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ORIGINAL ARTICLE **OPEN ACCESS**

Molecular Docking, ADMET and Molecular Dynamic Simulation Study on *Trachyspermum ammi* Phytochemicals as Anti-Breast Cancer Activity

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ABSTRACT
Breast cancer is the second most frequent cancer in women, accounting for 23% of all malignancies in women. Chemotherapeutic medicines are becoming resistant and harmful to patients with breast cancer. Anti-cancer medicines have been found to be abundant in plant-derived goods. The goal of this work was to use molecular docking, ADMET, and molecular dynamic simulation to look into the anti-cancer efficacy of Trachyspermum ammi phytochemicals. Trachyspermum ammi phytochemicals demonstrate good binding affinity and drug-like effects in human oestrogen receptors in all investigations.
Keywords: Trachyspermum ammi, molecular docking, ADMET, molecular dynamic, Breast cancer

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INTRODUCTION

Breast cancer is the most often diagnosed cancer in women worldwide [1]. It is a varied group of malignancies. Breast cancer-related morbidity remains high despite advances in early detection and the introduction of numerous targeted therapy strategies. Existing therapeutic approaches are linked to high toxicity, low efficacy, therapeutic resistance, and therapy-related morbidity and mortality. According to recent studies, natural products will pave the way for more effective, non-endocrine, nontoxic anticancer therapy approaches due to their cancer-preventive potential [2]. Phytomolecules have long been important in the research and development of new anticancer drugs [3].

Trachyspermum ammi, also known as Ajowan, is a plant that belongs to the Apiaceae family and is used to treat a variety of ailments in both humans and animals. *Trachyspermum ammi* is an annual herb with many branches that is mostly used as a digestive aid. It has been shown in pharmacological studies to have antihypertensive, antispasmodic, and bronchodilating activity, as well as hepatoprotective and antiinflammatory properties [4-6]. Anticancer activity is measured in vivo by generating tumours in animals using various approaches. Anticancer evaluation in vitro is a universal methodology for assessing cancer activity. In vitro procedures have an advantage over in vivo approaches since they are less time consuming, more cost effective, and allow for the testing of a large number of substances with a small amount of material. They are also easier to maintain. In vitro approaches have been preferred to test anticancer efficacy because of these advantages [7-10]. According to a literature review, *Trachyspermum ammi* has no anticancer activity that has been scientifically confirmed using the *In Silico* method. With this in mind, the primary goal of this work was to look into the *In Silico* anticancer activity of *Trachyspermum ammi* phytochemicals.

MATERIAL AND METHODS

In our present study, *In Silico* molecular docking ADMET toxicity studies and molecular dynamics simulation were carried out using Auto Dock Vina, Swiss ADME and Schrodinger's Desmond module software.

Preparation of protein

The Crystal Structure of the human oestrogen receptor alpha ligand-binding domain in association with 4-hydroxytamoxifen (PDB ID: 3ERT) with a resolution of 1.90 was chosen for this study. The protein energy was lowered by introducing hydrogens to the 3ERT protein using the Forcefield algorithm and

then utilising the CHARM force field in DS. We used the parameters previously specified in our molecular docking research.

Ligand preparation

The active phytochemical molecules of *Trachyspermum ammi*(1,8-Cineol, 2-(Octan-4-yl)phenol, 2-Nonyl phenol,3-Terpinolenone, 4-Vinyl guaiacol, 5-fluorouracil STD, alpha-Phellandrene, Anethole, Carvacrol, Cymen-8-ol, Eicosene, Laurenene, Limonene oxide, Myrcene, Nonadec-1-ene, Octadec-9-ene, o-Xylene, Palmitic acid, p-Cymene, Terpinen-4-ol, Thymol, α-Pinene, α-Terpineol, β-Pinene) from *Trachyspermum ammi* and standard drug Tamoxifen were drawn in chemdraw software, subsequently, energy of the all the molecules were minimized and saved in SDF file format for further docking studies.

Docking study

A molecular docking analysis was performed to determine the most frequent shape of the protein-ligand complex. A computer docking analysis was utilised to examine structural complexes of the 3ERT with gathered molecules as well as conventional compounds in order to better understand the structural basis of these target proteins. Within the (CHARMm-based DOCKER) methodology, various binding mechanisms between the ligands and these target proteins were investigated. The approach uses fields of CHARMm power to provide a full ligand. The ligand binding affinity was calculated using binding energy, interaction energy, hydrogen bonds, binding energies, protein energy, and ligand-protein complex energy. The energy is expressed as negative numbers. The ligands' increased binding affinity to the target protein results in more negative value energy.

ADMET Toxicity Analysis

Prediction of the ADMET profile for drug candidates and environmental contaminants is crucial in drug development and environmental hazard assessment. SWISS ADME software was used to estimate the ADMET properties of the filtered compounds in order to classify the probable detrimental effects of these chemicals 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.

Molecular Dynamics simulation

On Schrodinger's Desmond module, the MD simulation was run. To add water, the best phytpchemical and control Crystal Structures of human oestrogen receptor were positioned in the orthorhombic box with a buffer distance of 10 Å using the System Builder tool, and a water model was generated using single point charge (SPC). The systems were neutralised by adding Na+ and Cl- ions until they achieved a concentration of 0.15 M. Before running the simulation, the created solvated system was reduced and relaxed using OPLS3 force field settings as the default protocol associated with Desmond.The MD simulation was carried out with an isothermal isobaric ensemble (NPT) at 300° K and 1.013 bar pressure. 1000 frames were stored to the trajectory during a 250-picosecond simulation. Finally, the MD simulation trajectory was examined using the Simulation Interaction Diagram (SID) tool.

RESULT AND DISCUSSION

In this molecular docking study, the *Trachyspermum ammi*phytochemicals are subjected to analysis binding interaction with breast cancer induced protein human estrogenreceptor (3ERT). The secondary structure of the of human estrogen receptor with active site sphere is shown in Figure 1. The -CDOCKER energy of the docking results are listed out in Table 1. In this analysis, 5-fluorouracil used as a standard drug for compare the binding affinity of the *Trachyspermum ammi*phytochemicals.

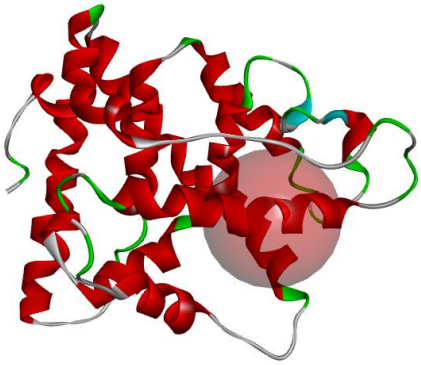

Figure 1. The secondary structure of the of human estrogen receptor with active site sphere.

Table 1. CDOCKER ENERGY of the *Trachyspermum ammi*phytochemicals

Mol. No	List of Compounds	CDOCKER Energy
1.	Palmitic_acid	44.3271
2.	Eicosene	39.5058
3.	Nonadec-1-ene	36.3657
4.	_2-(Octan-4-yl)phenol	36.2046
5.	2-Nonyl_phenol	33.8911
6.	Octadec-9-ene	27.1466
7.	Carvacrol	26.8034
8.	Cymen-8-ol	26.2459
9.	**5-fluorouracil (Standard drug)**	25.3186
10.	p-Cymene	25.2908
11.	Laurenene	23.8805
12.	4-Vinyl_guaiacol	19.6996
13.	o-Xylene	16.6639
14.	Anethole	12.2924
15.	Thymol	11.9557
16.	β-Pinene	0.554372
17.	Limonene_oxide	-1.97152
18.	Terpinen-4-ol	-2.34388
19.	1_8-Cineol	-2.87823
20.	Phellandrene	-5.44788
21.	Myrcene	-5.93632
22.	3-Terpinolenone	-17.934

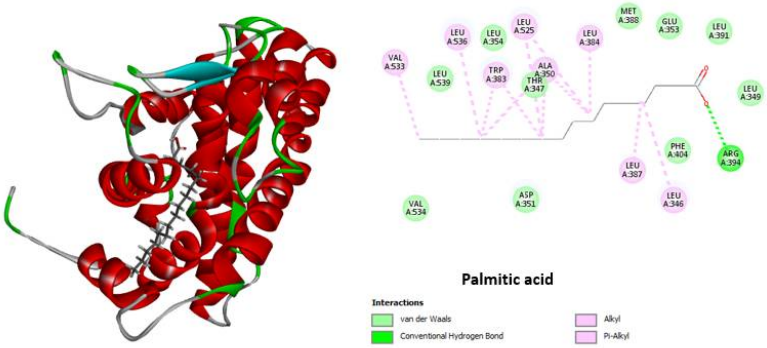

Figure 2. 3D and 2D interaction of the palmitic acid in the active site of human estrogen receptor.

From the docking result, the palmitic acid ligand shows more binding energy than other phytochemicals and standard drug. The -CDOCKER energy of the palmitic acid is 44.3271 Kcal/mol^{-1}.The -COOH group of the palmitic acid form one strong hydrogen bond Arg 394 amino acid of active site of human estrogen receptor.The aliphatic group of this ligand forms Alkyl, Pi-Alkyl interaction and Van der Waals interaction with most of the amino acids (Figure 2).Further, the Eicosene and Nonadec-1-ene molecule forms Alkyl, Pi-Alkyl interaction and Van der Waals interaction with most of the amino acids (Figure 3& 4).

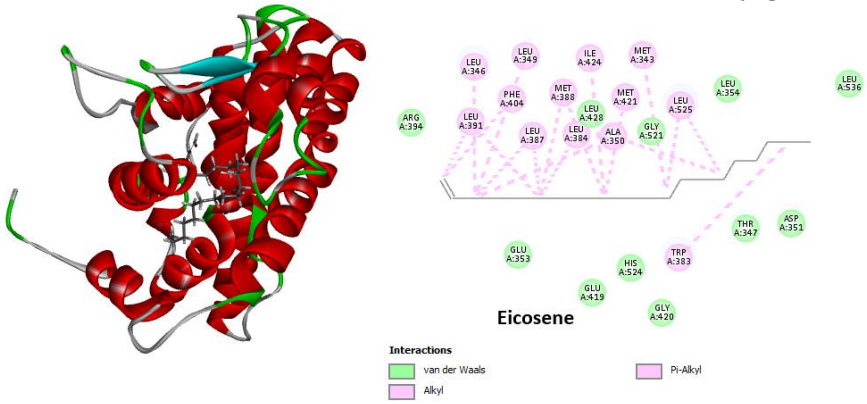

Figure 3. 3D and 2D interaction of the Eicosene in the active site of human estrogen receptor.

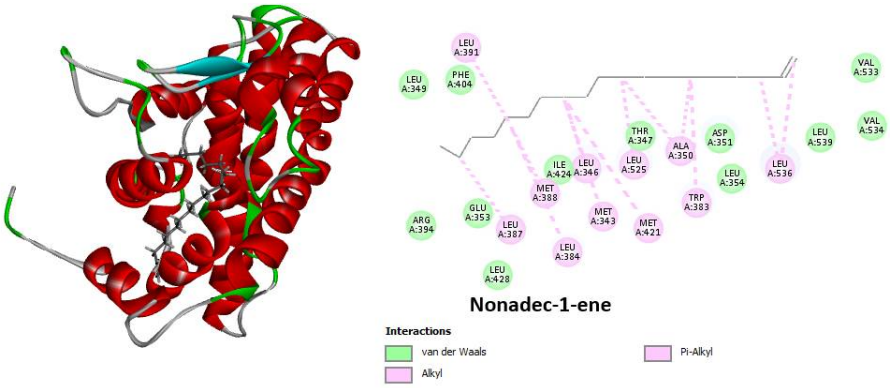

Figure 3. 3D and 2D interaction of the Nonadec-1-ene in the active site of human estrogen receptor

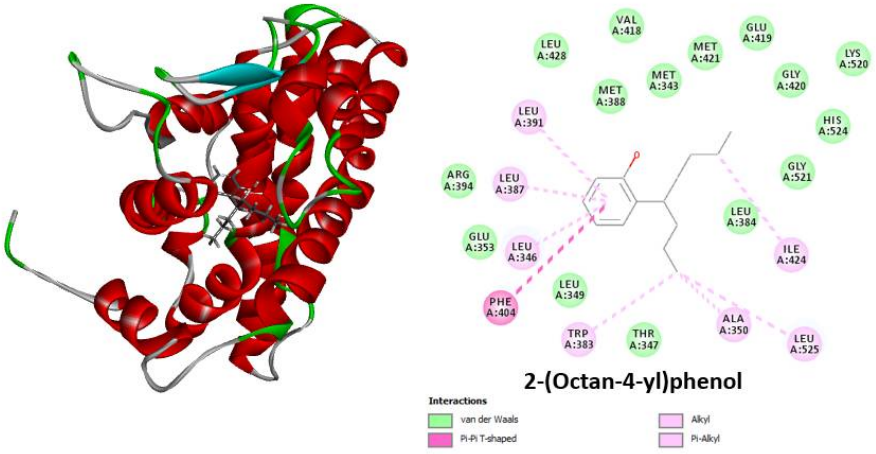

Figure 4. 3D and 2D interaction of the 2-(octane-4-yl) phenyl in the active site of human estrogen receptor.

Similarly, 2-(octane-4-yl) phenyl ligand shows Pi-Pi T-shaped interaction with Phe 404 amino acid. Further, the methyl group of the forms Alkyl and Pi-Alkyl interaction with Trp 383, Ala 350 and Leu 525 residues (Figure 4). The 2-Nonyl phenol forms non-bonded interaction with active site amino acid of the 3ERT receptor (Figure 5).The standard drug 5-fluorouracil forms two hydrogen bond with Arg 394 and Glu 353 amino acids (Figure 6). The standard drug shows less binding energy compared to most of the ligands (Table 1).

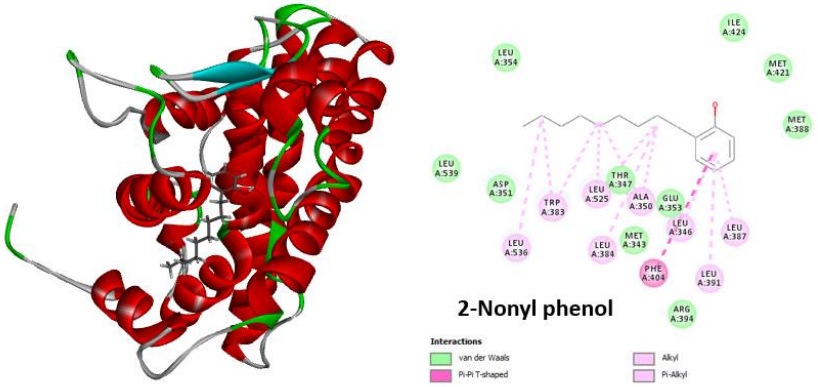

Figure 5. 3D and 2D interaction of the 2-Nonyl phenol in the active site of human estrogen receptor.

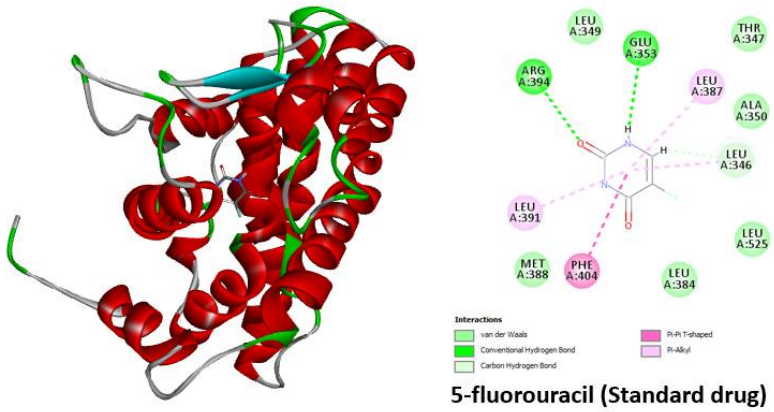

Figure 6. 3D and 2D interaction of the 5-fluorouracil in the active site of human estrogen receptor.

ADMET analysis

In the ADMET analysis, the Eicosene, Nonadec-1- and otadec-9-ene fall outside the ADMET prediction, which means there is no drug like properties obey in these molecules. The remaining all the phytochemicals shows drug like properties (Table 2). Figure 7 shows the ADMET properties of the *Trachyspermum ammi* phytochemicals. For drug likeness research, the ADMET descriptors of all the molecules were determined. Intestinal absorption and penetration of the blood brain barrier is predicted by the development of an ADMET model using 2D PSA and AlogP98 descriptors that include 95% and 99% confidence ellipses. These ellipses describe regions in which it is predicted that well-absorbed compounds will be contained. ADMET model screening findings have shown that all the compounds have 99 percent confidence levels for human intestinal absorption and penetration of the blood brain barrier (BBB). All the phytochemicals except Eicosene, Nonadec-1- and otadec-9-ene shows good Absorption level, Solubility level, BBB level, PPB level, Hepatotoxic level, CYP 2D6, PSA 2D and AlogP98 drug like properties.

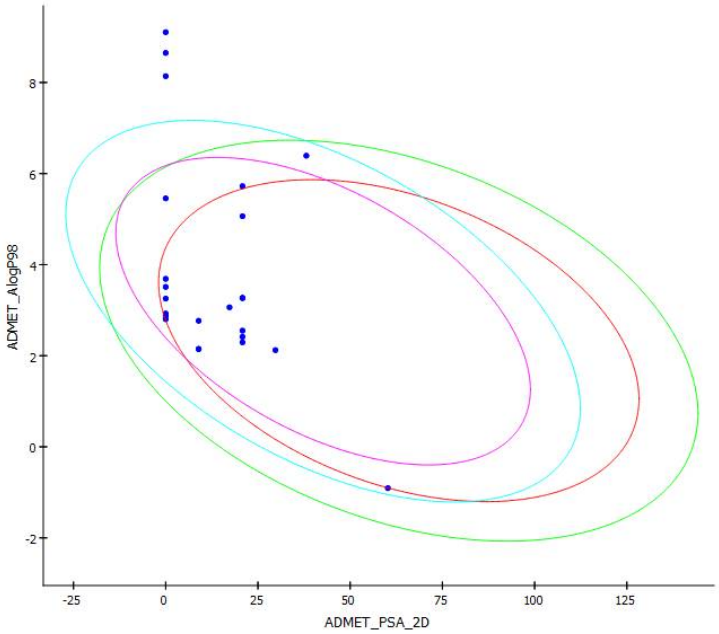

Figure 7. Absorption level, Solubility level, BBB level, PPB level, Hepatotoxic level, CYP 2D6, PSA 2D and AlogP98 properties of the *Trachyspermum ammi* phytochemicals.

Table 2. ADMET properties of the *Trachyspermum ammi* phytochemicals.

Molecule Name	Absorption level	Solubility level	BBB level	PPB level	Hepatotoxic level	CYP 2D6	PSA 2D	AlogP98
Palmitic_acid	good	Extremely good	Low	<90%	No	No	67.15	2.34
_2-(Octan-4-yl)phenol	good	Extremely good	Low	<90%	No	No	79.28	3.48
2-Nonyl_phenol	good	good	Low	<90%	No	No	65.17	3.56
Carvacrol	good	Extremely good	Low	<90%	No	No	88.12	3.78
Cymen-8-ol	good	Extremely good	Low	<90%	No	No	59.42	4.59
5-fluorouracil	good	Good	Low	<90%	No	No	52.33	4.6
p-Cymene	good	Low	Low	<90%	No	No	65.12	4.9
Laurenene	good	Low	Low	<90%	No	No	68.74	5.1
4-Vinyl_guaiacol	good	good	Low	<90%	No	No	84.23	3.6
o-Xylene	good	good	Low	<90%	No	No	69.16	3.8
Anethole	good	good	Low	<90%	No	No	75.21	3.9
Thymol	good	good	Low	<90%	No	No	51.26	4.5
β-Pinene	good	good	Low	<90%	No	No	59.31	4.1
Limonene_oxide	good	Low	Low	<90%	No	No	84.23	4.6
Terpinen-4-ol	good	good	Low	<90%	No	No	89.34	3.5
1_8-Cineol	good	good	Low	<90%	No	No	63.12	3.8
Phellandrene	good	good	Low	<90%	No	No	77.26	5.1
Myrcene	good	good	Low	<90%	No	No	81.32	5.3
3-Terpinolenone	good	good	Low	<90%	No	No	65.97	3.4

Molecular dynamic simulation

Following the docking calculations, the best palmitic ligands, 3ERT protein complexes, MD simulations were carried out using the Desmond Simulation Package for 250 ps. The MD trajectories were used to calculate the root mean standard deviation (RMSD), root mean square fluctuation (RMSF), and protein-ligand interactions. Based on the RMSD oscillations during the simulation, the solvated system of the ligand-protein docked complex was tested for binding stability. In the trajectory of MD simulation, the RMSD fluctuation is assessed independently for the protein and ligand structures; if it falls within 3Å, the complex is considered stable. In this solvation analysis, the NaCl and Water molecules were added for heating process (Figure 8). Figure 9 shows the RMSD and RSMF of the palmitic acid with 3ERT protein complex. Figure 10 and Figure 11 show the temperature and total energy changes based on the time change. All the results show the palmitic acid with 3ERT shows good stability and does not change the structure of the 3ERT protein.

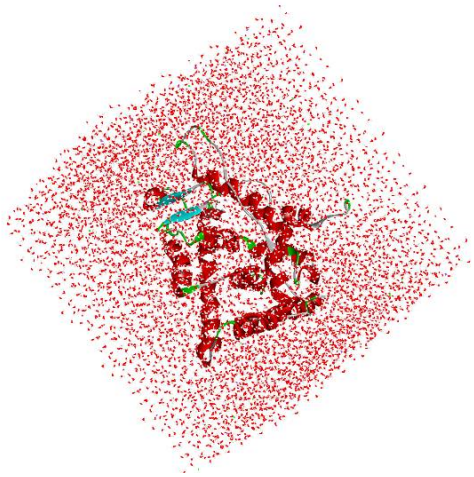

Figure 8. Solvation analysis of 3ERT protein with palmitic acid

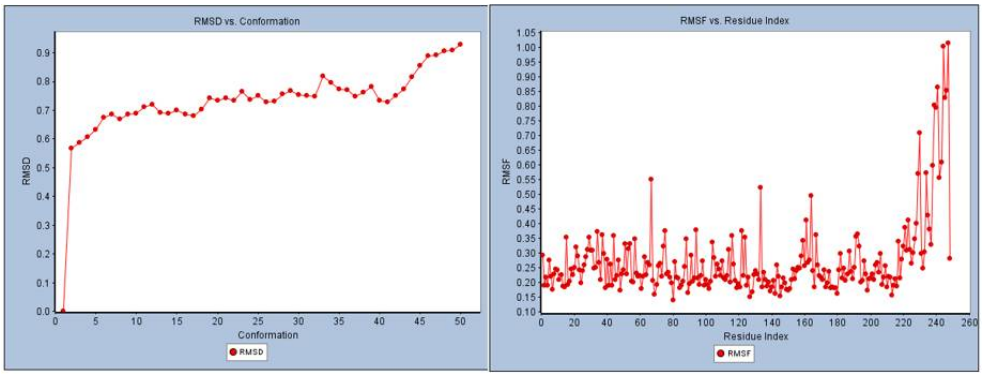

Figure 9 RMSD and RSMF analysis of 3ERT protein with palmitic acid

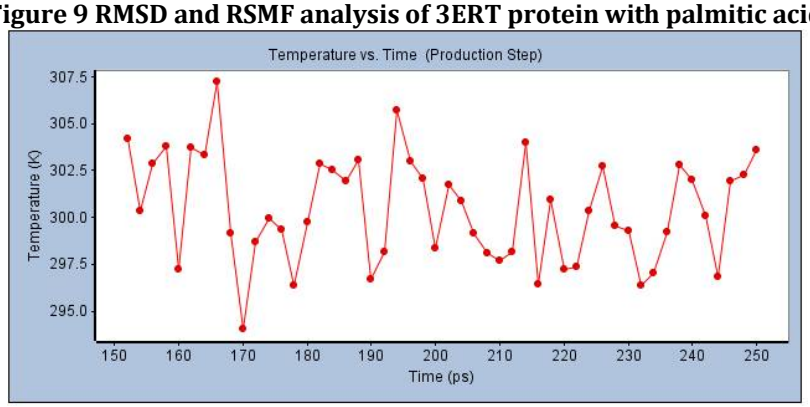

Figure 10. Temperature change analysis of 3ERT protein with palmitic acid

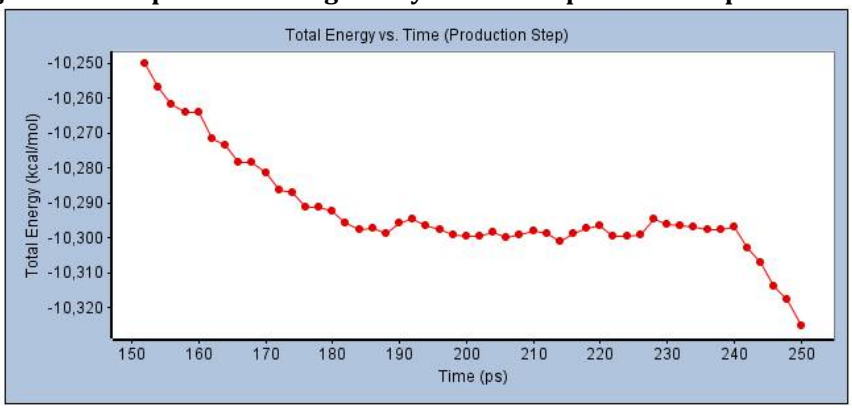

Figure 11. Total energy change analysis of 3ERT protein with palmitic acid

CONCLUSION

The present of molecular docking, ADMET and molecular dynamics simulation studies of *Trachyspermum ammi*phytochemicals shows excellent anti-breast cancer activity except Eicosene, Nonadec-1- and otadec-9-ene molecules.The docking results showed that the major influencing factors of molecular interactions between *Trachyspermum ammi* phytochemicals and 3ERT protein were H-bonds and hydrophobic and electrostatic interactions. The *In Silico* prediction of oral bioavailability (rule of five) and ADMET risk profiling were within their acceptable limit for active analogs. Molecular dynamic simulation shows good stability of the 3ERT with palmitic acid. These compounds have rationalized the structural requirement and need further lead optimization for designing of 3ERT inhibitors.

CONFLICT OF THE INTEREST

The authors declared no conflict of interest

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