecule M4.

ADMET analysis

The ADMET result of M4 and Anastrozole are declared in **Table 1**. The plot of polar surface area (2D PSA) and AlogP for these compounds are represented. The intestinal absorption and blood brain barrier penetration were predicted by 2D PSA and AlogP that include 95% and 99% confidence ellipses in ADMET study [10]. The region of ellipses defines, where the compounds are expected as well-absorbed. The absorption level (human intestinal absorption-HIA) of all the molecules shows good absorption (value 0 as good absorption). The absorption levels of HIA model are defined by 95% and 99% confidence ellipses in the ADMET.

Our results indicate that all compounds are nontoxic to liver (level 0), and thus they experience significant first-pass effect. According to the model for the all compounds to have an optimum cell permeability should follow the criteria (PSA

$< 140 \text{ \AA}^2$ and $\text{AlogP98} < 5$) [10]. All the compounds showed polar surface area (PSA) $< 140 \text{ \AA}^2$. Since the AlogP98 criteria, all the compounds had AlogP98 value < 5 . From the result of ADMET, we found that the molecules have drug likeness properties and also it will be useful as a potent new drug for anti-breast cancer.

Molecular Dynamic Simulation

The focus of this MD simulation is on properties such as receiver, drug-receiver-complex stability, temperature (K) mode conformation changes and energy function. (Kcal/mol^{-1}). In addition, MD simulation and linking, free energy measurements were sent to confirm the supremacy of Molocul M4. The study found that M4 molecule showed a strong connective affinity to the 3ERT Human Estrogen Receptor. For more MD research, we have therefore chosen this complex protein to calculate improvements

in stability. During the simulations, the root means square deviation (RMSD) and root mean square fluctuation were controlled to monitor the stability of any conformation of 3ERT with the M4 complex. (RMSF). **Figure 3** shows the RMSD values of $1.0 \text{ \AA}$ and $0.9 \text{ \AA}$ for 3ERT and 3ERT with M4 complex respectively. The M4 complex ligand does not alter the 3ERT structure and residue conformation as consequence of the RMSD and RMSF review. Figure 4 describes the overall energy difference and the protein complex stabilization temperature. At 250 ps from 300 to 304 K, the M4 molecule receptors were stabilized and the receptor strength was stabilized at $-18700. (\text{Kcal/mol}^{-1})$. The complex ligand, M4, does not at different temperatures and energization values affect RMSD or stability of the 3ERT protein based on MD performance.

Figure 1: The secondary 3D structure of the target 3ERT protein active site sphere (Red ball) of the protein

Figure 2: a) 3D and 2D) binding interaction of molecule M4 in Human Estrogen Receptor active site

Table 1: ADMET properties of the molecule M4

M4	0	3	4	0	0	0	52.46	4.66
Anastrozole	0	3	4	1	0	0	59.49	5.48

Figure 3: a) RMSF and RMSD of various confirmation of 3ERT with M4 complex

Figure 4: a) Time based total energy and b) temperature changes in different time scale of 3ERT and M4 complex

CONCLUSION

In this study 3ERT was based on the logical approach to inhibit the growth of breast cancer cells in conjunction with its silicon predictive potential. In studying molecules with high binding affinity and biologically important interactions the research explored the ability of pharmacophores modelling. Following the recognition of the screened compounds over the reported compounds, the docking experiments have been completed. The simulation of molecular dynamics tests the constancy of complex protein structures. The

effect of the relationship between RMSD, RMSF and hydrogen bond shows that the complex is very stable over the simulation time. Moreover, the MD simulations showed that during simulations the hits were stable without aberrations and in addition the interactions between gene networks illustrate the relationship of the 3ERT gene. Hence our belief that the hits found can be used against breast cancer diseases and of high clinical benefit. Molecular methods for the docking of M4 have been used for the molecular interaction and later have been confirmed by the ADMET risk test oral bioavailability

parameters. The possible targets of Molecule M4 for anti-breast cancer have been proposed, based on molecular docking energy, ADMET parameters. Finally, the findings of silicone show that the promiscuous inhibitors of breast cancer a M4. In future, new highly effective anti-breast cancer drugs will be developed by the further production and alteration of these derivatives.

Conflict of Interest: Nil

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