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Original Article

IN SILICO DOCKING STUDIES ON KAEMPFERITRIN WITH DIVERSE INFLAMMATORY AND APOPTOTIC PROTEINS FUNCTIONAL APPROACH TOWARDS THE COLON CANCER

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ABSTRACT

Objective: The objective of this research was to formulate the binding energies and interaction of amino acid residues in kaempferitrin with different types of apoptotic and inflammatory proteins of colon cancer.

Methods: AutoDock Vina and MGL tool were used for docking calculations. Both programs require the pdbqt input files and allow for flexibility of all the torsional bonds of small molecules. Discovery Studio Visualizer v3.5 was used for removal of water molecules and ligands and the pymol program was used to do analysis of the docking with various apoptotic proteins BAX, Bcl-2, COX-2, Protein kinase B.

Results: In our study was developed binding energy scoring function of kaempferitrin docked with different types of inflammatory proteins and apoptotic proteins. Binding score values for-6.9 (BAX),-7.2 (Bcl-2),-7.3 (caspase-3),-8.8 (Cox-2),-7.4 (Cytochrome P450),-6.7 (Proteinase kinase B),-8.0 (TNF-α) and-7.2 (VEGF) kcal/mol, respectively. Amino acid interaction of kaempferitrin with proteins for ARG-25, LEU-52, ASN-54, PHE-55, GLU-17, LYS-14, TRP-22, THR-21 GLY-16 (Protein Kinase B), ASP-102, ASN-48, GLN-52, ASP-104 (BAX), GLU-176, TRP-173, GLU-132, PHE-135 (Bcl-2), SER-249, ASP-2, ASN-208, GLN-217, LEU-242 (Caspase 3), TYR-55, HIS-39, SER-49, GLU-322, GLY-326 (COX-2), SER-95, LEU-94, ARG-82, VAL-123, ALA-96 (TNF-α), ASP-414, LYS-322, GLU-326, GLU-416, GLU-438, ALA-439, GLU-437 (Cytochrome P450) and LEU-47, GLN-46, CYS-61, CYS-60, ASP-63, GLU-67, GLY-65, LEU-66 (VEGF) respectively.

Conclusion: The results obtained in this research work clearly indicated the docking scores of apoptotic and Inflammatory proteins imply that kaempferitrin is an effective inhibitory compound for colon cancer.

Keywords: Kaempferitrin, AutoDock Vina, MGL Tool, Protein Kinase B, Bcl-2

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INTRODUCTION

Amongst all cancers known to affect mankind, colorectal cancer (CRC) is the third most cause of cancer deaths [1, 2]. There is increasing necessity to find a source of pioneering chemo preventive and chemotherapeutic agents for CRC. The American Cancer Society has estimated the epidemiological data of colon cancer to be 95,270 new cases and 49,190 deaths in 2016. Colorectal cancer represents the third most cancer frequently diagnosed malignancy in the world [3]. Colorectal cancer is the third foremost site of cancer in men and women and is the second leading cause of cancer-related deaths. Although the mortality of colorectal cancer has decreased by about 26% over the decades, only 3% has been due to improved treatment strategies. Suppression of apoptosis is often associated with increased expression of anti-apoptotic proteins and decreased expression of pro-apoptotic proteins [4]. For instance, anti-apoptotic protein Bcl-2 is over-expressed in various cancer cells, contributing to the inhibition of apoptosis. Colon cancers are relatively resistant to most conventional anti-tumor drugs and this resistance is closely linked to loss of apoptosis signaling. One of the important multi-domain pro-apoptotic Bcl-2 family proteins essential for initiating apoptotic cell death is BAX and subsets of colon cancers are found to be associated with BAX mutation [5].

Flavonoids have a C6–C3–C6 three-ring skeleton (the rings are termed the A-, B-, and C-rings) and can be divided into several classes in terms of structure; these are the flavonols, flavones, flavanones, anthocyanidins, and isoflavonoids. Flavonoids, the most common polyphenolic compounds of edible plants, exhibit a wide range of biological and pharmacological activities, including anti-inflammatory, antioxidant, and anticancer effects [6]. Several structures–activity relationship studies have revealed that the presence of a 2′-hydroxyl group on the B-ring is important in terms of enhancement of antitumor activity [7, 8]. Kaempferitrin is a chemical compound. It can be isolated from the leaves of *Hedyotis verticillate* [9]. Kaempferitrin induces apoptosis through the sequential activation of caspase-8 and caspase-3 (fig. 1).

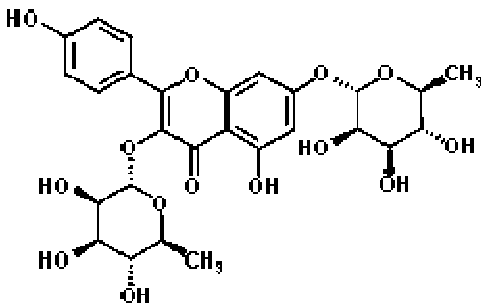

Fig.1: Chemical structure of kaempferitrin (molecular weight: 578.523 g/mol)

The Akt signaling is a constitutively activated pathway in the inherited colorectal cancer (FAP) and earn up to 80% of sporadic colorectal cancers (CRC) due to inactivating mutations of the adenomatous polyposis coli (APC) tumor suppressor gene. APC is a component of the β-catenin degradation complex whose mutations are indeed now clearly recognized as early and sufficient events to promote intestinal tumor development. Many chemotherapeutic drugs causing nucleolar stress will function independently from tumor suppressor protein p53 and still lead to cell cycle arrest and or apoptosis. Since it is known that most cancers lack functional p53, it is with great interest to explore these molecular mechanisms. It is known that more than 50% of human cancers lack functional p53.

Consequently, drugs triggering cell death in p53-null cells may have great potential in the treatment of many cancers [10].

A number of molecular abnormalities have been associated with CRC, including mutations in k-ras oncogenes; the inactivation of the tumor suppressor genes APC, p53 and DCC; mutations in the DNA mismatch repair regulators mutL-homolog 1and mutS alpha or mutS beta; and the dysregulation of DNA methylation, microsatellite stability, and non-coding RNAs [11]. *In silico* docking study performed here demonstrates the rationale for the different binding activities of kaempferitrin.

MATERIALS AND METHODS

Docking

In the present work two of the best docking programs, AutoDock Vina and MGL tool were used for docking calculations. Both programs require the pdbqt input files and allow for flexibility of all the torsional bonds of small molecules. For AutoDock program, the implemented empirical free energy function and the lamarckian genetic algorithm were used. Gastiger charges and hydrogen atoms were added to small molecules and protein structures. For all docking calculations, the amount of docking runs was set to 250 with 5,000,000 energy evaluations for each run. The size of the box that defines the search space was set at 1 Å around the small molecules. For each 2,5-DKP derivative, the first result (the lowest energy conformation) of Vina and AutoDock were selected as the docking result. Finally, the pymol program was used to do analysis of the docking results.

Preparation of receptors structures for docking

3D crystallographic structures of proteins were obtained from protein data bank (PDB) (http://www. pdb. rcsb. org), and those of small molecules were retrieved from PubChem compound database (http://www.ncbi.nlm.nih.gov/search). The structure of kaempferitrin was taken from chemspider (Chemspider code: 4588900) [20]. The 3D structures of proteins were retrieved as follows: BAX (Pdb: 4S0O), Bcl-2, (Pdb: 4MAN), Caspase-3 (Pdb: 5I9B), Cox-2 (Pdb: 1CX2), Cytochrome p450 (Pdb: 4NZ2), Protein Kinase B (Pdb: 1UNR), TNFα (Pdb: 4TWT) and VEGF (2C7W). Initially, DNA, ligand, and crystallographic water molecules were removed in the 3D structure using Discovery Studio Visualizer; AutoDock Tools assigned polar hydrogen, Kollman United atom charges, salvation parameters, and fragmental volumes to the protein. AutoDock saved the prepared protein file in PDBQT format.

Grid generation and molecular docking

The auto grid was used for the preparation of the grid map using a grid box. Points on a 3D grid were placed to cover the complete inner cavity of the receptor that constitutes the ligand. The grid size was set to 40×40×40 xyz points with grid spacing of 1 Å and grid center was designed at dimensions (x, y, and z): 23.844,-3.449, and 16.98 (Pdb: 4S0O),-26.06,-7.878 and-6.86 (Pdb: 4MAN),-2.946,-16.98 and-11.857 (Pdb: 5I9B), 35.926, 26.777 and 21.803 (Pdb: 1CX2), 21.748, 36.254 and-7.358 (Pdb: 4NZ2), 13.016,-0.696 and 3.25 (Pdb: 1UNR),-2.141, 89.766, 241.23 (Pdb: 4TWT) and-41.2,-23.19 and 0.366 respectively.

A scoring grid was computed using the ligand structure to reduce the computation time. Docking was carried out using AutoDock Vina with protein and ligand data together with the grid box properties in the configuration file. It uses iterated local search global optimizer with the AMBER force field. Throughout the docking studies, the protein molecule was kept as rigid and ligand molecules as flexible. The results<1.0Å in positional RMSD were grouped together, and the outcome with the most favorable free energy of binding was used for representation. The pose with lowest binding energy or binding affinity was used for subsequent analysis.

RESULTS AND DISCUSSION

Binding energy

The scoring function used in Vina was derived using the PDB bind data set, and the performance of Vina has been compared to that of AutoDock 4.0.1 on a set of 190 protein-ligand complexes that had been used as a training set for the AutoDock scoring function. Previous studies were proved the binding strength and interaction of amino acids using natural bio active flavonoids [12]. In that way, our study was developed binding energy scoring function of kaempferitrin docked with different types of inflammatory proteins and apoptotic proteins. The computational analysis of this drug was the first time to understand the mechanism of interaction [13] between kaempferitrin and apoptotic proteins.

Table 1 shows the values for-6.9 (BAX),-7.2 (Bcl-2),-7.3 (caspase-3),-8.8 (COX-2),-7.4 (Cytochrome p450),-6.7 (Proteinase kinase B),-8.0 (TNF-α) and-7.2 (VEGF) kcal/mol, respectively. All the proteins were having high affinity and strongly bonded with polar contacts (fig. 2). Most of these compounds tend to form H-bond and the residues and their binding energy showed in table 1.

Table 1: The binding energies of protein kinase B, BAX, Bcl-2, caspase-3, COX-2, TNF-α cytochrome P450 and VEGF with the known small molecule kaempferitrin

S. No.	Ligand	Target proteins gscore (kcal/mol)							
		Protein kinase B	BAX	Bcl-2	Caspase-3	COX-2	TNF-α	Cytochrome P450	VEGF
1.	Kaempferitrin	-6.7	-6.9	-7.2	-7.3	-8.8	-8.0	-7.4	-7.2

BAX: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma-2, COX-2: Cyclooxygenase-2, TNF-α: tumor necrosis factor alpha, VEGF: Vascular endothelial growth factor

Table 2: Apoptotic proteins with their residues

S. No.	Ligand	Macromolecules	Amino acid residues
1.	Kaepmferitrin	BAX	ASP-102, ASN-48, GLN-52, ASP-104
		Bcl-2	GLU-176, TRP-173, GLU-132, PHE-135
		Caspase-3	SER-249, ASP-2, ASN-208, GLN-217, LEU-242
		COX-2	TYR-55, HIS-39, SER-49, GLU-322, GLY-326
		Cytochrome p450	ASP-414, LYS-322, GLU-326, GLU-416, GLU-438, ALA-439, GLU-437
		Protein kinase B	ARG-25, LEU-52, ASN-54, PHE-55, GLU-17, LYS-14, TRP-22, THR-21 GLY-16
		TNF-α	SER-95, LEU-94, ARG-82, VAL-123, ALA-96
		VEGF	LEU-47, GLN-46, CYS-61, CYS-60, ASP-63, GLU-67, GLY-65, LEU-66

BAX: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma-2, COX: Cyclooxygenase-2, TNF-α: tumor necrosis factor alpha, VEGF: Vascular endothelial growth factor

Docked results with protein kinase B, BAX, Bcl-2 and caspase 3

To elucidate possible interaction between kaempferitrin and Protein Kinase B, BAX, Bcl-2, and Caspase 3 was carried out. Kaempferitrin docked well into protein kinase B and the docking score was-6.7 kcal/mol (fig. 2(A)). Nine residues residing in the binding site of protein kinase B ligand had hydrophobic interactions with kaempferitrin ARG-25, LEU-52, ASN-54, PHE-55, GLU-17, LYS-14,

TRP-22, THR-21 and GLY-16. The first evidence that Akt plays a major role in oncogenesis was produced by the isolation of the transforming retrovirus from an AKR mouse T-cell lymphoma [14], which was subsequently shown to contain transduced sequences of cellular origin [15]. The PI3K/Akt or Protein Kinase B pathway plays a main role in regulating censorious cellular survival, including cell division, apoptosis and metabolism [16].

Previous studies [17,18] proved that Akt docked with different types of compounds which could be interacted with amino acids as well. In our present study, proved that kaempferitrin interacted with various amino acid residues and having more binding energies.

BAX, Bcl-2 and Caspase 3 docked well into kaempferitrin and their docking scores were-6.9,-7.2, and-7.3 kcal/mol respectively. The docking score analysis of BAX interaction with kaempferitrin showed in fig. 2(B) and their residues were ASP-102, ASN-48, GLN-52, ASP-104. Fig. 2 (C) shows kaempferitrin docked with Bcl-2, docking score-7.2 kcal/mol and their residues were GLU-176, TRP-173, GLU-132, PHE-135. Whereas, Caspase-3 docked with kaempferitrin the binding residues were SER-249, ASP-2, ASN-208, GLN-217, and LEU-242 (fig. 2 (D). The intrinsic pathway is activated by the members of the Bcl-2 family proteins, including anti-apoptotic proteins, such as Bcl-2, pro-apoptotic proteins (BAX), and downstream mitochondrial signals [19]. Importantly, this cavity consists of amino acids essential for interaction with the BAX carboxyl-terminal transmembrane region [20]. By using this information, ~11 million small molecules were screened for binding to the pocket identified in the BAX hydrophobic groove. Bcl-2 family proteins are important integral membrane proteins located mainly on the outer membrane of mitochondria, which play a critical role in regulating and executing apoptosis [21]. Caspase-3 is an effector protein for the apoptosis, and it plays a role in both the intrinsic and extrinsic apoptosis pathway [22]. Caspase-3 gene sequences have been identified in common carp [23]. From the present study, it can be suggested that kaempferitrin interacted with apoptotic and anti-apoptotic proteins of BAX, Bcl-2, and Caspase 3. The binding energy and interaction of amino acid residues were showed in table 1 and table 2 respectively.

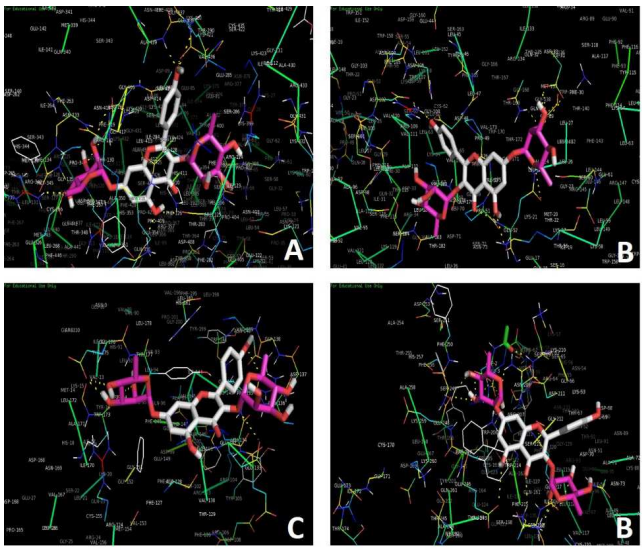

Fig. 2: Structural based docking of identifying compounds of kaempferitrin with proteins. Kaempferitrin docked with different types of proteins such as protein kinase B (A), BAX (B), Bcl-2 (C) and caspase 3 (D)

Docked results with COX-2 and TNF-α

Analysis of the docking results suggests that COX-2 and TNF-α has a binding affinity with kaempferitrin through the formation of one non-polar hydrogen bond with binding energies of-8.8 and-8.0 kcal/mol and hydrogen bond lengths of 1 Å. The interaction of amino acid residues of kaempferitrin with proteins were shown in fig. 3 and table 2. The docked interaction results and residues involved in van der waals forces are described in Supplementary table 2. Kaempferitrin exhibited more binding affinity or hydrogen bond formation with COX-2 and TNF-α.

These interaction results show that COX-2 and TNF-α interacts more highly with kaempferitrin. Cyclooxygenase (COX), known as prostaglandin (PG) H2 synthase, is the rate limiting enzyme in the conversion of arachidonic acid into PGs. Over expression of COX-2 has been frequently observed in colon tumors and COX-2 plays a major role in colon carcinogenesis. Many studies have revealed that PGE2, the metabolite of COX-2 enzyme reaction is an effective mitogen, which contributes to the development of colon cancer [24, 25]. Targeting COX-2 is one of the recent therapeutic methods for the treatment of colon cancer [26, 27]. Previous findings were demonstrated that natural products computationally inhibited the expression of COX-2 [28]. Based on the previous findings, our present docking studies proved that COX-2 has high binding affinity with their compounds. Kaempferitrin binds with COX-2 and have good binding score compared to the previous studies [29]. Tumor necrosis factor-alpha (TNF-α) is a central regulator of inflammation, and TNF-α antagonists may be effective in treating inflammatory disorders in which TNF-α plays an important pathogenetic role [30]. TNF-α also interacted with different types of chemo preventive compounds. In that way, our study demonstrated that kaempferitrin indicated more binding affinity with TNF-α.

Docked results with cytochrome P450

The docked results showed (Supplementary table 1) that kaempferitrin compounds found to have good binding affinity and the interaction of amino acid residues showed in table 2. fig 4 shows that kaempferitrin interacted with Cytochrome P450 and the amino acid residues of ASP-414, LYS-322, GLU-326, GLU-416, GLU-438, ALA-439, GLU-437. The cytochromes P450 (CYPs) constitute the major enzyme family capable of catalyzing the oxidative biotransformation of most drugs and other lipophilic xenobiotics and are therefore of particular relevance for clinical pharmacology [31-33]. Previous study showed that drug-drug interaction of Cytochrome P450 and their compounds [34]. Our results demonstrated that amino acid residues of Cytochrome P450 binds with kaempferitrin have high binding energy.

Docked results with VEGF

The docking results are ranked according to the binding energies with kaempferitrin. The docking binding energy of VEGF to kaempferitrin score was −7.2 and their residues were LEU-47, GLN-

46, CYS-61, CYS-60, ASP-63, GLU-67, GLY-65, LEU-66 (fig. 5). In table 1 and table 2, the binding affinity and the interaction of amino acid residues were showed clearly. Vascular endothelial growth factor is one of the most important factors for de novo-formation of new blood vessels [35]. Besides endothelial cells, it is also produced by a range of other cell types such as fibroblasts [36], neutrophils [37] and macrophages [38]. Previous study [39] screened the docking binding activity of the designed molecule of VEGF was to optimize the maximum binding efficiency. Similarly, our results confirmed that the kaempferitrin bind with VEGF and having maximum binding scores.

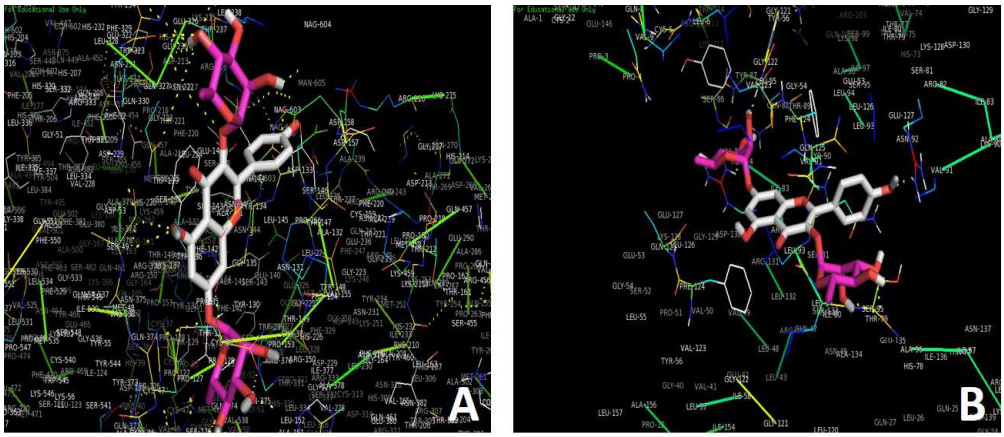

Fig. 3: Illustration of docked complexes of COX-2 (A) and TNF-α with kaempferitrin

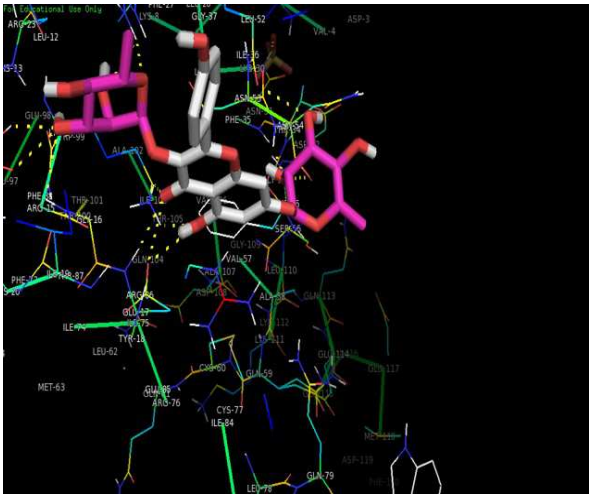

Fig. 4: Ligand-protein interactions of kaempferitrin with Cytochrome P450

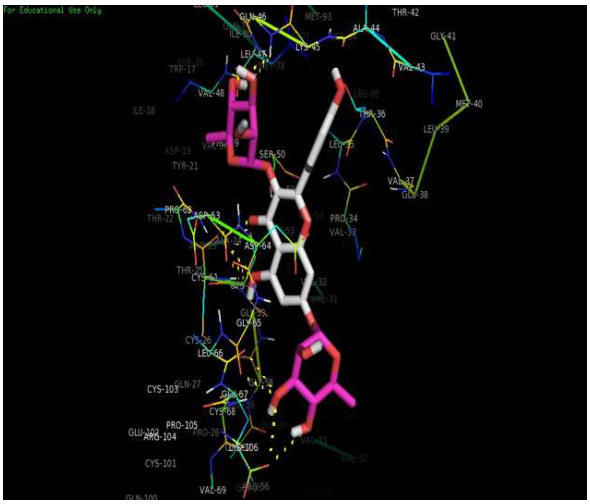

Fig. 5: Illustration of interaction of amino acid residues with kaempferitrin and VEGF

RMSD calculations

RMSD was used for the assessment of docking accuracy of the fraction of protein-ligand contacts [40] and the successful prediction of RMSD<1Å [41]. The RMSD prediction was evaluated from the lower and upper binding energies of proteins with kaempferitrin. Fig. 6 shows the calculation of RMSD for target proteins of Protein Kinase B, BAX, Bcl-2, Caspase-3, COX-2, TNF-α Cytochrome P450 and VEGF, with the lower binding energy of 14.898, 2.522, 40.654, 16.349, 46.168, 2.247, 34.964 and 2.597 and upper binding energies of 20.342, 3.266, 40.490, 20.388, 50.208, 10.878, 38.421 and 18.0, respectively.

In AutoDock Vina, we measured 3D structure by RMSD in optimal rigid body superposition. The quantitative comparison between protein and ligand was performed; the predicted structure of folded protein and ligand was also calculated.

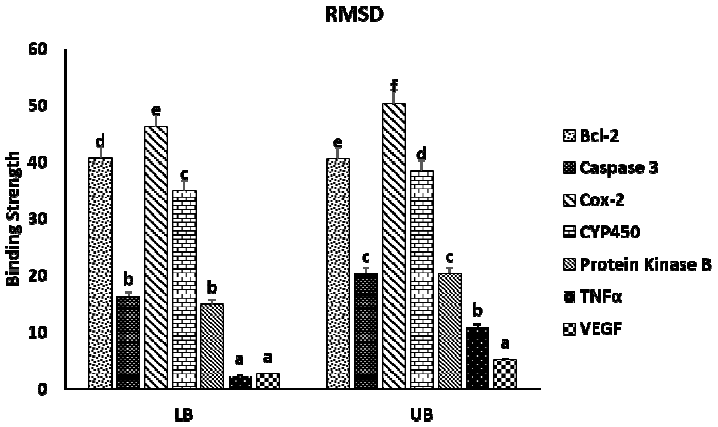

Fig. 6: Root mean square deviation difference from lower binding and upper binding energies of kaempferitrin with protein kinase B, BAX, Bcl-2, caspase-3, COX-2, TNF-α cytochrome P450 and VEGF. Data are presented as the mean±SD of each group. a–f *P*<0.05 the values not sharing a common superscript letter

CONCLUSION

The molecular docking simulations performed for the selected active genes BAX, Bcl-2, Cas-3, COX-2, Cyt p450, Protein kinase B, TNF-α, and VEGF revealed that kaempferitrin could occupy the active sites through hydrophobic and H-bonding interactions. Among those Protein Kinase B has binding affinity-6.7 kcal/mol with following lower binding energy 14.898 and upper binding energy 20.342. The kaempferitrin displayed H-bond interactions with such residues as, which were suggested to be essential for inhibitory activity. Altogether, molecular docking studies imply that kaempferitrin is an effective inhibitory compound for colon cancer. In conclusion, PI3K is a promising target for anticancer drug design. In our effort to develop novel PI3K inhibitors, we recruited structure-based design and molecular docking to optimize the lead PI3K an inhibitor. Additionally, kaempferitrin showed pronounced broad-spectrum antimicrobial, analgesic and anti-inflammatory, and antidepressant activity. Our future goal is to optimize this scaffold to enhance the antitumor activity and selectivity against colon cancer.

AUTHOR CONTRIBUTION

Mydhili Govindarasu and Manju Vaiyapuri designed the study. Maydhili Govindarasu and Mariyappan Palani collected and analyzed the data. Mariyappan Palani provided computational tools to deliver the docking results. Mydhili Govindarasu wrote the first draft of the manuscript. All authors interpreted the results and approved the final version of the manuscript. All authors are the guarantors.

CONFLICTS OF INTERESTS

All authors have none to declare

REFERENCES

1. Karthi N, Kalaiyarasu T, Kandakumar S, Mariyappan P, Manju V. Pelargonidin induces apoptosis and cell cycle arrest via a mitochondria mediated intrinsic apoptotic pathway in HT29 cells. RSC Adv 2016;6:45064-76.
2. Ragunath M, Nadanasabapathy S, Manju V. Anti-inflammatory and proapoptotic effects of umbelliferone in colon carcinogenesis. Hum Exp Toxicol 2016;35:1-14.
3. Valentina P, Assunta S, Emma M, Roberta B, Raffaella S, Giulia R, Annapina R. 5-FU targets rpL3 to induce mitochondrial apoptosis via cystathionine-β-synthase in colon cancer cells lacking p53. Oncotarget 2016;7:50333-48.
4. Lin J, Page C, Jin X, Sethi AO, Patel R, Nunez G. Suppression activity of pro-apoptotic gene products in cancer cells, a potential application for cancer gene therapy. Anticancer Res 2001;21:831-9.
5. Kaleigh F, Manabu K. Evading apoptosis in cancer. Trends Cell Biol 2013;23:620-33.
6. Alonso-Castro AJ, Ortiz-Sanchez E, Garcia-Regalado A, Ruiz G, Nunez-Martinez JM, Gonzalez-Sanchez I, *et al*. Kaempferitrin induces apoptosis via intrinsic pathway in HeLa cells and exerts antitumor effects. J Ethnopharmacol 2013;145:476-89.
7. Rong T. Chemistry and biochemistry of dietary polyphenols. Nutrients 2010;2:1231-46.
8. Kalaiyarasu T, Karthi N, Sharmila Gowri V, Manju V. *In vitro* assessment of antioxidant and antibacterial activity of green synthesized silver nanoparticles from *digitaria radicosa* leaves. Asian J Pharm Clin Res 2016;9:297-302.
9. The Human Metabolome Database. Available from: http:// www.hmdb.ca/metabolites/HMDB37438. [Last accessed on 01 May 2017].
10. Soussi T, Lozano G. p53 mutation heterogeneity in cancer. Biochem Biophys Res Commun 2005;331:834-42.
11. Fredericks E, Dealtry G, Roux S. Molecular aspects of colorectal carcinogenesis: a review. J Cancer Biol Res 2015;3:1057.
12. Mariyappan P, Karthi N, Manju V. Computational studies on different types of apoptotic proteins docked with a dietary flavonoid eriodictyol in colon cancer. Asian J Pharm Clin Res 2017;10:223-6.
13. Ranjan S, Dasgupta N, Chinnappan S, Ramalingam C, Kumar A. A novel approach to evaluate titanium dioxidenanoparticle–protein interaction through docking: an insight into mechanism of action. Proc Natl Acad Sci India B Biol Sci; 2015. p. 1-7.
14. Staal SP, Hartley JW, Rowe WP. Isolation of transforming murine leukemia viruses from mice with a high incidence of spontaneous lymphoma. Proc Natl Acad Sci USA 1977;74:3065-7.
15. Staal SP. Molecular cloning of the akt oncogene and its human homologues AKT1 and AKT2: amplification of AKT1 in a primary human gastric adenocarcinoma. Proc Natl Acad Sci USA 1987;84:5034-7.

16. Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase-AKT pathway in human cancer. Nat Rev Cancer 2002;2:489-501.
17. Alicia H, Israel V, Rafael C, Fabian L, Ping J, Yongping Y, *et al*. Docking of protein kinase B inhibitors: implications in the structure-based optimization of a novel scaffold. Chem Biol Drug Des 2010;76:269-76.
18. Sefika KU, Seval A, Elif O. Virtual screening and docking of potential protein kinase b inhibitors. Cell 2012;102:60-1.
19. Debatin KM. Apoptosis pathways in cancer and cancer therapy. Cancer Immunol Immun 2004;53:153-9.
20. Suzuki M, Youle RJ, Tjandra N. Structure of bax: coregulation of dimer formation and intracellular localization. Cell 2000; 103:645-54.
21. Reed JC. Mechanisms of apoptosis. Am J Pathol 2000;157:1415-30.
22. Wong RSY. Apoptosis in cancer: from pathogenesis to treatment. J Exp Clin Cancer Res 2011;30:87.
23. Gao D, Xu Z, Qiao P, Liu S, Zhang L, He P, *et al*. Cadmium induces liver cell apoptosis through caspase-3A activation in purse red common carp (Cyprinus carpio). Plos One 2013;8:83423.
24. Gupta RA, Dubois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat Rev Cancer 2001;1:11–21.
25. Han JA. Cyclooxygenase-2 promotes cell proliferation, migration and invasion in U2OS human osteosarcoma cells. Exp Mol Med 2007;39:469-76.
26. AI-Fayez M, Cai H, Tunstall R, Steward WP, Gescher AJ. Differential modulation of cyclooxygenase-mediated prostaglandin production by the putative cancer chemo-preventive flavonoids tricin, apigenin and quercetin. Cancer Chemother Pharmacol 2006;58:816-25.
27. O'Leary KA, de Pascual-Tereasa S, Needs PW, Bao YP, O'Brien NM, Williamson G. Effect of flavonoids and vitamin E on cyclooxygenase-2 (COX-2) transcription. Mutat Res 2004;551: 245-54.
28. Isnatin M, Jumina J, Sofia MH, Mustofa M. *In silico* molecular docking of xanthone derivatives as cyclooxygenase-2 inhibitor agents. Int J Pharm Pharm Sci 2017;9:98-104.
29. Sara C, Salvatore A, Angela Di C, Giovanna P, Adele P, Manuela S, *et al*. Synthesis, biological evaluation and docking analysis of a new series of methylsulfonyl and sulfamoyl acetamides and ethyl acetates as potent COX-2 inhibitors. Bioorg Med Chem 2015;23:810-20.
30. Esposito E, Cuzzocrea S. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia reperfusion injury and trauma. Curr Med Chem 2009;1:3152-67.
31. Nelson DR. Cytochrome P450 nomenclature. Methods Mol Biol 2004;320:1-10.
32. Guengerich FP. Cytochrome P450 and chemical toxicology. Chem Res Toxicol 2008;21:70-83.
33. Zanger U. The CYP2D Subfamily. In: C Ioannides. Ed. Cytochromes P450: Role in the metabolism and toxicity of drugs and other xenobiotics. Royal Society of Chemistry; 2008. p. 241-75.
34. Xuelin Z, Yan W, Tao H, Penelope MY, John W, Yiu Wa K, *et al*. Enzyme kinetic and molecular docking studies for the inhibitions of miltirone on major human cytochrome P450 isozymes. Phytomedicine 2013;20:367-74.
35. Bao P, Kodra A, Tomic-Canic M, Golinko MS, Ehrlich HP, Brem H. The role of vascular endothelial growth factor in wound healing. J Surg Res 2009;153:347-58.
36. Nissen NN, Polverini PJ, Koch AE, Volin MV, Gamelli RL, DiPietro LA. Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. Am J Pathol 1998;152:1445-52.
37. Gaudry M, Bregerie O, Andrieu V, Benna J, Pocidalo MA, Hakim J. Intracellular pool of vascular endothelial growth factor in human neutrophils. Blood 1997;90:4153-61.
38. Berse B, Brown LF, Van de Water L, Dvorak HF, Senger DR. Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. Mol Biol Cell 1992;3:211-20.
39. Shamsuddin SK, Amin Malik Shah AM, Muhammad AI, Aman Shah AM, Majed M, Rosenani SM. Designing the angiogenic inhibitor for brain tumor via disruption of VEGF and IL17A expression. Eur J Pharm Sci 2016;93:304-18.
40. Feinstein WP, Brylinski M. Calculating an optimal box size for ligand docking and virtual screening against experimental and predicted binding pockets. J Cheminform 2015;7:18.
41. Alhossary A, Handoko SD, Mu Y, Kwoh CK. Fast, accurate, and reliable molecular docking with QuickVina 2. Bioinfo 2015;31:214-6.

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