Original Article

Evaluation Of Curcumin Effects On Bad, Bak, And Bim: A Molecular Dynamics Simulation Study

Fateme D. Asl[1], Dhiya Altememy[2], Pegah Khosravian[3], Mehdi Rezaee[4], Javad Saffari-Chaleshtori[5]*

[1]Department of Medical Biotechnology, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran

[2]Department of Pharmaceutics, College of Pharmacy, Al-Zahraa University for Women, Karbala, Iraq

3Medical plants Research Centre, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran.

[4]Department of Medical Biotechnology, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran

[5]Clinical Biochemistry Research Centre, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran.

ABSTRACT

Curcumin (Cur) is a polyphenol compound with antioxidant and apoptotic effects. It can lead cells to death which is the ultimate goal in cancer research.

The effect of Cur on three pro-apoptotic factors of Bad, Bak, and Bim was investigated in this molecular dynamic and molecular docking simulation study. The PDB files of these three factors and the 3-D structure of Cur were obtained from www.rcsb.org and PubChem, respectively. All files were converted to PDB files by Avogadro v.1.2 software. The water and ion environment in GROMACS 2018 simulation package was used to conduct molecular dynamic simulation studies. Furthermore, AutoDock v.4.2.6 software performed the docking of Cur as a ligand and the proteins as receptors. LigPlot+ v.4.5.3 was used to determine the hydrogen and hydrophobic bonds at the binding sites.

Results showed that Cur could bind to Bad with -6.58 kcal/mol binding energy. In addition, the binding of Cur to proteins induced some changes in molecular dynamic factors such as radius of gyration (Rg), root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), binding energy (BE), estimated inhibition constant (EIC), and their secondary structures. A significant increase in Rg and RMSD and some variations in RMSF were seen in Bad and Bak after docking with Cur. Considering this study, Cur could bind to the proteins directly, induce conformational changes, and increase their likelihood of dimerization, leading to activating apoptotic pathways. These results suggested the apoptotic effects of Cur on cancer cells through influencing these proteins for the first time.

Keywords: Bad, Bak, Bim, Curcumin, Molecular dynamics

Introduction

Curcumin is an organic compound and a natural polyphenol product derived from the plant *Curcuma longa*. It has been used for medical purposes and dyes in foods for centuries.[1] This compound shows its anticancer effects by activating apoptotic pathways in cancer cells and inhibiting pre-cancerous processes, including inflammation, angiogenesis and metastasis.[2]

Annually, millions of deaths worldwide happen due to cancer. Despite outstanding progress that has been achieved in medicine, there are so many challenges that need to be dealt with to improve cancer therapy.[3,4] For instance, considering

Access this article online

Quick Response Code:

Website: www.pnrjournal.com

DOI: 10.47750/pnr.2022.13.03.002

Address for correspondence: Javad Saffari-Chaleshtori, *Clinical Biochemistry Research Centre, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran*

E-mail address: *j_saffari@yahoo.com*

Received: 06 June, 2022 **Accepted:** 10 July, 2022

Published: 23 August, 2022

How to cite this article: Asl FD, Altememy D, Khosravian P, Rezaee M, Saffari-Chaleshtori J. Evaluation Of Curcumin Effects On Bad, Bak, And Bim: A Molecular Dynamics Simulation Study. J Pharm Negative Results 2022;13(3): 8-14

long-term survival with specific regimens, upgrading regulatory endpoints for cancer immunotherapy, and constructive immunotherapy combinations in Early-Phase of cancer are some of these challenges.[5]

Phytochemicals (including Cur) modulate the signalling pathways that lead to cell cycle regulation or directly alter cell cycle-regulating molecules in cancer treatment.[6,7] Most human malignancies are caused by chromosomal mutations or other genetic alterations that directly affect the function of vital cell cycle proteins and tumour suppressors such as cyclins and p53, respectively.[8] In this regard, cell cycle regulation and modulation by Cur have attracted widespread attention in recent years. Extensive research has focused on the potential of chemotherapy for this compound.[9-11]

In some cancers, apoptosis induced by Cur can occur in two p53-dependent and independent pathways.[12,13] Induced apoptosis is time and dose-dependent and is regulated by various signalling factors.[14] In a p53-dependent way, Cur inhibits the expression of BCL2, which is an anti-apoptotic factor and increases levels of apoptotic factors such as Bax, Bad, Bim, and Bik in cancer cells. Whether or not a cell commits to cell death depends on the balance of expression of proteins that mediate cell death (such as Bax) and proteins that increase cell survival (such as BCL2).[15]

In this study, using different molecular dynamics and molecular docking software, we evaluated the changes in energy and structures of pro-apoptotic proteins in the presence and absence of Cur and compared these structures to each other. The results suggested the apoptotic effects of Cur on cancer cells through influencing Bad, Bak, and Bim for the first time.

Materials and Method

The PDB file of the pro-apoptotic proteins Bad (PDB ID:1G5J), Bak (PDB ID: 2YV6), and Bim (PDB ID: 4B4S) were prepared from the protein database at www.rcsb.org. Molecular information and structure of Cur from PubChem were received and converted to PDB files using Avogadro v.1.2 software. The proteins were simulated in an aqueous solvent using GROMACS 2018 simulation package. The study was performed in water and salt; Na^+ and Cl^- ions were added instead of the solvent to reach the concentration of 140 mM. The simulation time for each of the studied molecules was 30 nanoseconds. The simulation was performed using the relevant commands. The output (PDB files) was used as the docking input structures.[16]

Molecular docking was performed using Autodock v.4.2.6 software in the Linux operating system. Cur molecule was docked on Bad, Bak, and Bim pro-apoptotic proteins to find the best ligand-receptor binding sites and determine its most stable free energy state.[17]

In this study, PDBQ and PDBQT files for Cur were generated, and Cur was defined as a ligand. Also, the pro-apoptotic proteins were developed and defined these proteins as receptors. Molecular docking steps were then performed for each protein 200 times independently. LigPlot+ v.4.5.3 software was used to determine the number of hydrogen and hydrophobic interactions between the pro-apoptotic proteins with the Cur molecule and the type and the number of amino acids involved at the binding site. Grapher v.19.1.288 software was used for designing the graphs in blue (before docking) and red (after docking).[17,18]

Results

Various MD factors were measured to compare Cur alone to Cur bound to apoptotic proteins. For instance, table 1 demonstrates binding energy (BE), estimated inhibition constant (EIC), and hydrogen and hydrophobic interactions between Cur and the proteins.

Based on energy, the ranking in Table 1, docking methods resulted in the assessment of the possible loci of Cur for binding pro-apoptotic proteins and showed the amino acids that take part in hydrogen and hydrophobic interactions. The lowest BE belonged to Cur-Bad, while the highest BE was to Cur-Bim. As shown in table 1, EIC amounts were 15.02 μM, 8.34 μM and 54.21 μM for Bad, Bak and Bim, respectively.

BE; Estimated Free Energy of binding (kcal/mol), EIC; estimated inhibition constant (μM).

Through LigPlot+ software, we estimated the sites, amino acids, several hydrogens, and hydrophobic interactions (Figure 1). Cur made hydrogen bonds with Bad (through Arg136, Phe135, Val139, Asn132, Val131, Glu128, Leu182, and His 181), Bak (through Pro99, Asn103, Gln98, Gln95, Leu97, Leu94, Tyr107, and Thr92) and Bim (Leu83, Ala15, Gly79, Tyr24, Tyr80, Asp19, and Lys81). Figure 1 also demonstrates the two-dimensional (2-D) structures of Cur-Bad, Cur-Bak, and Cur-Bim and their molecular interactions.

Figures 2, 3 and 4 demonstrate root-mean-square deviation (RMSD), the radius of gyration (Rg) and root-mean-square fluctuation (RMSF), respectively. The simulation of free Bad, Bak and Bim before docking was shown in blue. Also,

Table 1. Various molecular dynamic factors were evaluated via GROMACS and LigPlot software.

	EIC	*BE*	*Hydrogen Bonds*	*Hydrophobic interactions*
Bad	15.02 μM	-6.58 kcal/mol	Asp137, Gly138, Tyr177	Arg136, Phe135, Val139, Asn132, Val131, Glu128, Leu182, His 181
Bak	18.34 μM	-6.46 kcal/mol	Thr100, His96, Lys110	Pro99, Asn103, Gln98, Gln95, Leu97, Leu94, Tyr107,Thr92
Bim	54.21 μM	-5.82 kcal/mol	Lys18, Asp82	Leu83, Ala15, Gly79, Tyr24, Tyr80, Asp19, Lys81

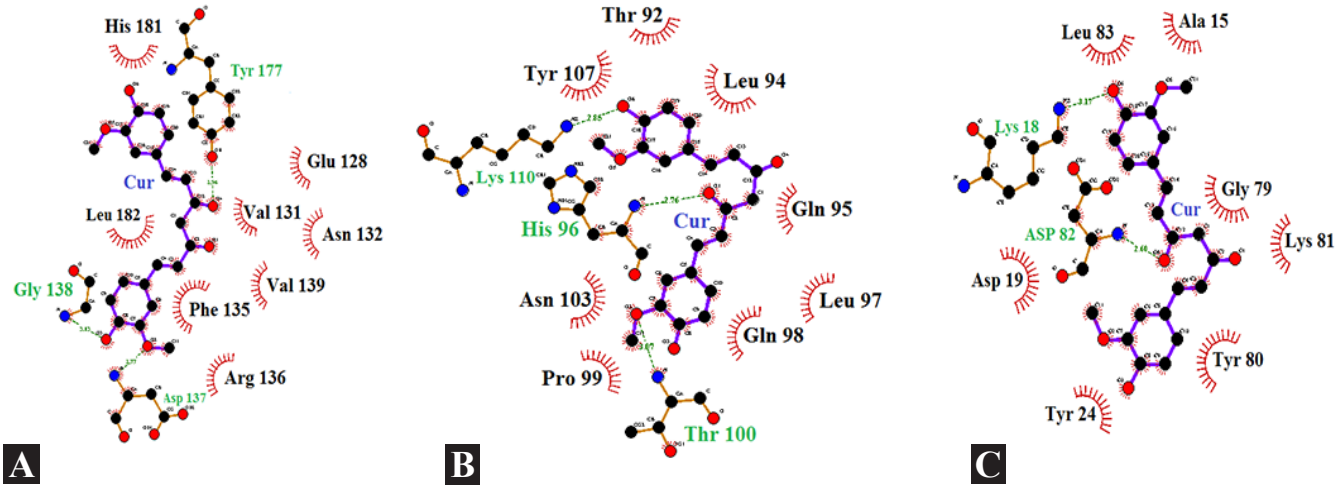

Fig. 1: 2-D figures of A) Cur-Bad, B) Cur-Bak, and C) Cur-Bim.

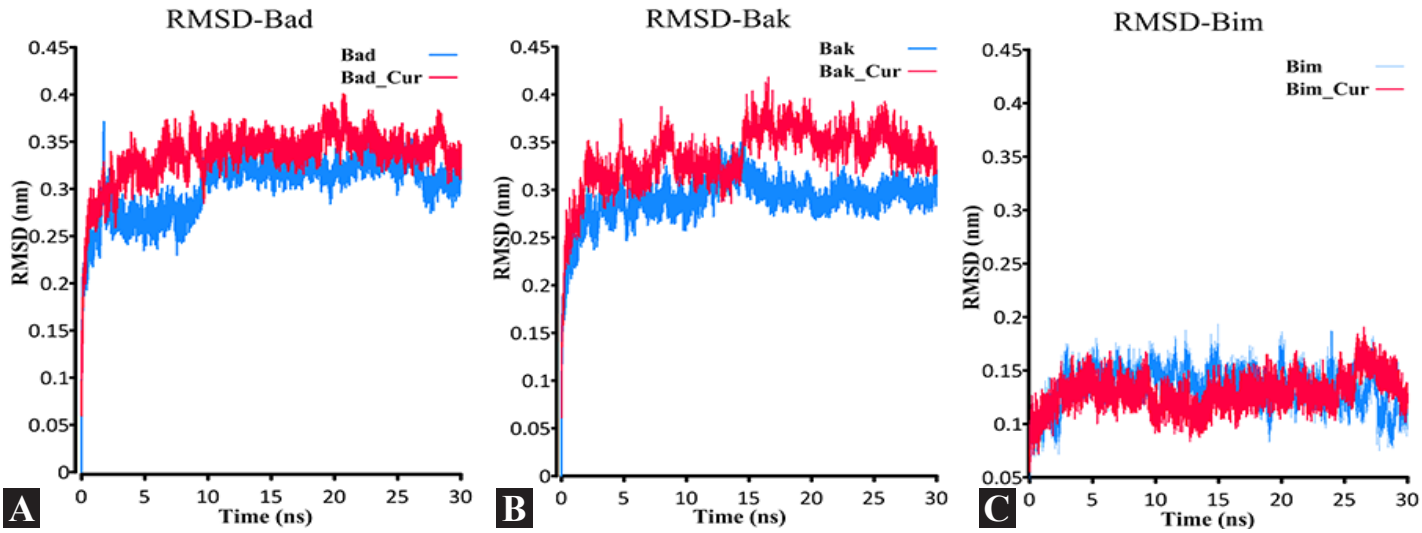

Figure 2. Root mean square deviation (RMSD); The blue lines show the RMSD of Bad, Bak and Bim before docking, and the red lines show the RMSD of Bad, Bak and Bim after docking with Cur.

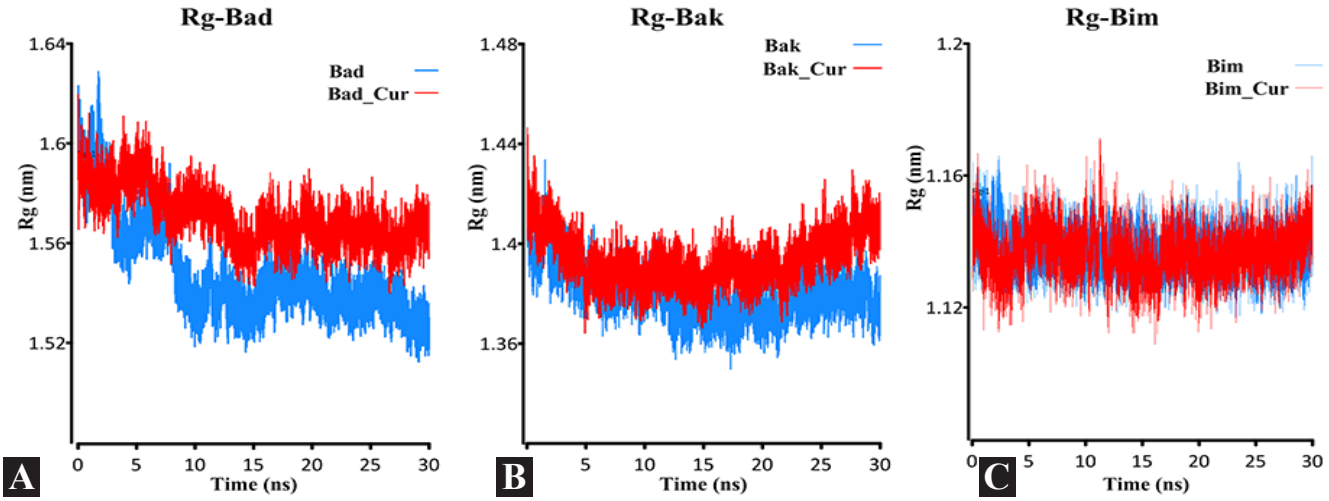

Fig. 3: The radius of gyration (Rg); The blue lines show the Rg of Bad, Bak and Bim before docking, and the red lines show the Rg of Bad, Bak and Bim after docking with Cur.

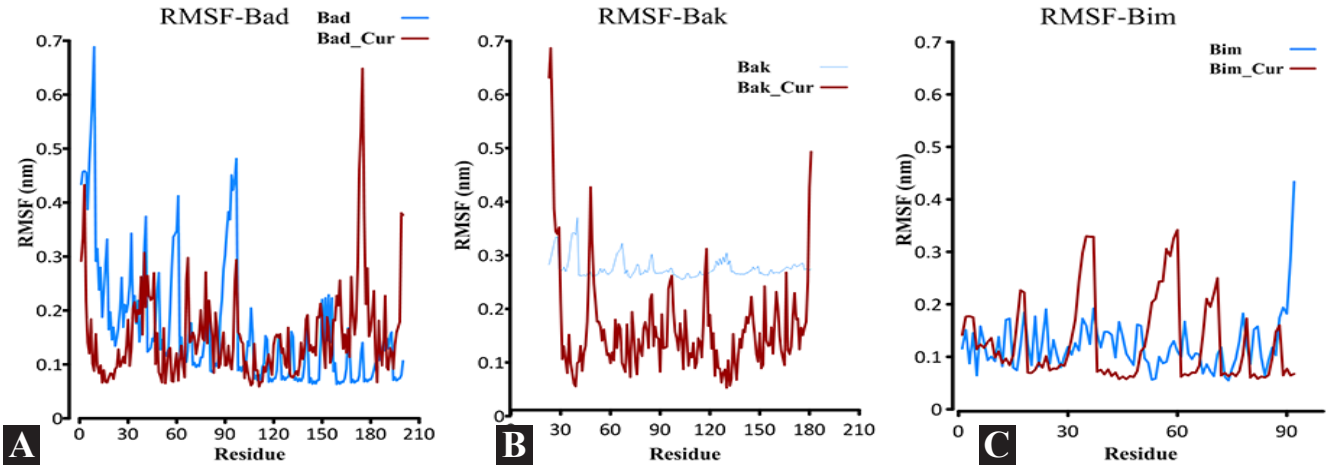

Fig. 4: Root mean square fluctuation (RMSF); The blue lines show the RMSF of Bad, Bak and Bim before docking, and the red lines show the RMSF of Bad, Bak and Bim after docking with Cur.

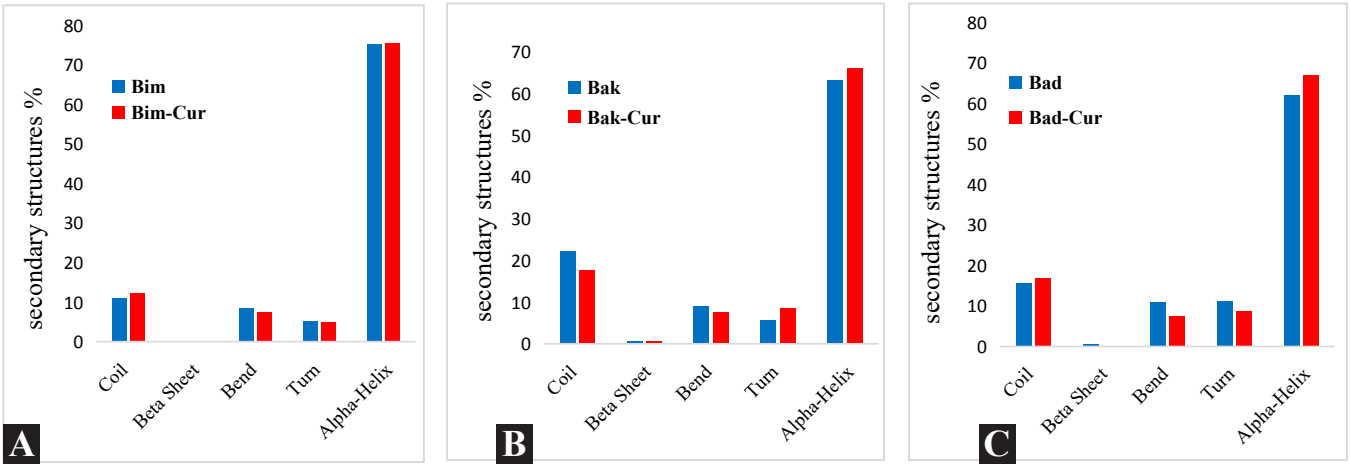

Fig. 5: Changes in the percentage of secondary structures of (A) Bad, (B) Bak and (C) Bim before and after the presence of Cur.

in the presence of Cur, all of these proteins after docking were shown in red.

The total amount of RMSD in Bad and Bak enhanced in the presence of Cur while Bim was stable, and no significant variation was seen. RMSD in figure 2 shows a total enhancement of this factor in Bad and Bak after docking. In fact, in the presence of Cur, we can see changes in RMSD, which prove possible variations in the structure of apoptotic proteins. RMSD in Bad and Bak was quite unstable and changed until 10 and 15 ns, respectively, while it became steady afterwards (Figure 2). In Bim protein, no dramatic changes were seen in RMSD amounts (Figure 2). It is important to note that the higher the changes in RMSD, the more different the structure and backbone of molecules.

In the presence of Cur, the total amount of Rg in Bad and Bak increased while Rg of Bim did not change noticeably. Around 14 ns, Rg of Bad was quite unstable while it became stable afterwards. On the other hand, Bak-Cur decreased to around 5 ns and hit stability. Again, Bim seemed to be steady during the simulation and no important variations were seen before and after docking (Figure 3).

Considering RMSF results in figure 4, fluctuations in all three proteins have changed. In both Bad and Bim increase in fluctuation can be seen comparing before and after docking. In contrast, Bak did not show significant enhancement in its RMSF amounts. In fact, RMSF in Bak-Cur decreased.

The following graphs demonstrate the variations in the percentage of different structures in each molecule. In the simulation of Bad, the greatest changes in structures belonged to alpha-helixes with around a 3% increase, while in Bak and Bim, the dramatic change was related to coils. In Bak, coils decreased by almost 4% after docking, in contrast with Bim, which had about 2% of enhancement in its coils. Coils and alpha-helixes increased while bends, beta-sheets and turns decreased. However, Bak showed a reduction in coils and bent instead of turns and alpha-helixes, which went up. Bad did not contain any beta-sheets. There were no changes in Bim secondary structures (Figure 5).

Discussion

This study confirms that Cur tends to bind Bad, Bak and Bim and has considerable impacts on the following molecular dynamic factors.

It is important to know that RMSD is the standard structural measure between coordinates. This factor measures the distance between a group of atoms like the backbone of a molecule. This factor can show the number of changes in protein structure [19]. RMSF measures the average deviation of each atom over time from the reference position. Thus, the RMSF analyzes parts of the structure that fluctuate most (or least) from their average structure [20]. Rg is used to measure the compaction of a structure and enables us to compare the difference before and after docking [21].

RMSD factor measures the variation of proteins backbones from the primary normal form to its final conformation after docking. The deviation produced during the simulation can help us determine the stability of the studied proteins. The higher the deviations, the more unstable the structures [22]. In this study, it is understood from the RMSD results that some changes were made in the backbone of molecules after docking. Considering the results in figure 2, the fluctuation of RMSD in Bad and Bak changed their structures after docking, but it became stable after 10 and 15 ns, respectively.

Interestingly, in Khezri *et al.*'s study, the RMSD of Cur docked with chitosan (Cur-chitosan nanoparticles) hit a plateau immediately after 4 ns, and afterwards, Cur was released after 20 ns. However, in this study, Cur stayed bound to Bad, Bak and Bim till the last ns of simulation [23]. It is known that Rel A (p65) plays an enhancing role in apoptosis by suppressing NF-kB. In Chen *et al.*'s study, the RMSD of Cur-Rel A increased dramatically in the first 5 ns.[24] In contrast, in this study, figure 2 presented a great rise in RMSD of Bad-Cur after 10 ns.

Analyzing the results of BE, Cur seemed to have a great tendency to bind Bad, Bak and Bim proteins. BE shows the amount of energy that is released when two molecules bind. The lower the BE of molecules, the higher their tendency to bind.[25] It is interesting to mention that comparing BE of Cur on the Bad (-6.58 kcal/mol) to BE of luteolin on BCL-2 (-6.59 kcal/mol) shows that these two materials (Cur and luteolin) can have the exact opposite effects on apoptosis [26]. It is known that Bad induces apoptosis while BCL-2 blocks it. The same amounts of BE in these chemicals can present those Bad causes of apoptosis as much as BCL-2 inhibits it [27]. It is noteworthy to consider that high binding affinity does not confirm the activation or suppression of the proteins. Still, it is simply a factor that predicts the attachment tendency of two materials.[25]

The inhibition constant demonstrates how potent an inhibitor is. This shows the concentration in which half of the maximum inhibition occurs [18]. However, in the simulation studies, the same factor is used to show the potential of a substance to activate or induce changes in proteins. The results of EIC confirmed BE amounts and the higher tendency of Bad compared to the other proteins. The IC_{50} of Cur on various cancer cell lines has been studied; for example, in MCF-7 and BT-20, the IC_{50} of Cur were 1.32 μM and 16.23 μM, respectively. At the same time, the lowest amount of EIC in this study was around 15 μM which belonged to Bad.[28]

Considering table 1, the number of amino acids contributing to the hydrogen and hydrophobic interactions, Bad and Bak seem to make stronger and more stable interactions with Cur than Bim. It is important to the amino acids that make the interactions. If a mutation changes these amino acids, Cur will not be effective on these proteins. Since Cur has antioxidant properties, it may increase cell proliferation which is not in the best interest of cancerous cases and can worsen cancer at certain concentrations.[29] Also, in Zhang *et al.*'s study, Cur levelled up the number of hydrogen bonds through hydrophilic carbonyl, hydroxyl and methoxy groups after docking with myosin.[30] Notably, the higher number of amino acids in contribution with Cur can be the reason for higher affinity and BE of Bad and Bak than Bim BE.

The compactness and the size of the proteins can be interpreted via Rg.[21] This factor is also known as the atom distribution of a protein around its axis.[32] An increase in the amount of Rg results in the reduction of molecular compactness. For example, in Farhadian et al.'s study, Curcumin was docked with αChymotrypsin and rose its Rg from 1.6402 nm to 1.6531 nm.[33] So it seems that in both Bad and Bak, the molecules became looser while Bim did not come with a dramatic change. Although Bad and Bak seemed to change after docking, Bad fluctuated much more than Bim in the first 14ns. Fluctuation in Rg represents an important structural transition [34]. It is important to know that an increase in Rg can enhance the likelihood of Cur accessing the active site of the molecules. Therefore, the activity of Bad and Bak will probably increase after binding to Cur compared to Bim, which did not show a dramatic change in Rg.

RMSF measures the displacement and fluctuations of residues and compares them to their initial structures, and also it is used to find the flexible region of a protein or complex.[22,35] Considering RMSF results, the changes in the structures of pro-apoptotic proteins were seen in various residues after docking. In Bad-Cur, the biggest variation was observed in residue 173, while in Bak-Cur, residues 20 and 48 were more different than their version before docking. The changes in Bim-Cur happened in residues 36, around 60 and 70. In the presence of Cur, it seems that Bim had higher flexibility compared to the other Bad and Bak.

Different secondary structures, such as coils, turns, bends, alpha-helices and beta-sheets, were observed in figure 5. Enhancing the secondary structures of proteins can increase the binding site regions for attaching downstream factors and inducing apoptosis.

In the apoptosis process, Bax and Bak's oligomerization leads to the release of cytochrome C, activation of initial and secondary caspases and finally, cell death.[36]

Hence, the changes in Bak structure can be a sign of its oligomerization. Certain alpha-helixes are exposed during active Bak and Bax activation to facilitate dimerization.[37] Therefore, an increase in the percentage of alpha-helix can be a sign of enhancing apoptosis. In contrast, although Bim plays the key role in apoptosis in some cases.[38] in this study, we did not find dramatic changes in any of the molecular dynamic factors, including the secondary structure. In apoptosis, Bad gets dephosphorylated and helps Bax and Bak in their oligomerization.[39] This work has not studied the phosphorylation process, but changes in secondary structures, specifically the alpha-helix, can be seen. In a nutshell, via the MD simulation, it is predicted that Cur is highly susceptible to binding Bad, Bak and Bim. This study showed for the first time that Cur changes the structure of these apoptotic proteins and can directly affect cell death.

Conclusion

According to this study, Cur could bind with a high tendency to Bad, Bak and Bim directly, induce conformational changes and increase their likelihood of dimerization, which leads to activating apoptotic pathways. These results confirmed the apoptotic effects of Cur on cancer cells. This study predicts that the apoptotic properties of Cur could be due to its molecular dynamic-related effects on the mentioned pro-apoptotic proteins.

FUNDING: Self-funding

Acknowledgement

The authors are grateful to our university and institute for performing the analytical methods in this study.

REFERENCES

1. Abd El-Hack ME, El-Saadony MT, Swelum AA, Arif M, Abo Ghanima MM, Shukry M, et al. Curcumin, the active substance of turmeric: its effects on health and ways to improve its bioavailability. J Sci Food Agric [Internet]. 2021 Nov 1;101(14):5747–62. Available from: https://doi.org/10.1002/jsfa.11372
2. Song X, Zhang M, Dai E, Luo Y. Molecular targets of Curcumin in breast cancer (Review). Mol Med Rep. 2019;19(1):23–9.
3. Pucci C, Martinelli C, Ciofani G. Innovative approaches for cancer treatment: current perspectives and new challenges. Ecancermedicalscience [Internet]. 2019;13:961. Available from: https://pubmed.ncbi.nlm.nih.gov/31537986
4. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin [Internet]. 2019 Sep 1;69(5):363–85. Available from: https://doi.org/10.3322/caac.21565
5. Hegde PS, Chen DS. Top 10 Challenges in Cancer Immunotherapy. Immunity [Internet]. 2020;52(1):17–35. Available from: https://www.sciencedirect.com/science/article/pii/S1074761319305308
6. Abdelfatah S, Naß J, Knorz C, Klauck SM, Küpper J-H, Efferth T. Pyrrolizidine alkaloids cause cell cycle and DNA damage repair defects as analyzed by transcriptomics in cytochrome P450 3A4-overexpressing HepG2 clone 9 cells. Cell Biol Toxicol [Internet]. 2021; Available from: https://doi.org/10.1007/s10565-021-09599-9
7. Xiang Y, Guo Z, Zhu P, Chen J, Huang Y. Traditional Chinese medicine as a cancer treatment: Modern perspectives of ancient but advanced science. Cancer Med [Internet]. 2019 May 1;8(5):1958–75. Available from: https://doi.org/10.1002/cam4.2108
8. Wang L-H, Wu C-F, Rajasekaran N, Shin YK. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. Cell Physiol Biochem [Internet]. 2018;51(6):2647–93. Available from: https://www.karger.com/DOI/10.1159/000495956
9. National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 969516, Curcumin [Internet]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Curcumin
10. Bhatia M, Bhalerao M, Cruz-Martins N, Kumar D. Curcumin and cancer biology: Focusing regulatory effects in different signalling pathways. Phyther Res [Internet]. 2021 Sep 1;35(9):4913–29. Available from: https://doi.org/10.1002/ptr.7121
11. Zoi V, Galani V, Lianos GD, Voulgaris S, Kyritsis AP, Alexiou GA. The Role of Curcumin in Cancer Treatment. Vol. 9, Biomedicines . 2021.
12. Méndez-García LA, Martínez-Castillo M, Villegas-Sepúlveda N, Orozco L, Córdova EJ. Curcumin induces p53-independent inactivation of Nrf2 during oxidative stress–induced apoptosis. Hum Exp Toxicol [Internet]. 2019 Apr 24;38(8):951–61. Available from: https://doi.org/10.1177/0960327119845035
13. Fu H, Wang C, Yang D, Wei Z, Xu J, Hu Z, et al. Curcumin regulates proliferation, autophagy, and apoptosis in gastric cancer cells by affecting PI3K and P53 signaling. J Cell Physiol [Internet]. 2018 Jun 1;233(6):4634–42. Available from: https://doi.org/10.1002/jcp.26190
14. Choi M-S, Park H-J, Oh J-H, Lee E-H, Park S-M, Yoon S. Nonylphenol-induced apoptotic cell death in mouse TM4 Sertoli cells via the generation of reactive oxygen species and activation of the ERK signaling pathway. J Appl Toxicol [Internet]. 2014 Jun 1;34(6):628–36. Available from: https://doi.org/10.1002/jat.2886
15. .Guvenmez, O., Keskin, H., Ay, B., Birinci, S., Kanca, M.F.The comparison of the effectiveness of lincocin® and azitro® in the treatment of covid-19-associated pneumonia: A prospective study (2020) Journal of Population Therapeutics and Clinical Pharmacology, 27 (SP1), pp. 5-10.
15. Zhou QM, Sun Y, Lu YY, Zhang H, Chen QL, Su SB. Curcumin reduces mitomycin C resistance in breast cancer stem cells by regulating Bcl - 2 family - mediated apoptosis. 2017;1–13.
16. Dehkordi MF, Farhadian S, Abdolvand M, Soureshjani EH, Rahmani B, Darzi S. Deciphering the DNA-binding affinity, cytotoxicity and apoptosis induce as the anticancer mechanism of Bavachinin: An experimental and computational investigation. Journal of Molecular Liquids. 2021 Nov 1;341:117373. https://doi.org/10.1016/j.molliq.2021.117373
17. Kandagalla S, Sharath BS, Bharath BR, hani U, Manjunatha H. Molecular docking analysis of curcumin analogues against kinase

domain of ALK5. Silico Pharmacol [Internet]. 2017;5(1):15. Available from: https://doi.org/10.1007/s40203-017-0034-0

18. Iman M, Saadabadi A, Davood A. Molecular docking analysis and molecular dynamics simulation study of ameltolide analogous as a sodium channel blocker. Turkish J Chem. 2015;39(2):306–16.
19. Velázquez-Libera JL, Durán-Verdugo F, Valdés-Jiménez A, Núñez-Vivanco G, Caballero J. LigRMSD: a web server for automatic structure matching and RMSD calculations among identical and similar compounds in protein-ligand docking. Bioinformatics [Internet]. 2020 May 1;36(9):2912–4. Available from: https://doi.org/10.1093/bioinformatics/btaa018
20. Peele KA, Potla Durthi C, Srihansa T, Krupanidhi S, Ayyagari VS, Babu DJ, et al. Molecular docking and dynamic simulations for antiviral compounds against SARS-CoV-2: A computational study. Informatics Med Unlocked [Internet]. 2020;19:100345. Available from: https://www.sciencedirect.com/science/article/pii/S2352914820301805
21. Liu P, Lu J, Yu H, Ren N, Lockwood FE, Wang QJ. Lubricant shear thinning behavior correlated with variation of radius of gyration via molecular dynamics simulations. J Chem Phys [Internet]. 2017 Aug 28;147(8):84904. Available from: https://doi.org/10.1063/1.4986552
22. Ahmad, L., Semotiuk, A.J., Liu, Q.R., Rashid, W., Mazari, P., Rahim, K., Sadia, S.Anti-hypertensive plants of rural Pakistan: Current use and future potential(2018) Journal of Complementary Medicine Research, 7, p. 138.
22. Aier I, Varadwaj PK, Raj U. Structural insights into conformational stability of both wild-type and mutant EZH2 receptor. Sci Rep. 2016;6(October):1–10.
23. Khezri A, Karimi A, Yazdian F, Jokar M, Mofradnia SR, Rashedi H, et al. Molecular dynamic of curcumin/chitosan interaction using a computational molecular approach: Emphasis on biofilm reduction. Int J Biol Macromol [Internet]. 2018;114:972–8. Available from: https://www.sciencedirect.com/science/article/pii/S0141813018305518
24. Chen T, Zhou R, Chen Y, Fu W, Wei X, Ma G, et al. Curcumin ameliorates IL-1β-induced apoptosis by activating autophagy and inhibiting the NF-κB signaling pathway in rat primary articular chondrocytes. Cell Biol Int. 2021;45(5):976–88.
25. Pantsar T, Poso A. Binding affinity via docking: Fact and fiction. Molecules. 2018;23(8):1DUMMY.
26. Verma S, Singh A, Kumari A, Tyagi C, Goyal S, Jamal S, et al. Natural polyphenolic inhibitors against the anti-apoptotic BCL-2. J Recept Signal Transduct [Internet]. 2017;37(4):391–400. Available from: http://dx.doi.org/10.1080/10799893.2017.1298129
27. Tzifi F, Economopoulou C, Gourgiotis D, Ardavanis A, Papageorgiou S, Scorilas A. The role of BCL2 family of apoptosis regulator proteins in acute and chronic leukemias. Adv Hematol. 2012;2012.
28. Hu S, Xu Y, Meng L, Huang L, Sun H. Curcumin inhibits proliferation and promotes apoptosis of breast cancer cells. Exp Ther Med. 2018;16(2):1266–72.
29. Bhoopathy S, Inbakandan D, Rajendran T, Chandrasekaran K, Kasilingam R, Gopal D. Curcumin loaded chitosan nanoparticles fortify shrimp feed pellets with enhanced antioxidant activity. Mater Sci Eng C [Internet]. 2021;120:111737. Available from: https://www.sciencedirect.com/science/article/pii/S0928493120336560
30. Zhang L, Wang P, Yang Z, Du F, Li Z, Wu C, et al. Molecular dynamics simulation exploration of the interaction between Curcumin and myosin combined with the results of spectroscopy techniques. Food Hydrocoll [Internet]. 2020;101:105455. Available from: https://www.sciencedirect.com/science/article/pii/S0268005X19302085
31. Arnittali M, Rissanou AN, Harmandaris V. Structure of Biomolecules Through Molecular Dynamics Simulations. Procedia Comput Sci [Internet]. 2019;156:69–78. Available from: https://doi.org/10.1016/j.procs.2019.08.181
32. Sneha P, George Priya Doss C. Chapter Seven - Molecular Dynamics: New Frontier in Personalized Medicine. In: Donev RBT-A in PC and SB, editor. Personalized Medicine [Internet]. Academic Press; 2016. p. 181–224. Available from: https://www.sciencedirect.com/science/article/pii/S187616231500067X
33. Farhadian S, Shareghi B, Asgharzadeh S, Rajabi M, Asadi H. Structural characterization of α-chymotrypsin after binding to Curcumin: Spectroscopic and computational analysis of their binding mechanism. J Mol Liq [Internet]. 2019;289:111111. Available from: https://www.sciencedirect.com/science/article/pii/S0167732219308906
34. Yahaya MAF, Bakar ARA, Stanslas J, Nordin N, Zainol M, Mehat MZ. Insights from molecular docking and molecular dynamics on the potential of vitexin as an antagonist candidate against lipopolysaccharide (LPS) for microglial activation in neuroinflammation. BMC Biotechnol. 2021;21(1):1–10.
35. Martínez L. Automatic identification of mobile and rigid substructures in molecular dynamics simulations and fractional structural fluctuation analysis. PLoS One. 2015;10(3):1–10.
36. Peña-Blanco A, García-Sáez AJ. Bax, Bak and beyond — mitochondrial performance in apoptosis. FEBS J [Internet]. 2018 Feb 1;285(3):416–31. Available from: https://doi.org/10.1111/febs.14186
37. Westphal D, Kluck RM, Dewson G. Building blocks of the apoptotic pore: How Bax and Bak are activated and oligomerize during apoptosis. Cell Death Differ [Internet]. 2014;21(2):196–205. Available from: http://dx.doi.org/10.1038/cdd.2013.139
38. Aguiló N, Uranga S, Marinova D, Martín C, Pardo J. Bim is a crucial regulator of apoptosis induced by Mycobacterium tuberculosis. Cell Death Dis. 2014;5(7):1–10.
39. Harada H, Becknell B, Wilm M, Mann M, Huang LJ, Taylor SS, et al. Phosphorylation and Inactivation of BAD by Mitochondria-Anchored Protein Kinase A. Mol Cell [Internet]. 1999;3(4):413–22. Available from: https://www.sciencedirect.com/science/article/pii/S1097276500804694