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by La Ode Aman

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MOLECULAR DOCKING AND MOLECULAR DYNAMIC STUDIES: SCREENING PHYTOCHEMICALS OF *Acalypha indica* AGAINST BRAF KINASE RECEPTORS FOR POTENTIAL USE IN MELANOCYTIC TUMOURS

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ABSTRACT

Melanocytic tumors are a type of cancer that is most commonly found on the skin. The melanoma prevalence rate has risen dramatically over the last 50 years. As a result, the discovery of new therapeutic agents is critical. The BRAF kinase is one of the receptors involved in cell apoptosis. Dabrafenib is a selective BRAF inhibitor with common side effects such as rash, photosensitivity, and hyperkeratosis. Meanwhile, *Acalypha indica* is a plant that has been widely reported as a source of antiproliferative and proapoptotic compounds. However, the phytochemicals in *A. indica* that play an important role in melanocytic tumors have yet to be discovered. Molecular docking is a structure-based drug design method that is used to identify potential hits during the drug discovery process. The aims of this study are to obtain candidate lead compounds for BRAF kinase based on binding mode interaction and binding stability by using AutoDock 4.2 and GROMACS 2019.6, respectively, for molecular docking and molecular dynamics (MD). The native ligand, SM5, has estimated free energy of binding and an inhibitory constant of -5.93 kcal/mol and 45.30 µM, respectively. 2-Methyl anthraquinone, chrysin, stigmasterol, and γ-sitosterol have higher binding energy, with an estimated free energy of binding of -6.24, -6.67, -6.35, and -6.14 kcal/mol, respectively. According to the MD simulation, stigmasterol and γ-sitosterol will be more effective at stabilizing the 6XFP complex during 100 ns. Finally, stigmasterol and γ-sitosterol are potential lead compounds as BRAF inhibitors.

Keywords: BRAF, Melanocytic tumors, *Acalypha indica*, Docking, MD.

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INTRODUCTION

Melanocytic tumors are a type of cancer that develops from the uncontrolled proliferation of melanocytes, pigment-producing cells.[1–4] While cutaneous melanoma is the most common type, it can also develop on mucosal surfaces, the uveal tract, and the leptomeninges. Malignant melanoma is the deadliest type of skin cancer.[5–7] Melanoma was once considered rare cancer, but its prevalence has risen faster in the last 50 years than that of almost any other.[6,8–10] In the United States alone, approximately 87,110 people are expected to be diagnosed with melanoma in 2017.[5,9] Melanoma causes less than 5% of all skin cancer deaths. Melanoma is a dangerous cancer that spreads far beyond its initial location.[7,8] Surgery is no longer effective in treating advanced melanoma, and the disease becomes more difficult to treat.[7,8,11,12] The long-term treatment, including immunotherapeutics such as Ipilimumab, ranges from 8 to 12 months.[5,11,12] However, newly developed combined immunotherapeutic and radiation treatments can increase survival by several years.[11] One of the receptors involved in cell apoptosis is the BRAF receptor. The Ras/Raf/MEK/ERK mitogen-activated protein kinase signaling cascade includes BRAF. In less than ten years, drug discovery of activating mutations in BRAF resulted in the FDA approval of vemurafenib as a BRAF inhibitor.[13]

Dabrafenib is a selective BRAF inhibitor that was first approved for the treatment of metastatic melanoma as a single agent. The most common side effects of dabrafenib and vemurafenib were dermatologic in nature, including photosensitivity, rash, and hyperkeratosis. Patients may also experience diarrhea, arthralgias, nausea, and extreme fatigue. Secondary cutaneous toxicities such as keratoacanthomas, hyperkeratotic lesions, and squamous cell carcinomas have been reported in patients taking these RAF inhibitors.[14] Finding a new lead compound with fewer side effects that induce the same or better biological responses than existing drugs via the same receptor is a difficult goal in drug design. Because phytochemicals in natural products have few side effects, many researchers use them to generate better lead compounds. As a result, there is still work to be done to improve the pharmacological properties of these phytochemicals by predicting molecular interactions against cancer receptors, and they can be developed further if they have unwanted side effects through computer-aided drug design and molecular modification or chemical reactions.[15,16] *Acalypha indica* is a weed plant that contains phytochemicals that are important for human health applications, including anti-bacterial, antioxidant[17], anti-fungal[18], anti-ulcer[19], asthma and bronchitis[20], and specific hormone stimulation[21]. Acalyphol acetate, aurantiamide, aurantiamide acetate, acalyphamide, acalyphamide acetate, 2-methyl antaquinone, and succinamide have all been found in the leaves and twigs of *A. indica*. The flowers and leaves have yielded citorin, kaempferol glycosides, mauritianin, nicotiflorin, quercitrin, naringin, hesperitin, and biorobin. This plant's herb contains stigmasterol, sitosterol, and its acetate. Alkaloids, catachols, flavonoids, phenolic compounds, saponins, and steroids are among the other constituents. There were also volatile oils and fatty acids discovered.[22,23] Although the anti-inflammatory and anticancer properties of *A. indica* have been widely reported, the phytochemicals that play an important role in melanocytic tumors have yet to be reported. Computer-aided drug design is a low-cost and quick method for identifying protein targets in natural product ingredients.[24] Molecular docking is a computer-aided drug design technique for the characterization of protein-ligand interactions. Molecular docking is more concerned with the binding mode of the ligand on the active side. Although docking analysis can provide an acceptable binding mode, the solvent effect and protein flexibility are not fully considered. Therefore, MD simulations were performed on all docked complexes to investigate the stability of protein-ligand interactions further. Therefore, the aim of this study was to develop phytochemicals from *A. indica* in order to obtain lead compounds that play an important role in cell apoptosis in melanocytic tumors. In this study, we used molecular docking studies followed by MD simulation to screen the phytochemicals of this plant against the BRAF kinase receptor.

EXPERIMENTAL

Hardware

The workstation has an Intel® Xeon E5-2670 V2 2.50GHz processor, 32 GB of RAM, and dual operating systems: Windows 10 Pro 64-bit and Linux Ubuntu 18.04 64-bit.

3D Structures of the BRAF Receptor and Phytochemical Preparation

The 3D structure of serine/threonine-protein kinase BRAF (Homo sapiens) (Uniprot: P15056) was prepared by using the SWISS-MODEL server.[25] Using AutoDockTools-1.5.6rc3, polar hydrogens were added to the 3D structure of 6XFP. The three-dimensional structures of *A. indica* phytochemicals were obtained from the NCBI PubChem Compound database.[26] Polar hydrogen atoms were added to the ligand structure with Discovery Studio Visualizer v21.1.0.20298 and AutoDockTools-1.5.6 rotation capability.

Molecular Docking

The AutoDock 4.2 Release 4.2.6 software was used to dock protein kinase BRAF and ligands.[27] The sizes (50, 45, and 35) and centers (2.043, 16.883, and 28.387) of the grid box were used based on the center of the grid box obtained from docking validation. The spacing has been set to 0.375 Å. The center of the grid box was used based on the center of the grid box obtained from docking validation. The protein coordinates remained rigid, whereas the ligands were flexible and moved around the grid map created around the native ligand, SM5. Polar hydrogens and Kollman charges were added to the receptor molecules using AutoDockTools 1.5.6rc3. To make the ligand, each ligand atom was given a Gasteiger charge. A Lamarckian genetic algorithm (LGA) with 150 independent runs per ligand was used to find the best docking conformations. The total number of participants was limited to 150. The total number of energy

evaluations is 2,500,000, and the total number of generations is 27,000. The binding interaction and related operations were then visualized in VIDA v4.4.0.4 software, which is available from Open Eye Scientific Software.[28,29]

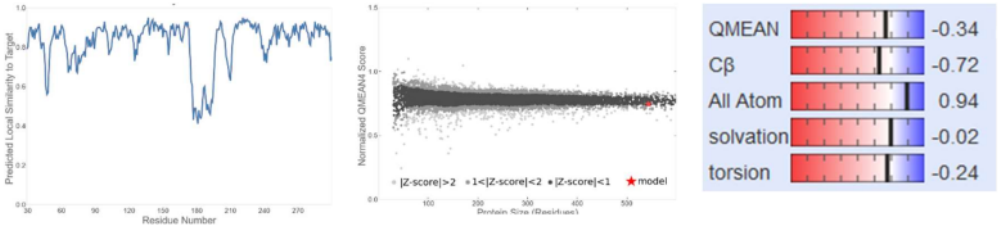
Molecular Dynamics Simulation

MD simulations were performed using the GROMACS[30] software package and the Gromos force-field 54a7. The ligand topology was generated by the Automated Topology Builder (ATB) server.[31] The MD was investigated using O.T.P. Kim's method (for details, refer to O.T.P. Kim, et al. 2016). Finally, the systems were tested in water under biological conditions, namely 300 K, a water density of approximately 1000 kg/m^3, and an average pressure of 1 bar. Each complex mode's run time was 100 ns. Rashmi Kumari's MM/PBSA method for GROMACS was used to calculate the binding energy of a single protein-inhibitor complex and the contribution of residues to the binding energy.[32,33]

RESULTS AND DISCUSSION

Protein Structure Model

When experimental structures are unavailable, homology modeling has become a common technique for generating 3D models of proteins. Homology modeling (or comparative modeling) generates a structural model of a protein of interest by using evolutionarily related structures (templates) as targets. Fully automated servers with user-friendly web interfaces, such as SWISS-MODEL, generate reliable models. The steps are typically as follows: template identification, template selection, model construction, and model quality estimation.[25,34] Using the uniport code P15056, the three-dimensional structure of protein kinase BRAF (Homo sapiens) was generated. The chosen template from several obtained through homology modeling is 6XFP with a native ligand of *(1E)-5-(1-piperidin-4-yl-3-pyridin-4-yl-1H-pyrazol-4-yl)-2,3-dihydro-1H-inden-1-one oxime* (ID: SM5). Several parameters, including identity, GMQE, sequence similarity, and QMEAN, were used to select this protein template. The number of amino acids with a completely aligned identity is indicated by identity. The identity for the chosen template is 100, indicating the number of amino acids with an aligned identity of 94.29 percent. The GMQE (global model quality estimate) scales from 0 to 1. If the GMQE score is close to one, the model's quality will be higher (Fig.-1a). This template has a GMQE of 0.77 (Fig.-1b), indicating that it is quite good in comparison to other protein models. The sequence similarity value for the two sequences for the selected template is 0.68. The QMEAN value of -0.34 indicates a relatively high similarity to the protein structure in the PDB data bank (Fig.-1c). The model used is adequate to meet the requirements based on the local quality estimate, normalized QMEAN score, and global quality estimate.



a b c

Fig.-1: The Parameters for the Chosen Protein Model, 6XFP. Normalized QMEAN Score (a), Local Quality Estimate (b), and Global Quality Estimate (c).

Molecular Docking

The binding interaction of a ligand with the receptor is predicted using molecular docking, and the interaction is evaluated using electrostatic and conformation properties.[35] To validate the docking method, SM5, a native ligand was docked into the binding site of the model protein 6XFP. The docking method quality is reliable if the root-mean square deviation (RMSD) of the overlapping pose between the docked and crystal structures is less than 2.0 Å.[36] The RMSD between the docked and crystal structures of SM5 (Fig.-2a) was 1.673 (less than 2), which is acceptable. The smaller RMSD indicates the position of the re-docking ligand, which is approaching the crystallographic ligand.[37] SM5 has estimated free energy of

binding of -5.93 kcal/mol and estimated inhibition constant of 45.30 µM. The interaction between SM5 and the 6XFP protein from the RCSB protein data bank revealed four hydrogen bonds with the amino acid residues Glu501, Cys532, and Asp594 and six hydrophobic interactions with the amino acid residues Thr529 (Pi-Sigma), Val471, Ala481, Leu505, and leu514 (Fig.-2b). Meanwhile, the interaction of SM5 with 6XFP protein homology with SWISS-MODEL revealed two hydrogen bonds with Glu501 and four hydrophobic interactions with Val471, Ala481, and Lys482 (Fig.-2c). This suggests that improving the structure of the 6XFP protein has a significant impact on the interaction pattern between SM5 and amino acid residues in the binding pocket.

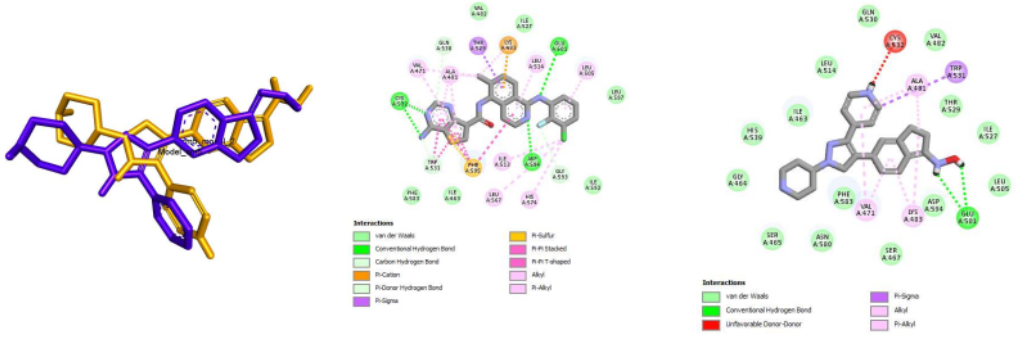


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Fig.-2: Overlapping of Native Ligand (SM5) Docked (gold) and X-ray Crystal Structures (blue) [a]; 2D Interaction of Native Ligand SM5 into the Binding Pocket of the 6XFP (RCSB protein data bank) [b], and 2D Interaction of Native Ligand SM5 into the Binding Pocket of the 6XFP (SWISS-MODEL) [c].

Table-1: Binding Energy and Inhibitory Constant of A. Indica Phytochemicals in the Binding Pocket of BRAF Kinase (6XFP)

Entry	Ligand	Estimated Free Energy of Binding (ΔG), (kcal/mol)	Estimated Inhibition Constant (Ki), µM
SM5	(1E)-5-(1-piperidin-4-yl-3-pyridin-4-yl-1H-pyrazol-4-yl)-2,3-dihydro-1H-inden-1-one oxime (ID: SM5)	-5.93	45.30
23	1,3-Dioxolane,4-Ethyl-5-Octyl-2,2-Bis (Trifluoromethyl)-, Trans-	-1.37	98,960
24	2-Methyl anthraquinone	-6.24	26.57
25	3,8-Nonadien-2-one, E	-3.99	1,200
26	4,4′,5,5′,6,6′ Hexahydroxy diphenic acid	-4.99	218.67
27	4-Amino-3-methoxypyrazolo[3,4-d] pyrimidine	-4.82	294.21
29	Acalyphin amide	-1.26	118,890
30	Caffeic acid	-4.29	719.88
31	Catechol	-4.31	691.48
32	Chrysin	-6.67	12.88
34	Ellagic acid	-5.15	167.56
35	Ferulic acid	-4.43	568.08
36	Galangin	-5.53	88.04
37	Gallic acid	-4.24	783.06
39	Glucogallin	-2.65	11,440
40	Hesperetin	-5.67	70.23
41	Kaempferol	-5.86	50.23
42	Naringenin	-5.58	81.67
43	Naringin	-0.66	328,300

45	Quebrachitol	-2.96	6,730
46	Quercetin	-5.40	109.74
47	Quinine	-4.66	386.02
48	Stigmasterol	-6.35	22.17
49	Syringic acid	-3.48	2,810
51	Tri-*O*-methylellagic acid	-5.45	100.60
52	β-Sitosterol acetate	-5.00	217.16
54	γ-Sitosterol acetate	-4.83	287.45
55	γ-Sitosterol	-6.14	31.60

We only show 28 of 60 phytochemicals *A. indica* from various sources that are capable of interacting with the 6XFP receptor while representing for the Lipinski aspect and the complexity of the bonding torque (Table-1). Four phytochemicals (2-methyl anthraquinone, chrysin, stigmasterol, and γ-sitosterol) had binding energies that were higher than SM5, with binding energies of -6.24, -6.67, -6.35, and -6.14 kcal/mol, respectively.

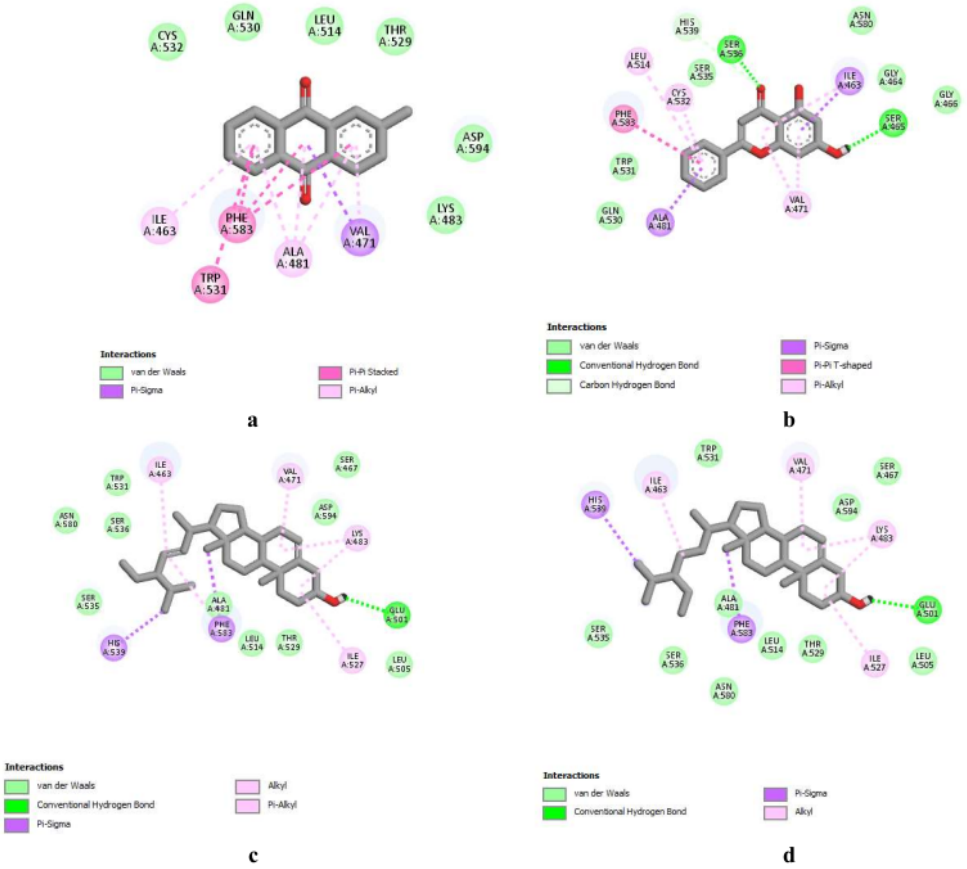

Fig.-3: Hydrogen and Hydrophobic Bonds in the 6XFP Protein-Binding Pocket are depicted. Protein Interactions with 2-methyl anthraquinone (a), Chrysin (B), Stigmasterol (c), and γ-sitosterol (d). The Ligands are represented by a Stick Model.

Complex 6XFP-2-methyl anthraquinone lacks hydrogen bonds but interacts hydrophobically with the amino acid residues Ile463, Val471, Ala481, Trp531, and Phe583. This is due to 2-methyl anthraquinone's lack of a proton acceptor and donor group. Complex 6XFP-chrysin forms two hydrogen bonds with Ser465 and Ser536 and has hydrophobic interactions with Ile463, Val471, Ala481, Leu514, Cys532, and Phe583. Complexes 6XFP-stigmasterol and 6XFP-γ-sitosterol form one hydrogen bond with Glu501 and have quite

similar mode of hydrophobic interactions with the amino acid residues of Ile463, Val471, Lys483, Ile527, His539, and Phe583 (Fig.-3). Furthermore, MD simulation was used to further evaluate chrysin, stigmasterol, and γ-sitosterol, while 2-methyl anthraquinone was dropped due to its inability to form h-bonds with the active site and rigid structure. Because hydrogen bonds are generally thought to be facilitators and play a role in the stability of the complexes, it can be assumed that 2-methyl anthraquinone is unable to stabilize the complex.

Molecular Dynamics Simulation

We used MD simulations to find the best ligand capable of stabilizing the complex BRAF kinase. MD simulations were performed using GROMACS 2019.6. To assess the stability of the 6XFP-ligand complex, the RMSD values as well as the binding free energies of the 6XFP-ligand complex and the contribution of residues to the binding energy of complexes for 100 ns were monitored. The simulation was performed on protein-ligand complexes (SM5, chrysin, stigmasterol, and γ-sitosterol). The coordinate files and topology for the protein were generated using the GROMACS package's pdb2gmx program and parameters from the ATB force field.[38]

RMSD

The RMSD of the 6XFP ligand complex, which refers to the complex's initial structure, was used to monitor the dynamic stability of the MD trajectory. The RMSD is a similarity metric commonly used in the study of macromolecular structures and dynamics. All ligands fluctuated with an RMSD of < 2.0 Å, indicating that the ligand was capable of stabilizing the protein BRAF kinase over a 100 ns simulated range. The fluctuation ranges for SM5, chrysin, stigmasterol, and γ-sitosterol with RMSD of 0.5–0.5; 0.45-0.6; 0.25-0.73; and 0.15-0.5 Å, respectively (Fig.-4). The MD trajectories for each complex remained < 2.0 Å of the initial structure, indicating that all the complexes are structurally stable.

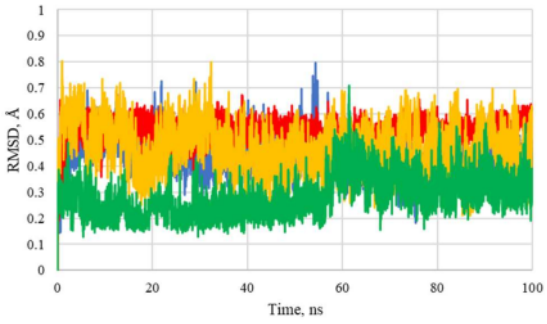

Fig.-4: The RMSDs of Protein-Ligand Complexes for SM5, Chrysin, Stigmasterol, and γ-sitosterol are Colored Blue, Red, Yellow, and Green, respectively.

Binding Free Energies of the 6XFP-Ligand Complex

We used a MM-PBSA method to estimate the binding free energy of the 6XFP–ligand interaction strength. The MM-PBSA method calculates the interaction energies of protein-ligand complexes, including entropic contributions and conformational fluctuations to the binding energy of MD simulations.[39] Binding free energies of a complex are related to vacuum potential energy, also known as molecular mechanics potential energy, which includes the energy of both nonbonded and bonded interactions. We concentrate on electrostatic energy, van der Waal energy, and total energy because they are important in protein-ligand interactions. RashmiKumari's method for calculating the energy of binding of a single protein-inhibitor complex was used.[32] The binding free energies of the 6XFP-SM5 complex are electrostatic energy, van der Waal energy, and total energy, with energies ranging from -22.783 to 5.838, -176.168 to 21.744, and -100.741 to 14.668 kJ/mol, respectively. Electrostatic, Van der Waal, and total energy each contribute in the range of -17.264 to 11.288, -136.294 to 11.408, and -64.142 to 9.407 kJ/mol to the binding energy of the 6XFP-chrysin complex. Stigmasterol and γ-sitosterol are structurally similar, so the total energy for the complex is nearly the same. Electrostatic energy, Van der Waal energy, and total energy are the binding free energies of the 6XFP-stigmasterol complex, with energies ranging from -9.525 to 5.855, -193.466 to

10.475, and -123.926 to 12.604 kJ/mol, respectively. The 6XFP-γ-sitosterol complex has electrostatic energy, Van der Waal energy, and total energy with energies ranging from -6.452 to 4.833, -190.854 to 13.748, and -123.638 to 11.740 kJ/mol, respectively (Fig.-5).

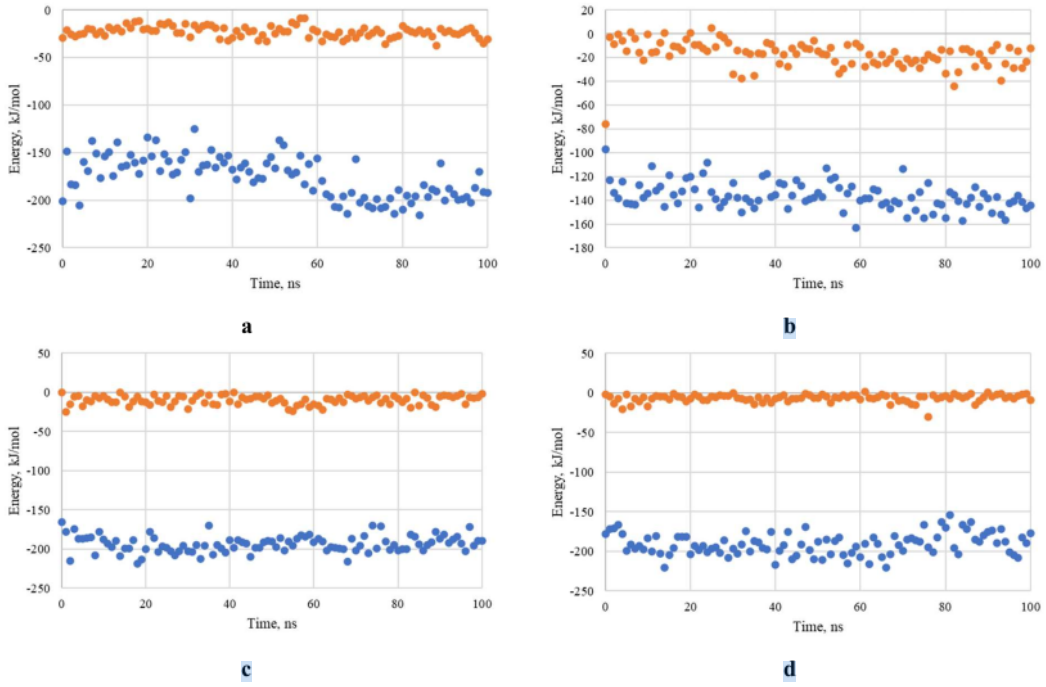

Fig.-5: The Binding Free Energies of the Protein-Ligand Complex for SM5 (a), Chrysin (b), Stigmasterol (c), and γ-Sitosterol (d). Orange and Blue Are Colors That Represent Electronic Energy and Van Der Waals Energy, respectively.

Amino Acid Residues' Contribution to Binding Energy

We observed and analyzed the active sites to gain insight into the interactions of SM5 as well as the three phytochemicals with the 6XFP receptor by using a snapshot of the profile of residue contributions to binding energy from MD simulations at 80 ns (Fig.-6). All ligands still have interactions with residues that are similar to those obtained from the docking pose's binding mode. Of course, there is a slight difference due to the protein and ligand's flexibility during the MD simulation. The amino acid residues with a negative energy value indicate a favorable interaction in this frame. The amino acid residues with energy assigned a positive indicate an unfavorable interaction. The amino acid residues' contributions to binding energy (assigned negative) in the 6XFP-SM5 complex are Ile463, Gly464, Gly466, Ser467, Val471, Asp479, Ala481, Lys483, Leu514, Trp531, Glu533, Tyr538, His539, and Phe583 with a total energy of -6.1497, -1.8839, -1.8182, -1.9431, -7.965, -1.0781, -1.6543, -2.1096, -2.7475, -4.1258, -1.5155, -2.0141, -1.0181, and -7.4004 kJ/mol, respectively. (Fig. 5), in which the amino acid residues are similar to the binding mode profile in the docking pose (Fig. 1c). The amino acid residues Ile463, Gly464, Ser467, Val471, Ala481, Lys483, Leu514, Trp531, and Phe583 each contribute -4.5078, -1.1921, -1.03, -7.0119, -2.6023, -1.0874, -4.3269, -2.7108, and -7.6098 kJ/mol to the binding energy of the 6XFP-chrysin complex. Ile463, Gly464, Gly466, Ser467, Val471, Ala481, Leu514, Trp531, Ser535, and Phe583 contribute -5.9498, -1.9006, -1.3438, -1.8408, -7.9113, -2.1248, -3.7162, -3.9544, -1.1995, and -7.2038 kJ/mol, respectively, to the binding energy of the 6XFP-stigmasterol complex. The contribution of residues to binding energy in the 6XFP-γ-sitosterol complex is similar to that of the 6XFP-stigmasterol complex. The amino acid binding energy to binding energy (assigned negative) in the 6XFP-γ-sitosterol complex are Ile463, Gly464, Gly466,

Ser467, Val471, Tyr472, Ala481, Leu514, Trp531, Glu533, Ser535, and Phe583 with a total energy of -6.9367, -2.0264, -1.4116, -2.0845, -7.9079, -0.703, -2.4185, -3.9149, -3.8168, -0.8913, -0.8929, and -7.0148 kJ/mol, respectively.

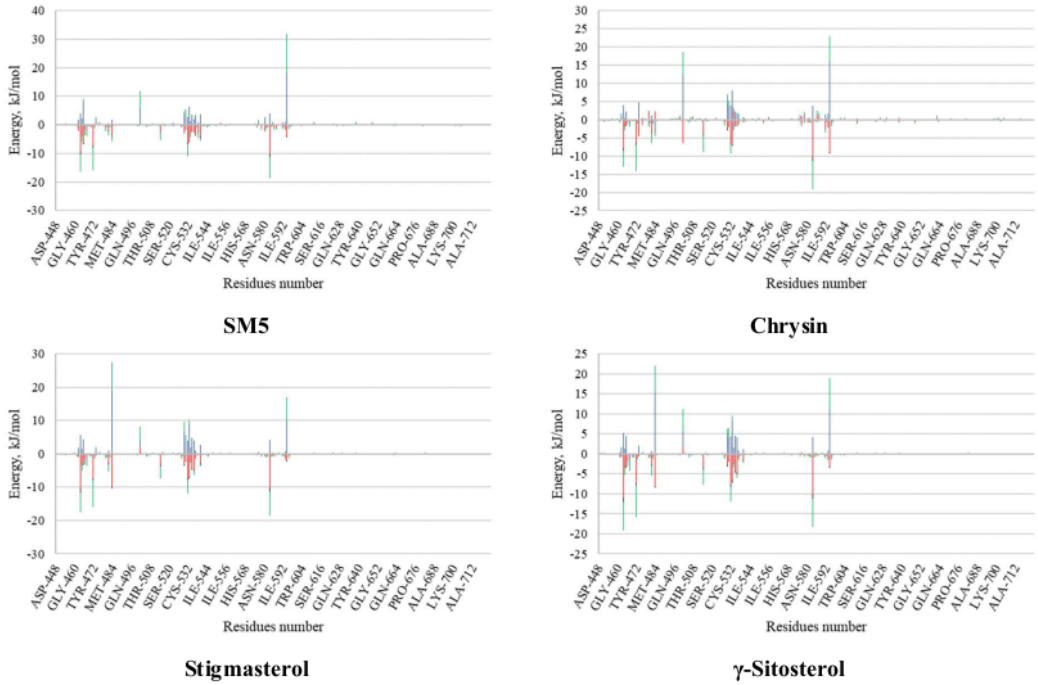

Fig.-6: Contribution of Residues to the Binding Energy of the Protein-Ligand Complex at 80 ns. MM, Polar, Non-Polar, and Total Energy are Colored Red, Blue, Black, and Green, respectively.

The BRAF kinase consists of 766 amino acids and is divided into 3 domains.[40] Residues 457–717, conserved region 3, are the most important catalytic domain that phosphorylates consensus substrates. There are two lobes joined by a short hinge region. The N-lobe (residues 457–530) is in charge of binding adenosine triphosphate (ATP). The C-lobe (residues 535–717) is responsible for binding substrate proteins.[41] ATP is anchored in a pocket formed by Val471, Ala481, Leu514, Thr529, Trp531, and Cys532. A DFG motif is formed by D (Asp) 594, F (Phe) 595, and G (Gly) 596, and it determines whether the BRAF protein is inactive or active. The binding free energies of chrysin, stigmasterol, and γ-sitosterol with 6XFP are higher than those of SM5. Furthermore, the inhibitory constants of stigmasterol and γ-sitosterol are higher than those of SM5 and chrysin. As a result, stigmasterol and γ-sitosterol will be able to stabilize the 6XFP complex more effectively.

CONCLUSION

In conclusion, four ligands (2-methyl anthraquinone, chrysin, stigmasterol, and γ-sitosterol) had higher binding energies than SM5 based on molecular docking studies. Furthermore, stigmasterol and γ-sitosterol have higher inhibitory constants than SM5 and chrysin. While the MD simulation results show that stigmasterol and γ-sitosterol are candidates for BRAF inhibitors, as a result, these phytochemicals have the potential to be lead compounds for melanocytic tumors.

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