Original Article:
Molecular Docking of Curcumin With Breast Cancer Cell Line Proteins

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ABSTRACT

Background: Breast cancer is known as the most widely recognized dangerous tumors; therefore, the most common reason for mortality among all instances of harmful neoplastic illness in females. This is because the lack of specific signs and symptoms at the early stage and at the aggressive nature. Currently, breast cancer treatment such as chemotherapy, surgery and radiotherapy has not been effective.

Objectives: In this study, Three-Dimensional (3D) structures of caspase 3, mucosal addressin cell adhesion molecule 1 (MADCAM1) and nuclear factor NF-kappa-B-p105 subunit (breast cancer cell line proteins) were created; and their binding interaction between proteins and curcumin through molecular docking approach were studied.

Methods: The proteins were created using Swiss model and viewed by PyMol software. The physical and chemical characters of the proteins were analysed by Expasy's ProtParam Proteomics server. Besides that, the secondary structures of the proteins were analysed by SOPMA (Self Optimized Prediction Method from Alignment) server. After that, they were evaluated by PROCHECK, ProQ, ERRAT, and Verify3D analysis. Lastly, the breast cancer cell line proteins were docked with curcumin using BSP-Slim server.

Results: All the protein structures were good quality and within the acceptable range. The curcumin showed the binding energy with caspase 3, mucosal addressin cell adhesion molecule 1 and nuclear factor NF-kappa-B-p105 subunit at 4.140, 7.201 and 3.165 kcal/mol respectively.

Conclusion: The nuclear factor NF-kappa-B-p105 subunit had the strongest bond with curcumin. Curcumin can be potential drug for breast cancer treatment. Therefore, it can further be investigated in laboratory experiments.

Introduction

Breast cancer is a known-recognized malignant tumor, causing the highest mortality rate among cancers in women [1]. The reason is the lack of specific signs and symptoms at the early stage of this cancer and its aggressive nature. Currently, breast cancer treatments such as chemotherapy, surgery, and

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radiotherapy have not been effective. Moreover, these treatments have side effects such as liver, kidney, heart failure and mutation to healthy cells [2].

Plant compounds can be candidates for finding new anticancer agents [3-6]. Curcumin, which is an active compound from turmeric, has been accounted to have an anti-cancer and chemoprevention effect on breast cancer. According to previous studies, curcumin is a useful herb in cancer treatment. It affects cancer growth, development, and spread at the molecular level. Besides, it kills cancer cells and reduces the growth of new blood vessels in tumors (angiogenesis) and spread of cancer (metastasis). Curcumin exerts its anticancer impact through a complicated molecular signaling network, including multiplication, Estrogen Receptor (ER), and human epidermal growth factor receptor 2 (HER2) pathways [7].

Curcumin is an anti-inflammatory molecule with anticancer properties, similar to fish oil. According to previous studies, curcumin is a potential therapeutic agent in diseases such as inflammatory bowel syndrome, arthritis, and chronic anterior uveitis [8] and prevents heart disease, Alzheimer's, and cancer. It also alleviates the symptoms of depression.

Computational biology tool helps design substrate-based drug and study the interaction between the phytocompounds and cancer cell proteins. This computer-based approach reduces cost and saves energy and time.

This study aims to generate Three-Dimensional (3D) structures of proteins of breast cancer cell lines, i.e., nuclear factor NF-kappa-B-p105 subunit, caspase 3, and Mucosal Addressin Cell Adhesion Molecule 1 (MADCAM1) and then evaluate their binding affinities with curcumin through local docking.

Materials and Methods

Target sequence

The complete amino acid sequences of nuclear factor NF-kappa-B-p105 subunit, caspase 3, and MADCAM1 were obtained from the National Centre of Biotechnology Information (NCBI) [9]. The template protein PDB file and amino acid sequence in the FASTA format were downloaded from the Protein Data Bank [10].

Homology modeling of protein structure

To date, the 3D models of nuclear factor NF-kappa-B-p105 subunit, caspase 3, and MADCAM1 are not available in Protein Data Bank. Hence, the protein models were generated using the Swiss Model and visualized by the PyMol software [11].

Physiochemical characterization of the protein models

The number of disulfide bonds was calculated using the Cys_Rec program [12]. Protein structural analysis was carried out using the Expasy's ProtParam Proteomics server [13].

Secondary structure prediction of the protein structure

The secondary structure features were predicted with Self Optimized Prediction Method with Alignment (SOPMA) [14].

Validation of the protein models

The protein structures were validated with PROCHECK by Ramachandran plot analysis [15]. The protein models were further analyzed by ProQ [16], ERRAT [17], and Verify3D [18].

Identification of active sites

The protein models were submitted to active site prediction server-SCFBio to identify the binding sites of the nuclear factor NF-kappa-B-p105 subunits, caspase 3, and MADCAM1 [19].

Protein-ligand docking

The 3D protein model of nuclear kappa NF-kappa-B-p105 subunit, caspase 3, and MADCAM1 subunit were performed for molecular docking with the 3D structure of curcumin using BSP-Slim server [20]. The top-ranked conformation with the lowest binding energy was selected. The same docking simulation approach was performed with the other two protein molecules.

Results

Physiochemical characterization of the protein models

The calculated isoelectric point (pI) value for MADCAM1 and nuclear factor NF-kappa-B-p105 subunits were less than 7, which indicated the acidic characteristics while the pI for caspase 3 was more than 7. Furthermore, the molecular weight of caspase 3, MADCAM1, and nuclear factor NF-kappa-B-p105 were 31641.92,

40155.28, and 1053561.00 Da, respectively. The extinction coefficient was calculated using the extent of light being absorbed by the protein at a particular wavelength range of 27,960-60, and 740 M/cm. The total number of negatively charged residues are (ASP+GLU) is -R, where the total number of positively charged residues are (ARG+LYS) is +R. There were a total of 23 negatively charged and 27 positively charged residues for caspase 3, while 40 negatively charged and 26 positively charged residues for MADCAM1. There are 133 negatively charged and 93 positively charged residues in the amino acid sequence of nuclear factor NF-kappa-B-p105 subunit.

Based on the Expasy's ProtParam instability index, the nuclear factor NF-kappa-B-p105 subunit was stable because its value was less than 40. Caspase 3 and MADCAM1 had an instability index value of 41.13 and 63.75, respectively. Table 1 presents the aliphatic indexes of

Table 1. Physiochemical characters of the NF-kappa-B-p105 subunit, caspase 3, and MADCAM1 were determined using Expasy's Prot-Param program

Protein	Length	Molecular Weight	pI	-R	+R	Extinction Coefficient	Instability Index	Aliphatic Index	GRAVY
Caspase 3	197	31641.92	8.72	23	27	27.960	41.13	93.10	-0.322
Mucosal addressin cell adhesion molecule 1	382	40155.28	5.00	40	26	31.970	63.75	84.27	-0.250
Nuclear factor NF-kappa-B-p105 subunit	968	1053561.00	5.20	133	93	60.740	38.15	84.74	-0.339

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Table 2. Presence of disulfide (S-S bond) predicted by Cys_Rec server

Protein	Cys_Rec	Score
Caspase 3	Cys_47	-67.8
	Cys_116	-60.0
	Cys_148	-66.7
	Cys_163	-68.7
	Cys_170	-44.6
	Cys_184	-57.9
	Cys_220	-58.3
	Cys_264	-59.4
Mucosal addressin cell adhesion molecule 1	Cys_47	56.0
	Cys_51	61.7
	Cys_94	50.9
	Cys_98	46.7
	Cys_134	24.7
	Cys_204	42.1
	Cys_345	-21.6
Nuclear factor NF-kappa-B-p105 subunit	Cys_61	-44.9
	Cys_87	-60.8
	Cys_118	34.5
	Cys_123	48.4
	Cys_161	-60.1
	Cys_261	-32.9
	Cys_272	-35.6
	Cys_446	-0.3
	Cys_666	-38.2
	Cys_703	-37.8
	Cys_925	-24.1

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Table 3. Secondary structures of the nuclear factor NF-kappa-B-p105 subunits, caspase 3, and mucosal addressin cell adhesion molecule 1

Secondary Structure	Alpha Helix (Hh)	Extended Strand (Ee)	Beta Tturn (Tt)	Random Coil (Cc)
Caspase 3	52.79	14.72	8.63	23.86
Mucosal addressin cell adhesion molecule 1	28.27	14.40	6.28	51.05
Nuclear factor NF-kappa-B-p105 subunit	32.54	18.39	11.47	37.60

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Table 4. Composition of α helix in the nuclear factor NF-kappa-B-p105 subunit, caspase 3, and mucosal addressin cell adhesion molecule 1

Amino Acid	Longest α Helix	Residues	Shortest α Helix	Residues
Caspase 3	α9	20	α8	1
Mucosal addressin cell adhesion molecule 1	α1	17	α2, α3	1
Nuclear factor NF-kappa-B-p105 subunit	α20	26	α11,α3, α4,α6 ,α8,α9,α13, α14,α16,α19,α27,α29,α32, α44,α50	1

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Table 5. Validation of nuclear factor NF-kappa-B-p105 subunits, caspase 3, and mucosal addressin cell adhesion molecule 1 using PROCHECK and ProQ

Structure	Ramachandran Plot Statistics (%)				Goodness Factor			ProQ	
	Most Favored	Additional Allowed	Generously Allowed	Disallowed	Dihedral Angles	Covalent Forces	Overall Averages	LG Score	MaxSub
Caspase 3	81.5	16.0	2.5	0.0	-0.03	-0.25	-0.10	3.218	0.617
Mucosal addressin cell adhesion molecule 1	82.2	10.7	5.3	1.8	-0.68	-0.39	-0.53	4.212	0.348
Nuclear factor NF-kappa-B-p105 subunits	78.6	17.3	2.6	1.5	-0.46	-0.09	-0.30	5.977	0.404

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all the mutant proteins. The very low grand average of hydropathicity (GRAVY) index (a negative value GRAVY) of all proteins demonstrated their hydrophilic nature. The thermostability of a molecule increases in the presence of arginine in the protein structure by giving more electrostatic interactions through their guanidine group. Therefore, all proteins have the same stability. Furthermore, the Cys_Rec analysis demonstrated that the number of disulfide bonds was 11 in nuclear factor NF-kappa-B-p105 subunit contrasted with just 8 in caspase 3 and 7 in MADCAM1 (Table 2).

Secondary structure prediction of the protein structures

SOPMA view shows the presence of an alpha helix dominated among secondary structure elements followed by random coils, extended strand, and beta turns at various positions in all protein models (Table 3). Helix structure enhances the stability of the protein structure. The result from this analysis indicates that nuclear factor NF-kappa-B-p105 subunits, caspase 3, and MADCAM1 consist of 15, 18, and 19 α helices, respectively. Table 4 presents the shortest and longest α helix of the proteins.

Validation of the protein models

The 3D protein models were evaluated by Ramachandran plot calculations using PROCHECK software for stereochemical quality and geometry of protein. PROCHECK analysis shows that the quality of the MADCAM1 was excellent. The PROCHECK study confirmed that the residues of all the protein structures are

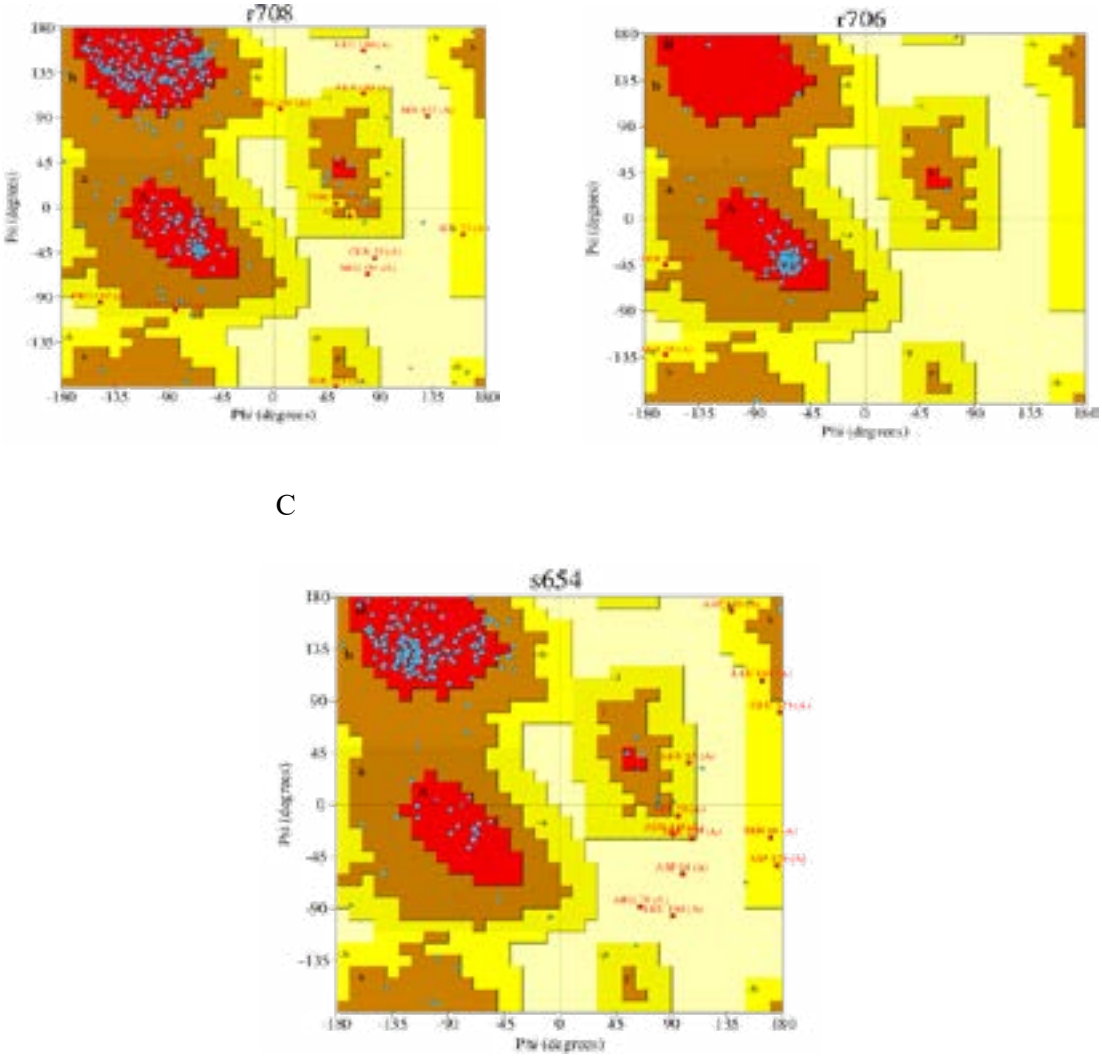


Figure 1. Ramachandran plots

A. Nuclear factor NF-kappa-B-p105 subunit; B. Caspase 3; C. Mucosal addressin cell adhesion molecule 1 generated through PROCHECK shows the residues in most favored (red), additionally allowed (yellow), generously allowed (pale yellow), and disallowed regions (white).

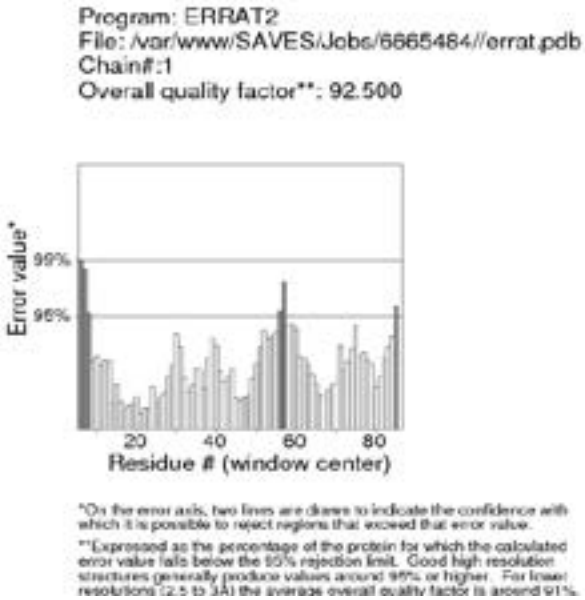
in the most favorable area which was more than 80% (Table 5 and Figure 1).

ProQ was used to evaluate the quality of protein models using the Levitt-Gerstein (LG) score and maximum subarray (MaxSub). The results demonstrated the anticipated LG score (>1.5: good model) and predicted the MaxSub score (>0.1 good model) for all protein structures. The protein models were in the acceptable range to generate a good structure.

ERRAT analysis depends on the quality factor for nonbonded atomic interactions in the 3D protein structures. The higher scores suggest the better quality of the protein model. For a good model, the acceptable range is more than 50%. In this study, the ERRAT score for caspase 3 was the highest (92.5%) (Figure 2). Furthermore, this confirmed that the caspase 3 structure has a good high resolution and quality contrasted with other protein models. The score for MADCAM1 was 86.928% while it was 80.137% for nuclear factor NF-kappa-B-p105 subunit which was the lowest score.

Verify 3D server showed 96.81%, 96.63%, and 95.69 % of the residues in the nuclear factor NF-kappa-B-p105 subunit, caspase 3, and MADCAM1, respectively. They had an average 3D-1D score of more than 0.2, showing that all protein structures had good quality (Figure 3). Thus, docking analysis with ligand will proceed.

A



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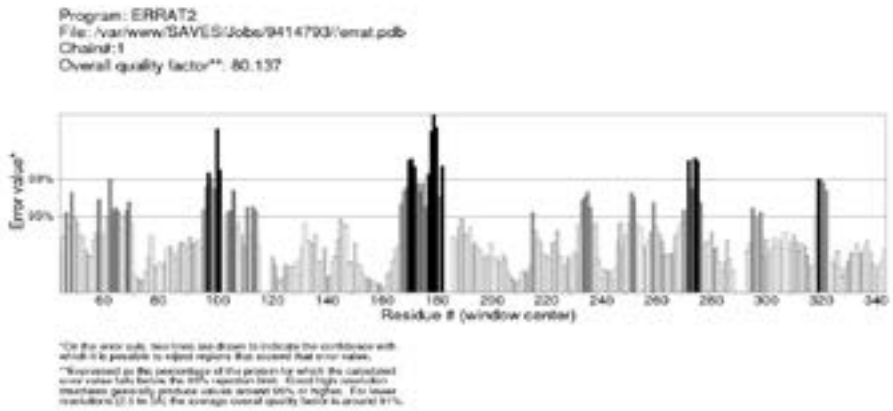

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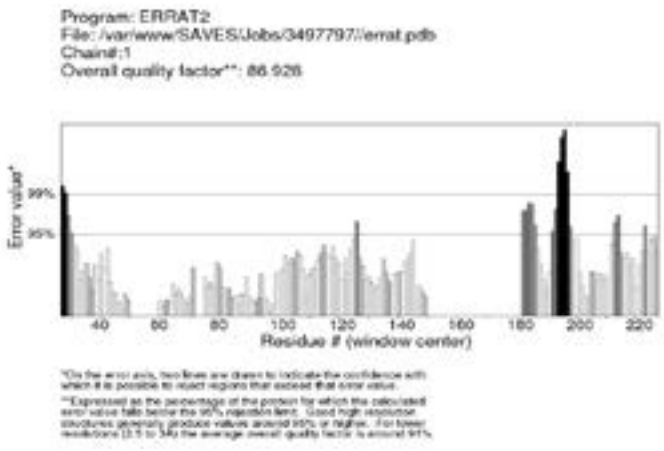
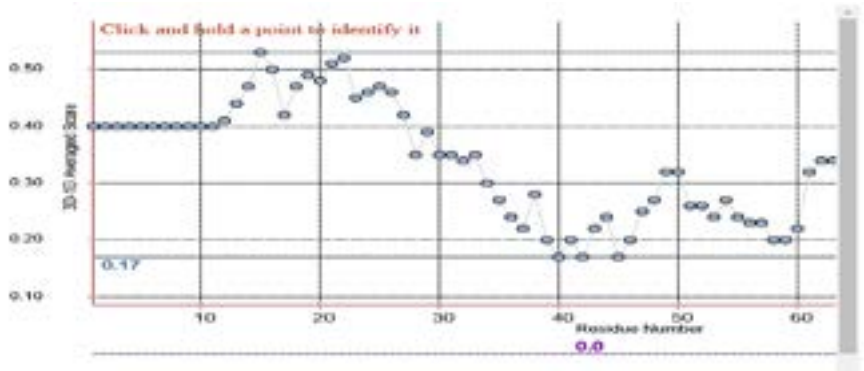


Figure 2. ERRAT plots

A. Caspase 3; B. Nuclear factor NF-kappa-B-p105 subunit; C. Mucosal addressin cell adhesion molecule 1 proteins

A



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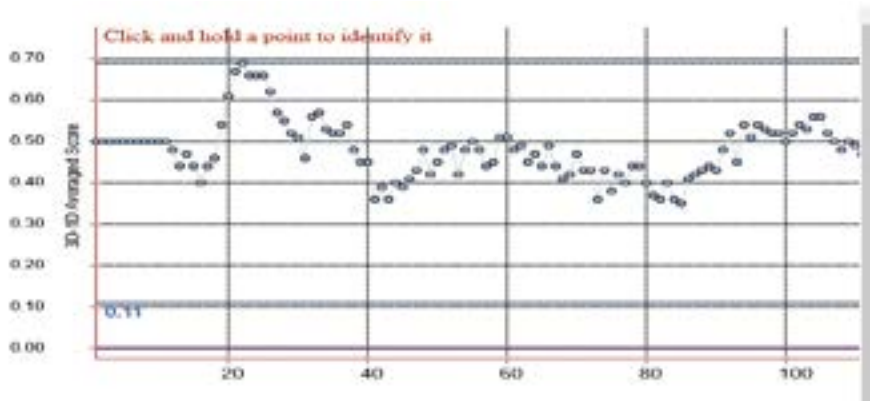

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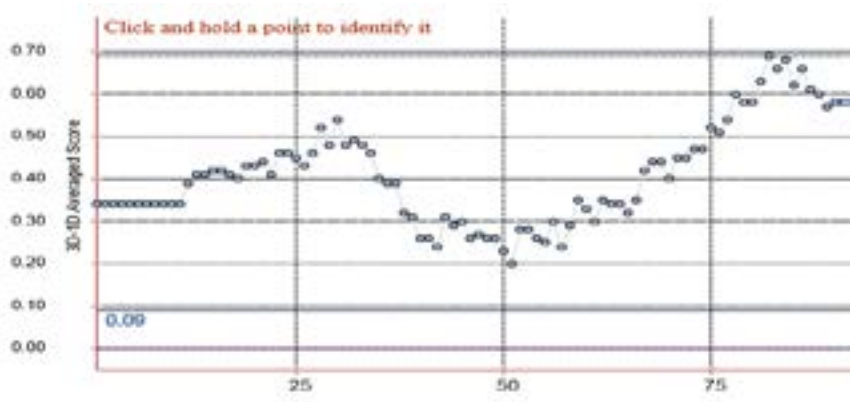

Figure 3. Verify 3D plots

A. Caspase 3; B. Mucosal addressin cell adhesion molecule 1; and C. Nuclear factor NF-kappa-B-p105 subunit proteins

Table 6. Active site predictions of the nuclear factor NF-kappa-B-p105 subunits, caspase 3, and mucosal addressin cell adhesion molecule 1 proteins

Protein	Volume (A^3)	Residues That Forming the Pocket
Caspase 3	740	LYS10,LEU11,PHE12,JLE13,HIE14,SER15,MET16,ASP2,LEU24,LEU25, LYS3,VAL33,LEU34,ASN35,GLU38,VAL4,LYS41, VAL42,ASN46,LEU5,MET50,ASP51,ARG54,ALA55,ILE57,ASP58,SER59,LYS6,VAL60,ILE61,PRO62,LYS63,GLY64,ALA6 5,GLN66,ALA67,CYS68,GLN69,GLU7,TLE70,CYS71,ILE72,ILE75,LYS8,LEU88,ARG9
Mucosal addressin cell adhesion molecule 1	938	LYS116,THR118,PRO119,VAL12,VAL120,ASP121,PRO122,ASN123,ALA124,LEU125,PHE127,PRO144,GLU145,VAL14 6,GLN147,GLU148,GLU149,GLU150,GLU157,ASP158,VAL159,ALA16,LEU160,PHE161,VAL163,LEU17,GLU18,ARG1 87,LEU188,PRO189,LEU41,THR43,LEU45,SER63,LEU64,SER65,ALA66,ALA67,GLY68,THR69,ARG70,GLN86,LEU87,L EU88,VAL89,TYR90,PHE92,PRO93,ASP94.
Nuclear factor NF-kappa-B-p105 subunits	1311	ALA116,ARG117,THR119,GLU120,ALA121,CYS122,ILE123,ARG124,GLY125,TYR126,ASN127,PRO128,GLY129,LEU1 30,VAL132,ALA137,TYR138,LEU139,GLN140,ALA141,GLU142,GLY143,GLY144,GLY145,ASP146,ARG147,MET176,T HR178,PHE188,THR189,ARG190,ARG191,LEU192,GLU193,PRO194,VAL195,PRO53,ALA54,LYS55,ILE57,GLN59,LEU 60,VAL61,LEU69,HIE70,HIE78,GLU80,ASP81,ILE83,CYS84,THR85,THR87.

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Table 7. The binding energy of the caspase 3, mucosal addressin cell adhesion molecule 1, and nuclear factor NF-kappa-B-p105 subunit proteins

Protein	Binding Energy (kcal/mol)
Caspase 3	4.140
Mucosal addressin cell adhesion molecule 1	7.201
Nuclear factor NF-kappa-B-p105 subunits	3.165

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Identification of active sites

The size, protein volume, and the residues of active sites in caspase 3, MADCAM1, and nuclear factor NF-kappa-B-p105 subunit were obtained using active site prediction server (Table 6).

Molecular docking

In this study, nuclear factor NF-kappa-B-p105 subunit, caspase 3, and MADCAM1 were successfully docked with curcumin using the BSP-slim server. The best docking orientation was chosen based on the lowest energy value (DG_{bind}) and negative. Docking analysis showed a strong bond between nuclear factor NF-kappa-B-p105 subunit and ligand because it had the lowest energy value (3.165) compared with the other protein models (Table 7).

Discussion

According to Sohilait et al. study (2017), three analogues of curcumin, i.e., 1-(1,3-benzodioxol-5-yl)-5-(4-hydroxy-3-methoxyphenyl) penta-1, 4-dien-3-one, 1-(3,4 dimethoxyphenyl)-5-(4-nitrophenyl) penta-1, 4-dien-3-one, and 1-(4-hydroxy-3- methoxyphenyl)-5-(4-methoxyphenyl) penta-1, 4-dien-3-one could successfully dock into COX-2 active site. Their binding energies were -8.2, -7.6, and -7.5 kcal/mol, respectively. Curcumin analogues were analysed for COX-2 inhibitory as anti-inflammatory activities [21].

Also, proanthocyanidin (PAC) exhibited better binding affinity with BCL-XL and CDK2 proteins. Their binding energies were -5.23 and -5.17 kcal/mol. This study shows that the proanthocyanidin compound has anticancer activity. Therefore, the PAC compound could be a potential drug for colon cancer treatment [22].

Based on Pusphalatha et al. study (2017), the binding score results of curcumin with breast cancer proteins (HER2, estrogen receptor, ERBB2, tyrosine kinase, and HSP90) were -12.1, -9.92, -8.30, -8.22, and -8.05 kcal/mol, respectively. The highest docking score of curcumin with HER2 was -12.1 kcal/mol. The more negative docking score indicates stronger binding between the plant compound and breast cancer protein. This study

revealed that curcumin had a strong bond with HER2 protein [23].

According to Iheamgham et al. study (2019) [24], seven phytochemical compounds (7-hydroxy-4′-methoxy-3,11-dehydrohomoisoflavanone, 4,4′-dihydroxy-2'-methoxy-chalcone, 7,4′-dihydroxy-3,11-dehydrohomoisoflavanone, luteolin, quercetin-3-methyl, kaempferol-3-O-β-d-xylopyranoside, and kaempferol-3-O-α-l-rhamnopyranosyl-(1 → 2)-β-D-xylopyranoside) from young twigs and leaves of C bonduc had the strong interactions with cancer target proteins such as Tyrosine Kinase (TK), Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMP). These phytocompounds can be designed as putative lead compounds for developing new anti-cancer drugs.

Based on Mishra et al. study (2019) [25], Flavonoid Compound (FRC-1) of the plant (*Launaea procumbens*) acts as a potential anticancer agent for the target protein, tyrosine-protein kinase, Fyn. Molecular docking results showed that the binding between the phytocompound and target protein was strong. FRC-1 has high possibilities of being an anticancer drug.

In this study, the nuclear factor NF-kappa-B-p105 subunit strongly interacted with the curcumin due to its lowest energy value (3.165) compared with the other protein models.

Conclusion

Nuclear factor NF-kappa-B-p105 subunits, caspase 3, and MADCAM1 were docked successfully with the curcumin. Curcumin can be a potential medication for breast cancer. Further studies of this research can be conducted through lab work.

Ethical Considerations

Compliance with ethical guidelines

There was no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, methodology, supervision, and funding acquisition: Asita Elengoe; Investigation, writing-review & editing, resources, and writing-original draft: Asita Elengoe and Nishalini Devi Sundramoorthy.

Conflict of interest

The authors declared no conflict of interest.

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