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In silico study on p53 protein interaction with Streptomyces compounds

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ABSTRACT
Pharmaceutical research has successfully integrated a plethora of molecular modelling methods into a variety of drug discovery programs to study complex biological and chemical systems. Integration of computational and experimental strategies has proven extremely beneficial in the discovery and developing of novel promising compounds. In silico studies are frequently used to identify suitable antitumor compounds that are appropriate for the cancer targets. The current study aims to assess the interactions of some antitumor compounds isolated from Streptomyces against cancer target proteins. Five compounds from Streptomyces parvus and Streptomyces californicus were chosen and tested for interactions with cancer target proteins using an in silico molecular docking approach. The metabolites 1-Heptadecene, 1,3-Benzenedicarboxylic acid and 1-Tetradecanol were derived from Streptomyces parvus. Phenol 2, 4 bis(1,1-dimethyl ethyl) and Pentatriacone were derived from Streptomyces californicus. The 3D structures of both bioactive compounds and transcription factors were obtained from Pubchem and PDB databases respectively. Docking studies were carried out by using AutoDock method. When the docking results were examined, it was discovered that all of the bioactive compounds had a high affinity for their targets. The best binding affinity values were -3.7, -4.6, -3.6, -6.9, and -5.9. Our findings indicate that all five compounds are better cancer drug targets for therapy.
Keywords: *Molecular modelling, AutoDock, p53 gene, Streptomyces, molecular interaction and antitumor compounds.*

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INTRODUCTION

Cancer is one of the major causes of death around the world, it is expected to remain the leading cause of death due to inefficient diagnosis and treatment in the coming years [1]. In invertebrates, the p53 family of transcription factors consists of three members (p53, p63, and p73), all of which are descended from a common ancestral gene [2]. In the cell cycle, the three paralogs perform overlapping and different tasks. p53 is an important tumor suppressor gene [3-5]. If they have donor atoms and affect the polarity of the bioactive molecule, symmetric ligands in organic synthesis could provide increased chelating abilities. This function is critical because the polarity index has a significant impact on the binding affinity of ligand molecules to related proteins. As a result, increasing or reducing binding affinity could be a deciding factor in whether a molecule is chosen as a pharmacological inhibitor.

Drug discovery process begins when there is a clinical disease for which there is no effective treatment. In academics, the initial stage in research is to generate a hypothesis, such as a blockage or stimulation of a protein or pathway as a therapeutic impact in a clinical condition [6]. Molecular docking is a computational method that predicts binding site complementarity between a drug and its therapeutic target [7] and it has been widely utilized to aid drug repositioning for a variety of disorders, including cancer [8-11]. Molecular dynamics, on the other hand, is widely used to predict protein-ligand binding locations, including binding pockets and binding residues inside each pocket [12, 13]. In this study, we report the interactions of bioactive compounds from *Streptomyces parvus* and *Streptomyces californicus* with target proteins of cancer and amino acids involved in interactions with the ligand.

MATERIAL AND METHODS

Protein Preparation

The protein for our investigation (Tetramerization domain) was obtained from the Protein Data Bank (PDB ID: 4D1L). With a resolution of 1.97 AO, it is one among the X-ray diffracted crystal structures [14].

With Discovery Studio File, all water molecules, hetatoms, and other protein chains in the protein structure were eliminated (Figure 1). It was finally converted to PDBQT format [15].

Ligand Preparation

Five compounds from *Streptomyces* were selected as ligands based on anticancer activity reported previously. The metabolites 1-Heptadecene, 1,3-Benzenedicarboxylic acid and 1-Tetradecanol were derived from *Streptomyces parvus.* Phenol 2, 4 bis(1,1-dimethyl ethyl) and Pentatriacone were derived from *Streptomyces californicus.* This compound has been shown to possess significant cytotoxicity against MDA-MB-231 breast cancer cell lines as well as antibacterial and antifungal activity. Finally, the five bioactive compounds was selected and docked with cancer target proteins and the binding energy was calculated.

The ligands or small compounds used for the study were gathered from the PubChem database. The ligands were 1-Heptadecene, 1,3 Benzenedicarboxylic acid, 1-Tetradecanol, Phenol 2,4 bis(1,1-dimethyl ethyl) and Pentatriacone in SDF format were obtained. After that, Open Babel software was used to convert SDF format into PDB format. It is then transformed to the PDBQT format [16].

Molecular Docking

The receptor lattices were built using 34x41x25 network focuses in xyz with a network box centered within the run of -8.9494, -21.8671, 15.8103 co-crystallized after the protein and ligand were converted to PDBQT data. After that, choose the protein and ligand for docking and run it. Positional root-mean-square deviation (RMSD) results were grouped and discussed by the result with the most ideal free vitality of the official. Biovia discovery studio was used to examine the protein-ligand interaction. The yields were examined using their atomic surfaces and various bonds. As PNG records, the yields are spared.

RESULTS AND DISCUSSION

Drug discovery is a labor-intensive and time-consuming process. A new medicine takes an average of 10-15 years to create. Because of its low cost and low risk, drug repositioning, or the use of old treatments for new conditions, is an effective technique. As a result, molecular docking was performed in a computer to find a cancer-fighting medication. 1-Heptadecene, 1,3-Benzenedicarboxylic acid, 1-Tetradecanol, Phenol 2, 4 bis (1,1-dimethyl ethyl) and Pentatriacone were docked with Tetramerization domain, with a PDB ID:4D1L in molecular docking experiments. For our work Tetramerization domain, hetatoms such as water molecules and ligand groups were removed from the protein and converted to an autodock compatibility file in PDBQT format (Figure 1).

The energy minimization for the small molecules 1-Heptadecene, 1,3-Benzenedicarboxylic acid, 1-Tetradecanol, Phenol 2,4 bis(1,1-dimethyl ethyl), and Pentatriacone were 52.59, 74.31, 58.55, 672.29, and 590.69, respectively. Finally, the file was translated to PDBQT format and saved (Figure 2). The cast identified and defined the active sites of this protein, which contain the residues Leu 307, Leu 318, Lys 319, Tyr 315, Unk 1, Val 309, Leu 318, Phe 305, and Glu 326. The protein conformations with each ligand were investigated. -3.7, -4.9, -3.6, -6.9 and -5.9 were the best binding affinity values. H-bond distances and H-bond interacting residue distances were in (Table 1). The root means square deviation value for that conformation will be zero. The binding affinity of those compounds with the macromolecule in various configurations, as well as the Root Mean Square Deviation (RMSD) values of the interacting molecules (Protein and Ligand), were in the range (Table 2). Protein-ligand interactions (1-Heptadecene, 1,3-Benzenedicarboxylic acid, 1-Tetradecanol, Phenol 2,4 bis(1,1-dimethyl ethyl) and Pentatriacone) were studied (Figures 3 and 4). The criteria currently followed for selecting antitumor compounds include agents that can target apoptosis inhibitor proteins and cancer cell markers. *In silico* studies are frequently used to identify antitumor compounds that are appropriate for the cancer targets.

In silico molecular docking approach of nine compounds from marine *Streptomyces* were evaluated for their interactions with cancer target proteins. PatchDock docking software was used to investigate these ligand-target protein interactions. Marmycin A interacted very well with the human epidermal growth factor receptor 2 (HER2), with the lowest binding energy of 472.92 kcal/mol. Proximycin A, chandrananimycin C, echinosporin, streptochlorin, and streptokordin all had binding energies of 341.11 kcal/mol, 313.31 kcal/mol, 305.64 kcal/mol, 291.91 kcal/mol, and 222.34 kcal/mol with CDK4 protein, respectively. Our findings suggest that HER2 and CDK4 are better cancer drug targets for therapy [17].

An isoprenoid compound altemicidin isolated from the marine *Streptomyces sioyaensis* SA-1758 and found it to have anti-tumor and acaricidal activity. The compound altemicidin had the lowest binding energy -415.66 kcal/mol with cyclin dependent kinase 4 (CDK4) [18].

Table 1. Molecular docking studies of compounds with Tetramerization (Crystal form)

S. No	Compound name	Docking score (kcal/mol)	H-Bond interaction	Distance
1.	1-Heptadecene,	-3.7	Leu 318 Leu 307 Tyr 315 Lys 319	4.85 5.48 4.65 4.28 5.45 5.17 5.35 5.09
2.	1,3Benzenedicarboxylic acid,	-4.9	Leu 307 Lys 319	3.82 3.21
3.	1-Tetradecanol	-3.6	Leu 307 Val 309 Leu 318	4.50 6.07 5.46 5.43
4.	Phenol2,4bis(1,1-dimethyl ethyl)	-6.9	Phe 305 Leu 307	4.38 5.39 3.66 4.90 5.31
5.	Pentatriacone	-5.9	Glu 326	2.93 3.75

Table 2. Displays the binding affinity and root mean square deviation (RMSD) Upper and Lower Bound values of 1-Heptadecene, 1,3 Benzenedicarboxylic acid, 1-Tetradecanol, Phenol 2,4 bis(1,1-dimethyl ethyl), and Pentatriacone.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
4d1l_A_A_1-Heptadecene_uff_E=52.59	-3.7	0	0
	-3.6	5.929	2.295
	-3.6	20.185	17.995
	-3.5	3.714	1.42
	-3.4	20.115	18.154
	-3.4	19.276	17.78
	-3.3	6.93	2.635
	-3.3	20.166	18.088
	-3.3	4.616	1.49
4d1l_A_A_1,3Benzenedicarboxylicacid_uff_E=74.31	-4.9	0	0
	-4.9	4.396	0.197
	-4.7	4.493	2.337
	-4.7	3.437	2.382
	-4.6	3.502	2.405
	-4.6	4.543	1.562
	-4.5	4.1	2.16
	-4.5	5.197	2.696
	-4.5	19.57	18.711
4d1l_A_A_1-Tetradecanol_uff_E=58.55	-3.6	0	0
	-3.6	6.137	2.662
	-3.5	19.496	18.449
	-3.5	6.788	3.432
	-3.4	4.634	1.51
	-3.4	4.636	1.924
	-3.4	3.416	2.368
	-3.4	19.847	18.577
	-3.4	5.459	2.254
4d1l_A_A_Phenol 2,4-bis(11-dimethylethyl)_uff_E=672.29	-6.9	0	0
	-6.7	8.133	4.377
	-6.6	7.765	3.389
	-6.5	3.857	2.89
	-6.5	3.955	1.406

	-6.4	3.198	2.559
	-6.3	7.275	3.259
	-6.3	7.018	3.16
	-6.2	4.038	2.62
4d1l_A_A_Pentatriacontane_uff_E=590.69	-5.9	0	0
	-5.9	9.955	6.016
	-5.8	11.473	6.866
	-5.7	9.458	5.547
	-5.6	7.273	3.349
	-5.3	9.453	5.557
	-5.3	12.339	7.153
	-5.2	9.94	6.102
	-5.1	11.955	7.611

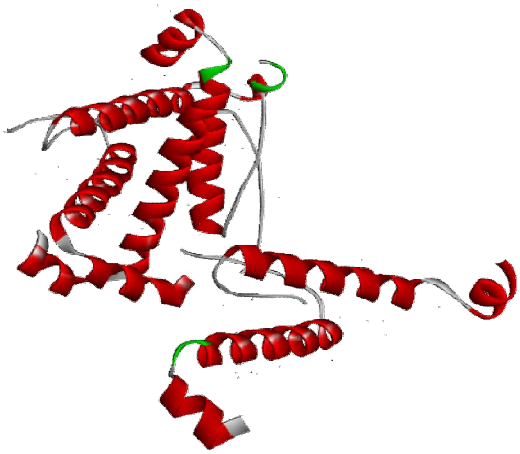


Figure 1. 3D structure of of targeted p53 Tetramer protein (Crystal form) [PDB ID: 4D1L]

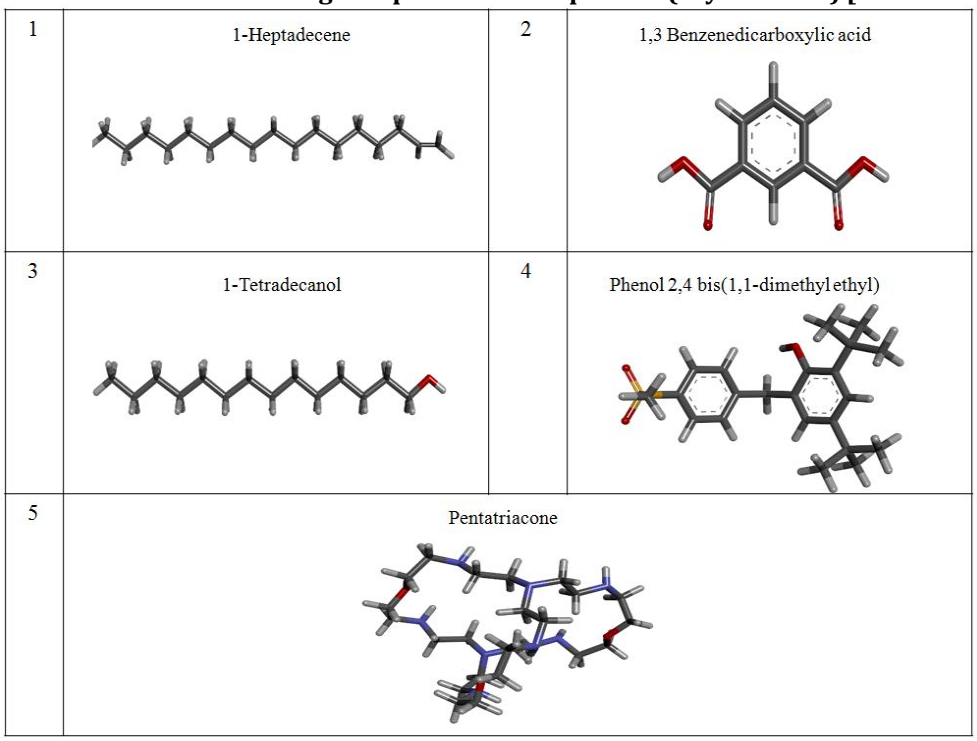
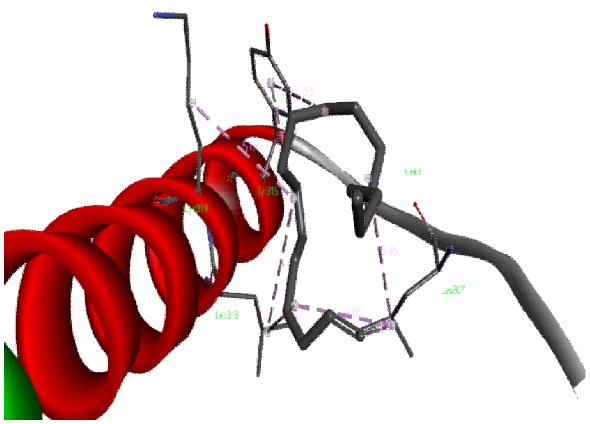
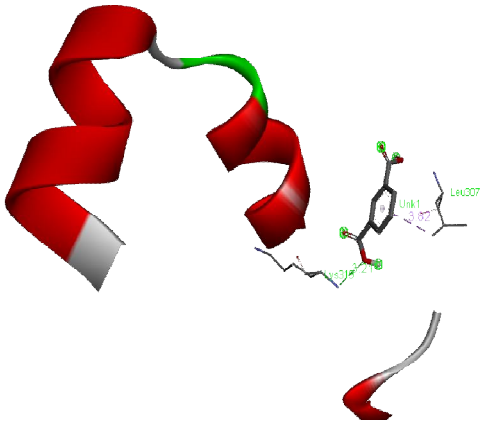


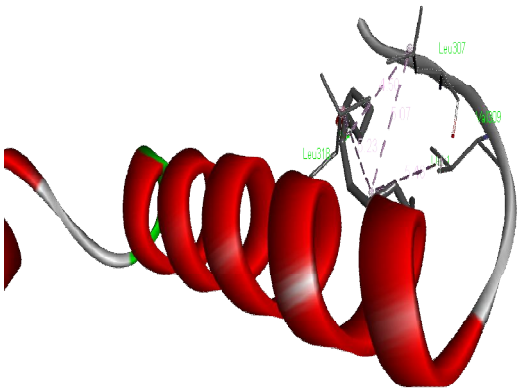
Figure 2. 3D structures of *Streptomyces parvus* and *Streptomyces californicus* derived bioactive compounds retrieved from PubChem database.



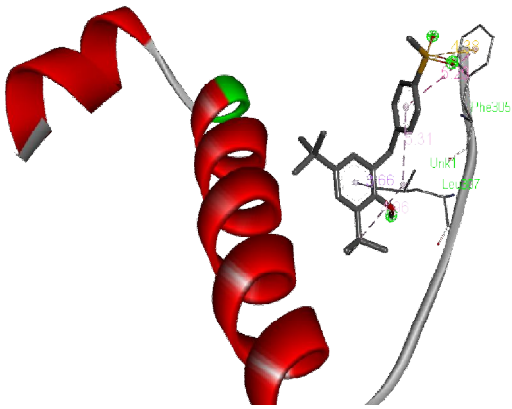
1-Heptadecene



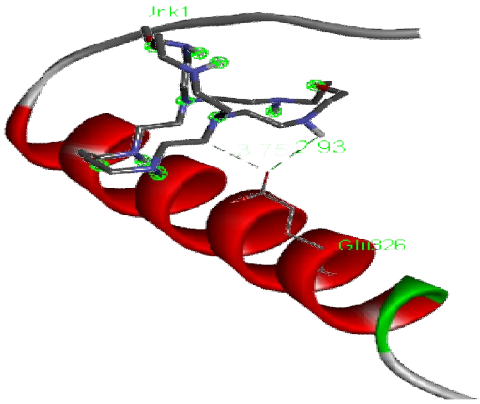
1,3 Benzenedicarboxylic acid



1-Tetradecanol



Phenol 2,4 bis(1,1-dimethyl ethyl)



Pentatriacone

Figure 3. *Streptomyces parvus* and *Streptomyces californicus* derived bioactive compounds interacting with their p53 protein receptor.

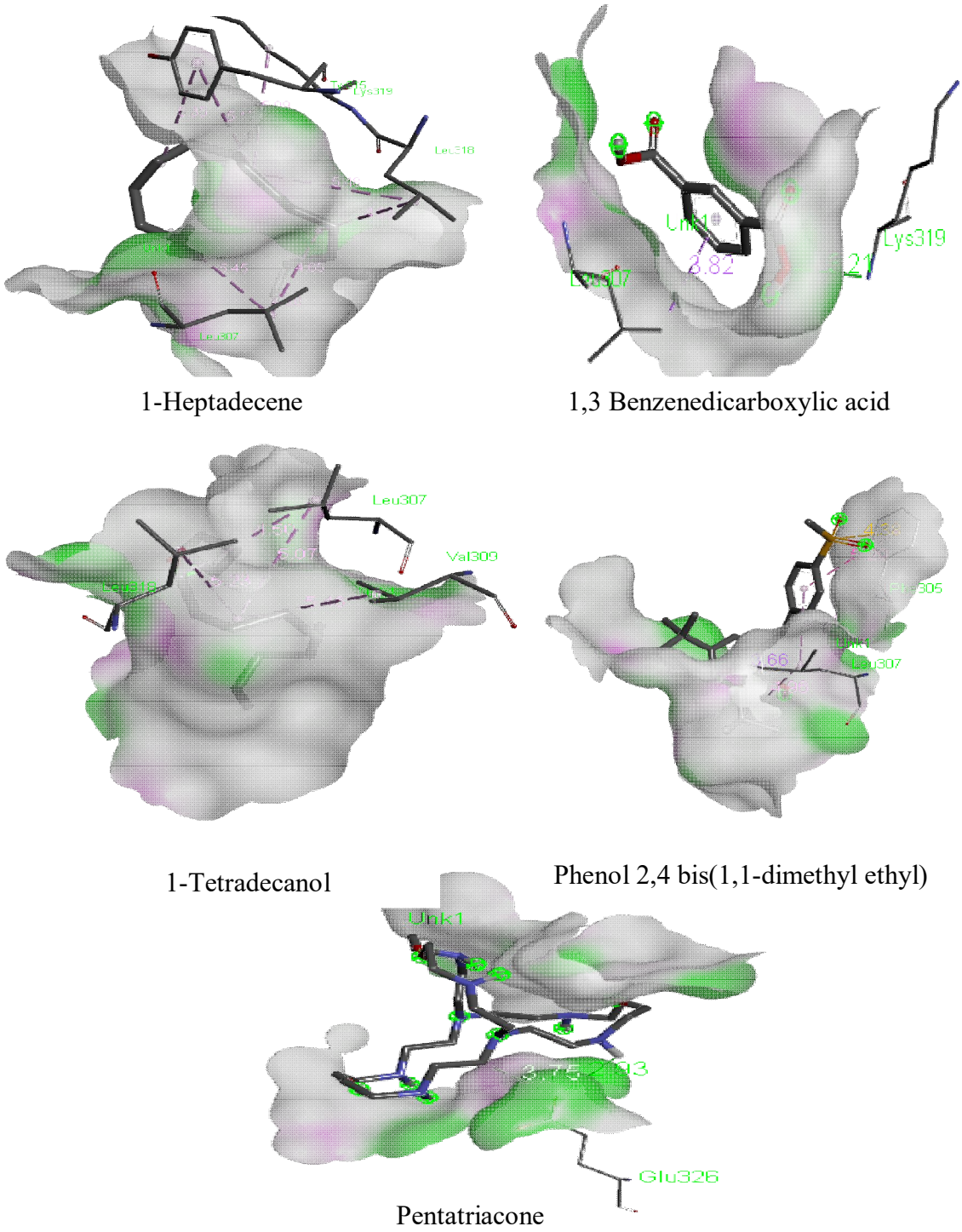


Figure 4. *Streptomyces parvus* and *Streptomyces californicus* derived bioactive compounds interacting with their p53 protein H-Bond.

CONCLUSION

Computational medicinal chemistry studies are being used in search for bioactive with the optimal multi-target interactions. Molecular Dynamic Simulations (MD) was created using 1-Heptadecene, 1, 3 Benzenedicarboxylic acid, 1-Tetradecanol, Phenol 2,4 bis(1,1-dimethyl ethyl) and Pentatriacone, as well as Tetramerization (Crystal form). Those compounds had the best binding affinity of -3.7, -4.9, -3.6, -6.9, and -5.9. Tetramerization (Crystal form) interacts strongly with important residues such as Leu 307, Leu 318, Lys 319, Tyr 315, Unk 1, Val 309, Leu 318, Phe 305, and Glu 326. The tiny chemical was strongly attached to the Tetramerization (Crystal form) that was being studied. As a result, the evaluated and developed compounds can be used as a drug for treating the cancer lead candidates. However further

studies with the clinical trials are required to give the full mechanism how tetramerization act against the cancer cells.

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CONFLICT OF INTERESTS
The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

1. Arthur, D E. (2017). Toxicity modelling of some active compounds against k562 cancer cell line using genetic algorithm-multiple linear regressions. Journal of the Turkish Chemical Society Section A: Chemistry., 4(1):355-374.
2. Vlasiou, M C., Petrou, C C., Sarigiannis, Y., & Pafiti, K S. (2021). Density functional theory studies and molecular docking on Xanthohumol, 8-Prenylnaringenin and their symmetric substitute diethanolamine derivatives as inhibitors for colon cancer-related proteins. Symmetry., 13(6):948.
3. Belyi, V A., Ak, P., Markert, E., Wang, H., Hu, W., Puzio-Kuter, A., & Levine, A J. (2010). The origins and evolution of the p53 family of genes. Cold Spring Harbor Perspectives in Biology., 2(6): a001198.
4. Lane, D P. (1992). p53, guardian of the genome. Nature., 358(6381):15-16.
5. Levine, A J., Tomasini, R., McKeon, F D., Mak, T W., & Melino, G. (2011). The p53 family: guardians of maternal reproduction. Nature Reviews Molecular cell Biology., 12(4):259-265.
6. Vousden, K H., & Prives, C. (2009). Blinded by the light: the growing complexity of p53. Cell., 137(3):413-431.
7. Hughes, J P., Rees, S., Kalindjian, S B., & Philpott, K L. (2011). Principles of early drug discovery. British Journal of Pharmacology., 162(6):1239-1249.
8. Cardoso, W B., & Mendanha, S A. (2021). Molecular dynamics simulation of docking structures of SARS-CoV-2 main protease and HIV protease inhibitors. Journal of Molecular Structure., 1225:129143.
9. Stefaniu, A., Pirvu, L., Albu, B., & Pintilie, L. (2020). Molecular docking study on several benzoic acid derivatives against SARS-CoV-2. Molecules., 25(24):5828.
10. Yoshino, R., Yasuo, N., & Sekijima, M. (2020). Identification of key interactions between SARS-CoV-2 main protease and inhibitor drug candidates. Scientific Reports., 10(1):1-8.
11. Wu, Q., Peng, Z., Zhang, Y., & Yang, J. (2018). COACH-D: improved protein–ligand binding sites prediction with refined ligand-binding poses through molecular docking. Nucleic Acids Research., 46(W1):W438-W442.
12. Yang, J., Roy, A., & Zhang, Y. (2013). Protein–ligand binding site recognition using complementary binding-specific substructure comparison and sequence profile alignment. Bioinformatics., 29(20):2588-2595.
13. Joerger, A C., Wilcken, R., & Andreeva, A. (2014). Tracing the evolution of the p53 tetramerization domain. Structure., 22(9):1301-1310.
14. Morris, G M., Goodsell, D S., Halliday, R S., Huey, R., Hart, W E., Belew, R K., & Olson, A J. (1998). Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of Computational Chemistry., 19(14):1639-1662.
15. Binkowski, T A., Naghibzadeh, S., & Liang, J. (2003). CASTp: computed atlas of surface topography of proteins. Nucleic Acids Research., 31(13):3352-3355.
16. Xue, H., Li, J., Xie, H., & Wang, Y. (2018). Review of drug repositioning approaches and resources. International Journal of Biological Sciences., 14(10): 1232.
17. Amulya Ruby Lankapalli., & Kannabiran, K. (2013). Interaction of marine *Streptomyces* compounds with selected cancer drug target proteins by *in silico* molecular docking studies. Interdiscip Sci Comput Life Sci., 5:37-44.
18. Takahashi, A., Kurasawa, S., Ikeda, D., Okami, Y., & Takeuchi, T. (1989). Altemicidin, a new acaricidal and antitumor substance. I. Taxonomy, fermentation, isolation and physico-chemical and biological properties. J Antibiot (Tokyo)., 42:1556-1561.

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