In Silico Analysis To Identify The Inhibitory Potential Of Endogenous Superoxide Dismutase On Apoptotic Markers Relevant To Breast Cancer.

Running Title :- Interaction of superoxide dismutase in apoptotic markers

Type of article :- Original Research

Authors :- **Gopika, Lavanya Prathap,Dr. Selvaraj Jayaraman,Preetha. S**

[1]**Gopika. G.G**
Department of Anatomy
Saveetha Dental College and Hospitals
Saveetha Institute of medical and technical sciences
Saveetha university,
Chennai - 600077
Email id: gopikagopi1610@gmail.com

[2]**Lavanya Prathap**
Associate Professor
Department of Anatomy
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai - 600077

[3]**Selvaraj Jayaraman**
Associate Professor
Department of Biochemistry
Saveetha Dental college and Hospitals,
Saveetha Institute of Medical and Technical Sciences,
Saveetha university,
Chennai - 600077

[3]**Preetha. S**
Assistant Professor
Department of Physiology
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai – 600077

Corresponding Author :-
Lavanya Prathap
Associate Professor
Department of Anatomy
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai - 600077
Email ID: lavanyap.sdc@saveetha.com

ABSTRACT:

BACKGROUND :

Breast cancer arises when certain breast cells start to grow abnormally they divide and replicate at a greater rate than normal cells. Regular exercise helps to reduce breast cancer by 10 to 20 percent. **AIM**: To analyse the inhibitory potential of endogenous over expression of superoxide dismutase (SOD) on apoptotic markers in breast cancer through silico analysis.

METHOD:

The molecular docking analysis is a bioinformatic study. The endogenous substance SOD which is secreted after exercise is used as a target protein. The interaction of SOD with proteins relevant to breast cancer namely Bcl-2, Bcl-xl, Bax are included for docking analysis. The protein structure is retrieved using protein data bank, protein protein docking done using patch dock server followed by visualisation of protein -protein interaction using pymol.

RESULTS:

The docking study suggests that Bcl-2 interacts with the B chain of SOD.. Bcl-xl also showed the interaction with the B chain of SOD through the same amino acids residues and Bax interacted with the B chain of SOD (Figure 1, 2, 3).It’s clearly shown that amino acids of SOD in all chains make significant contributions in complex formation.

CONCLUSION:

The study concludes that the role of exercised induced endogenous SOD might act as regulator of wtn/bax protein signalling in breast carcinoma. By regulating the wnt/beta signalling pathway, the exercise may aid in maintaining gene expression balance and act as a protective factor in preventing, controlling the metastasis and aid as an adjunct therapy for breast carcinoma with good prognostic value.

KEYWORD:

Breast cancer; superoxide dismutase; apoptotic markers,’ exercise’ bcl-2; bcl xl; bax proteins; Innovative.

INTRODUCTION:

Cancer incidence decreases with increasing physical exercise to regulate hormone level. It is most common in women and rare in men. In women 90% of breast cancer patients survive 5 years. In India 66% survive. With regular exercise we can lower the risk for breast cancer. Women with breast cancer are not active. Regular exercise can lower the risk by 10 - 20 percent.

Exercise programmes (for sedentary individuals) necessitate behaviour change, and these interventions should be supported by behaviour modification measures. Furthermore, due to the possibility of long-term negative effects, a long-term evaluation is required.(1).

Most cancer patients, particularly those with breast cancer, die as a result of metastasis, which is difficult to remove surgically and frequently develops resistance to conventional chemotherapy(2). Breast cancer has a complex aetiology. In the development of breast cancer, hormonal, genetic, and environmental variables appear to interact. Increased lifetime exposure to endogenous or exogenous hormones has been identified as a major risk factor for breast cancer development (3). Apoptosis is easily produced in hormone-dependent tissues like the breast and prostate gland by hormone ablation and treatment with antiestrogens or antiandrogens (8, 9). During the involution of the lactating breast, programmed cell death is also detected. (4,5).The experience from our previous studies (6) (7,8) (7)(9)(10)(11)(12)(10,12)(13)(14) (15) have led us to concentrate on the study.

Bcl-xL can boost anchorage-independent growth, which can lead to metastasis, by improving cell survival without cellular attachment and in the bloodstream. Several lines of evidence imply that the capacity to withstand apoptosis may aid metastasis. Furthermore, highly metastatic cancer cells have a higher potential to survive and fight apoptosis than poorly metastatic cancer cells(16),(17)(18). Studies at molecular levels were performed by our team of researches which insisted us to proceed this study (19–26),(27),(28),(29),(30,31),(32),(33),(34–38) The present study attempted to analyse the inhibitory potential of endogenes over expression of superoxide dismutase (SOD) on apoptotic markers in breast cancer through silico analysis.

MATERIALS AND METHODS:

The molecular docking analysis is a computer based study conducted in a private dental college. The endogenous substance SOD which is secreted after exercise is used as a target protein. The interaction of SOD with proteins relevant to breast cancer namely bcl-2, bcl-xl, bax are included for docking analysis.

Retrieval of Target proteins structures from Protein data bank:

In order to study the mechanism of interaction between SOD with Bcl-2, Bcl-xl, Bax proteins, the three dimensional structures were downloaded from Protein Data Bank using the respective ids(Pdb ids: SOD: 2GDS; Bcl-2- 4MAN;Bcl-xl-4QVF;Bax- 6EB6)

Protein-Protein Docking.

A geometry-based molecular docking algorithm called Patch Dock (http://bioinfo3d.cs.tau.ac.il/PatchDock) [2,3] was used to study the interaction between SOD with Bcl-2, Bcl-xl, Bax proteins. The server of the Patch Dock calculates docked transformations that produce strong complementarity of molecular shape. The algorithm splits the molecules' Connolly dot surface representation into concave, convex, and flat patches. In order to produce various transformations, the patches were paired according to their complementarity. For clustering, a default value of 4 Å was used and redundant solutions were discarded by RMSD clustering. The geometric score, desolvation energy, interface area scale, and the actual rigid transformation of the solutions are created by the Patch Dock output. For each complex, twenty solutions were created, from which one complex was selected for further analysis based on the scoring geometric shape for both complexes.

Visualization of Protein – Protein interactions:

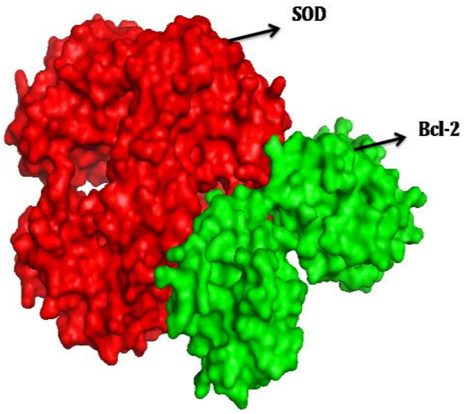
The remaining interactions between docked complexes were examined using the Pymol academic version. The intensity of colour for interactions was readily visualised and exported for findings [4]. Pdbsum was used to determine the types of interactions that occur between SOD and the proteins Bcl-2, Bcl-xl, and Bax.

RESULTS:

The results of this docking study showed that Bcl-2 interacts with the B chain of SOD. The amino acids residues ILE 58, ALA-59, GLN-61, PRO-62, LYS-65,PHE-66, PHE-101, LYS-110, ALA-113, ALA-114, GLY-117, VAL-118, GLN-119, SER-121, ASN-129, GLU-131, AGR-132, HIS-134, GLN-136, ILE-137, ALA-138 AND CYS -140 were involved in the formation of SOD-Bcl-2 complex. Bcl-xl also showed the interaction with the B chain of SOD through the same amino acids residues and Bax interacted with the B chain of SOD (Figure 1, 2, 3).It's clearly shown that amino acids of SOD in all chains make significant contributions in complex formation.

Table 1: Molecular docking results of SOD with Bcl-2, Bcl-xl, and BAX

S.No	**Protein Name**	**Score**	**ACE (Atomic contact energy)**
1	Bcl-2	16858	-414.63
2	Bcl-xl	13814	-444.09
3	BAX	14668	-434.16



.

Figure 1:Protein- protein interaction of SOD with Bcl-2

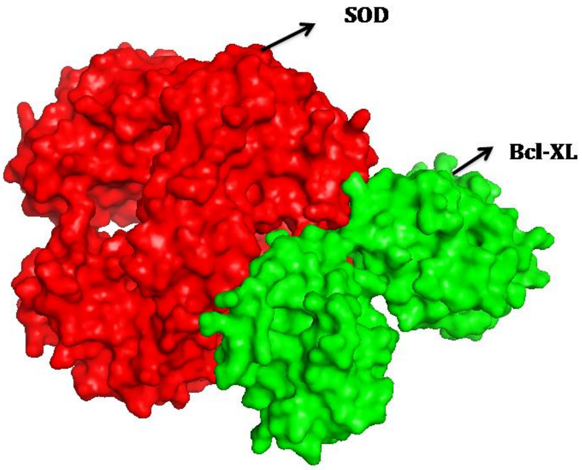


Figure 2: Protein- protein interaction between SOD with Bcl-xl

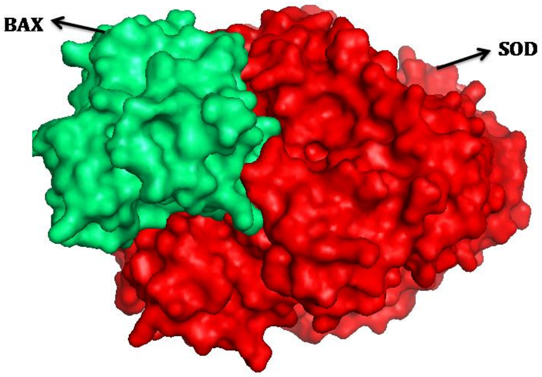


Figure 3: Protein –protein interaction of SOD with Bax

DISCUSSION:

Interacting residues can be found in both conserved and non-conserved areas of SOD, according to our findings. As we assume that this SOD-Bcl-2, Bcl-xl, Bax interaction plays a key role to inhibit the overexpression of SOD in breast cancer. . Furthermore, we found that the SOD B, C chain acts as a binding site for Bcl-2 Bcl-xl and Bax proteins. This inhibit the expression of SOD through apoptotic markers. The results presented here have numerous potential medicine aspects particularly to its may acts as potential inhibitors for breast cancer after experimental validation.

Virtually all cellular mechanisms, such as signal transduction, protein expression regulation and DNA replication, are concerned with protein-protein interactions (PPIs). Therefore it is essential to determine their complex structures to understand the fundamental molecular mechanisms of essential biological processes and also develop molecules that interact with PPIs with therapeutic significance(39) . Hence in the present study, interaction between the SOD with Bcl-2, Bcl-xl, Bax proteins were studied using patch docking server. The structure of SOD is composed of four chain structures (A, B, C and D)(40)(41)(42).

MnSOD, through activating MMPs and inhibiting antiproteases, has been demonstrated to contribute to this ability. This activity is caused by H2O2, which either directly activates pro-MMPs or boosts their gene expression by activating redox-sensitive transcription factors. (18,43),(45).

Exercise oncology research is greatly expanding particularly in relevance to breast cancer. The author addressed the current perspectives on the importance of aerobic exercise in breast cancer survivors. Evidence supports the fact that moderate-intensity exercise lowers the risk of breast cancer recurrence. Though exercise is said to be beneficial for overall well being and maintaining the quality of life, Still there is lack of enough evidence to emphasize the role of exercise in risk reduction and recurrence of breast cancer. (46) (47)

In a 2018 study, Kirsteen J Camphell found that mitochondrial apoptosis is regulated by the balance of pro-apoptotic and anti-apoptotic gene expression modulation. This ensures the equilibrium of programmed cell death and modulates the cell division in moderation. The author reported targeting the BCL-2 gene expression can aid in the prevention of the occurrence of cancer and also can have a good prognostic effect in early-stage tumors. Deregulation of BCL2 is becoming a target activity in various types of cancer and targeted cancer therapies can aid in maintaining the quality of life of cancer survivors. (48)

Ma Ming et al in their study attempted to identify the role of miRNA-125a-5p regulation in controlling hepatocellular carcinoma by targeting BCL2 gene expression. The study concluded the miRNA-125a-5p expression is downregulated in patients with hepatocellular carcinoma. Its upregulation is observed to inhibit the proliferation of hepatocellular cancer cells and its metastasis by targeting BCL2 gene expression. ((48,49)

JiaNan Ji et al in the year 2019 reported Tetrandrine (Tet) a compound isolated from Menispermaceae species to have an anti-cancer effect by targeting BCL2 gene expression. The study revealed the effect of dopamine in controlling the cell proliferation in cancer cells based on dosage by targeting BCL2 mRNA gene expression. (50)

A 2018 study looked at the role of exercise in regulating apoptotic pathway in oral squamous epithelial cell cancer. The study's findings imply that moderate-intensity aerobic exercise increases the Bax/Bcl-2 ratio and works as a cancer-prevention factor. The study's findings are consistent with those of the current study.(51),(52). The entertainment training stimulus consisted of two stores: one exercise. (52–54).

It is a computer based study, it can be further proceeded to in vitro study,humans or animal study. Regular exercise lowers the chances of breast cancer. Exercise helps your body to regulate hormone levels. Breast cancer commonly seen in women, rarely seen in male.

CONCLUSION:

It can be concluded that the inhibitory potential of endogenous over the expression of superoxide dismutase on apoptosis markers is relevant to breast cancer. Exercise modulates wnt/bax signalling path and act as a factor in preventing, controlling the metastasis and aid as an adjunct therapy for breast cancer with good prognostic value.

ACKNOWLEDGEMENT: We thank saveetha dental college and hospitals for the successful completion of the study.

SOURCE OF FUNDING:

The present study was supported by the .

- Saveetha Institute of Medical and Technical Sciences (SIMATS)
- Saveetha Dental College and Hospitals
- Saveetha University
- Indo Vietnam Association, Pondicherry

CONFLICT OF INTEREST: All the authors declare that there was no conflict of interest in the present study.

REFERENCES:

1. Markes M, Brockow T, Resch K-L. Exercise for women receiving adjuvant therapy for breast cancer [Internet]. Cochrane Database of Systematic Reviews. 2006. Available from: http://dx.doi.org/10.1002/14651858.cd005001.pub2

2. Fu A, Ma S, Wei N, Tan BXX, Tan EY, Luo KQ. High expression of MnSOD promotes survival of circulating breast cancer cells and increases their resistance to doxorubicin. Oncotarget. 2016 Aug 2;7(31):50239–57.

3. Tsai S-M, Hou M-F, Wu S-H, Hu B-W, Yang S-F, Chen W-T, et al. Expression of manganese superoxide dismutase in patients with breast cancer. Kaohsiung J Med Sci. 2011 May;27(5):167–72.

4. Hanke J. Apoptosis and occurrence of Bcl-2, Bak, Bax, Fas and FasL in the developing and adult rat endocrine pancreas [Internet]. Vol. 202, Anatomy and Embryology. 2000. p. 303–12. Available from: http://dx.doi.org/10.1007/s004290000112

5. Bargou RC, Wagener C, Bommert K, Mapara MY, Daniel PT, Arnold W, et al. Overexpression of the death-promoting gene bax-alpha which is downregulated in breast cancer restores sensitivity to different apoptotic stimuli and reduces tumor growth in SCID mice. J Clin Invest. 1996 Jun 1;97(11):2651–9.

6. Shruthi M, Preetha S. Effect of Simple Tongue Exercises in Habitual Snorers [Internet]. Vol. 11, Research Journal of Pharmacy and Technology. 2018. p. 3614. Available from: http://dx.doi.org/10.5958/0974-360x.2018.00665.0

7. Preetha S, Packyanathan J. Comparison of the effect of Yoga, Zumba and Aerobics in controlling blood pressure in the Indian population [Internet]. Vol. 9, Journal of Family Medicine and Primary Care. 2020. p. 547. Available from: http://dx.doi.org/10.4103/jfmpc.jfmpc_607_19

8. J SK, Saveetha Dental College and Hospitals, Road PH, Chennai, Tamilnadu, Preetha S, et al. Effect of aerobics exercise and yoga on blood pressure in hypertensives [Internet]. Vol. 6,

International Journal of Current Advanced Research. 2017. p. 3124–6. Available from: http://dx.doi.org/10.24327/ijcar.2017.3126.0200

9. Prathap L, Suganthirababu P, Ganesan D. Fluctuating Asymmetry of Dermatoglyphics and DNA Polymorphism in Breast Cancer Population [Internet]. Vol. 10, Indian Journal of Public Health Research & Development. 2019. p. 3574. Available from: http://dx.doi.org/10.5958/0976-5506.2019.04141.x

10. Lavanya J, Prathap S, Alagesan J. Digital and palmar dermal ridge patterns in population with breast carcinoma. Biomedicine. 2014 Jul 1;34(3):315–21.

11. Prathap L, Jagadeesan V. Association of quantitative and qualitative dermatoglyphic variable and DNA polymorphism in female breast cancer population. Online J Health [Internet]. 2017; Available from: https://www.researchgate.net/profile/Prathap_Suganthirababu/publication/321606278_Association_of_Quantitative_and_Qualitative_Dermatoglyphic_Variable_and_DNA_Polymorphism_in_Female_Breast_Cancer_Population/links/5a28c8f1a6fdcc8e8671c0cd/Association-of-Quantitative-and-Qualitative-Dermatoglyphic-Variable-and-DNA-Polymorphism-in-Female-Breast-Cancer-Population.pdf

12. Lavanya J, Kumar VJ, Sudhakar N, Prathap S. Analysis of DNA repair genetic polymorphism in breast cancer population. Int J Pharma Bio Sci [Internet]. 2015; Available from: https://scholar.google.ca/scholar?cluster=8949053652564257518&hl=en&as_sdt=0,5&sciodt=0,5

13. Prathap L, Suganthirababu P. Estrogen Exposure and its Influence in DNA Repair Genetic Variants in Breast Cancer Population [Internet]. Vol. 13, Biomedical and Pharmacology Journal. 2020. p. 1321–7. Available from: http://dx.doi.org/10.13005/bpj/2001

14. Ravikumar H, Prathap L, Preetha S. ANALYSIS OF PALMAR ATD ANGLE IN POPULATION WITH MALOCCLUSION. 2020 Jan 1;1174–82.

15. Prathap L. INTERPLAY OF OXIDATIVE STRESS AND LIPOPROTEINS IN BREAST CARCINOMA INITIATION, PROMOTION AND PROGRESSION -A SYSTEMATIC REVIEW. PalArch's Journal of Archaeology of Egypt/ Egyptology [Internet]. 2021 Jan 7 [cited 2021 Mar 9];17(7). Available from: http://dx.doi.org/

16. Cai Q, Shu X-O, Wen W, Cheng J-R, Dai Q, Gao Y-T, et al. Genetic polymorphism in the manganese superoxide dismutase gene, antioxidant intake, and breast cancer risk: results from the Shanghai Breast Cancer Study. Breast Cancer Res. 2004 Sep 22;6(6):R647–55.

17. Klaunig J. Faculty Opinions recommendation of Manganese superoxide dismutase (MnSOD) genetic polymorphism is associated with risk of early-onset prostate cancer [Internet]. Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature. 2008. Available from: http://dx.doi.org/10.3410/f.1119779.575864

18. Ahmad A. Breast Cancer Metastasis and Drug Resistance: Challenges and Progress. Springer Nature; 2019. 427 p.

19. Sekar D, Lakshmanan G, Mani P, Biruntha M. Methylation-dependent circulating microRNA

510 in preeclampsia patients. Hypertens Res. 2019 Oct;42(10):1647–8.

20. Princeton B, Santhakumar P, Prathap L. Awareness on Preventive Measures taken by Health Care Professionals Attending COVID-19 Patients among Dental Students. Eur J Dent. 2020 Dec;14(S 01):S105–9.

21. Logeshwari R, Rama Parvathy L. Generating logistic chaotic sequence using geometric pattern to decompose and recombine the pixel values. Multimed Tools Appl. 2020 Aug;79(31-32):22375–88.

22. Johnson J, Lakshmanan G, M B, R M V, Kalimuthu K, Sekar D. Computational identification of MiRNA-7110 from pulmonary arterial hypertension (PAH) ESTs: a new microRNA that links diabetes and PAH. Hypertens Res. 2020 Apr;43(4):360–2.

23. Paramasivam A, Priyadharsini JV, Raghunandhakumar S, Elumalai P. A novel COVID-19 and its effects on cardiovascular disease. Hypertens Res. 2020 Jul;43(7):729–30.

24. Pujari GRS, Subramanian V, Rao SR. Effects of Celastrus paniculatus Willd. and Sida cordifolia Linn. in Kainic Acid Induced Hippocampus Damage in Rats. Ind J Pharm Educ. 2019 Jul 3;53(3):537–44.

25. Rajkumar KV, Lakshmanan G, Sekar D. Identification of miR-802-5p and its involvement in type 2 diabetes mellitus. World J Diabetes. 2020 Dec 15;11(12):567–71.

26. Ravisankar R, Jayaprakash P, Eswaran P, Mohanraj K, Vinitha G, Pichumani M. Synthesis, growth, optical and third-order nonlinear optical properties of glycine sodium nitrate single crystal for photonic device applications. J Mater Sci: Mater Electron. 2020 Oct;31(20):17320–31.

27. Wu S, Rajeshkumar S, Madasamy M, Mahendran V. Green synthesis of copper nanoparticles using Cissus vitiginea and its antioxidant and antibacterial activity against urinary tract infection pathogens. Artif Cells Nanomed Biotechnol. 2020 Dec;48(1):1153–8.

28. Vikneshan M, Saravanakumar R, Mangaiyarkarasi R, Rajeshkumar S, Samuel SR, Suganya M, et al. Algal biomass as a source for novel oral nano-antimicrobial agent. Saudi J Biol Sci. 2020 Dec;27(12):3753–8.

29. Alharbi KS, Fuloria NK, Fuloria S, Rahman SB, Al-Malki WH, Javed Shaikh MA, et al. Nuclear factor-kappa B and its role in inflammatory lung disease. Chem Biol Interact. 2021 Aug 25;345:109568.

30. Rao SK, Kalai Priya A, Manjunath Kamath S, Karthick P, Renganathan B, Anuraj S, et al. Unequivocal evidence of enhanced room temperature sensing properties of clad modified Nd doped mullite Bi2Fe4O9 in fiber optic gas sensor [Internet]. Vol. 838, Journal of Alloys and Compounds. 2020. p. 155603. Available from: http://dx.doi.org/10.1016/j.jallcom.2020.155603

31. Bhavikatti SK, Karobari MI, Zainuddin SLA, Marya A, Nadaf SJ, Sawant VJ, et al. Investigating the Antioxidant and Cytocompatibility of Mimusops elengi Linn Extract over Human Gingival Fibroblast Cells. Int J Environ Res Public Health [Internet]. 2021 Jul 4;18(13). Available from: http://dx.doi.org/10.3390/ijerph18137162

32. Marya A, Karobari MI, Selvaraj S, Adil AH, Assiry AA, Rabaan AA, et al. Risk Perception of SARS-CoV-2 Infection and Implementation of Various Protective Measures by Dentists Across Various Countries. Int J Environ Res Public Health [Internet]. 2021 May 29;18(11). Available from: http://dx.doi.org/10.3390/ijerph18115848

33. Barma MD, Muthupandiyan I, Samuel SR, Amaechi BT. Inhibition of Streptococcus mutans, antioxidant property and cytotoxicity of novel nano-zinc oxide varnish. Arch Oral Biol. 2021 Jun;126:105132.

34. Vijayashree Priyadharsini J. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. J Periodontol. 2019 Dec;90(12):1441–8.

35. Priyadharsini JV, Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species [Internet]. Vol. 94, Archives of Oral Biology. 2018. p. 93–8. Available from: http://dx.doi.org/10.1016/j.archoralbio.2018.07.001

36. Uma Maheswari TN, Nivedhitha MS, Ramani P. Expression profile of salivary micro RNA-21 and 31 in oral potentially malignant disorders. Braz Oral Res. 2020 Feb 10;34:e002.

37. Gudipaneni RK, Alam MK, Patil SR, Karobari MI. Measurement of the Maximum Occlusal Bite Force and its Relation to the Caries Spectrum of First Permanent Molars in Early Permanent Dentition. J Clin Pediatr Dent. 2020 Dec 1;44(6):423–8.

38. Chaturvedula BB, Muthukrishnan A, Bhuvaraghan A, Sandler J, Thiruvenkatachari B. Dens invaginatus: a review and orthodontic implications. Br Dent J. 2021 Mar;230(6):345–50.

39. Schneidman-Duhovny D, Inbar Y, Polak V, Shatsky M, Halperin I, Benyamini H, et al. Taking geometry to its edge: fast unbound rigid (and hinge-bent) docking. Proteins. 2003 Jul 1;52(1):107–12.

40. Berman H. Establishing the Next Generation of the Protein Data Bank [Internet]. The Winnower. 2014. Available from: http://dx.doi.org/10.15200/winn.140076.68556

41. Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ. Geometry-based flexible and symmetric protein docking [Internet]. Vol. 60, Proteins: Structure, Function, and Bioinformatics. 2005. p. 224–31. Available from: http://dx.doi.org/10.1002/prot.20562

42. Alexander N, Woetzel N, Meiler J. bcl::Cluster : A method for clustering biological molecules coupled with visualization in the Pymol Molecular Graphics System. IEEE Int Conf Comput Adv Bio Med Sci. 2011 Feb;2011:13–8.

43. Becuwe P, Ennen M, Klotz R, Barbieux C, Grandemange S. Manganese superoxide dismutase in breast cancer: from molecular mechanisms of gene regulation to biological and clinical significance. Free Radic Biol Med. 2014 Dec;77:139–51.

44. Rogers LQ, Markwell SJ, Verhulst S, McAuley E, Courneya KS. Rural breast cancer survivors: exercise preferences and their determinants. Psychooncology. 2009 Apr;18(4):412–21.

45. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of

exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ. 2006 Jul 4;175(1):34–41.

46. Rahman KM, Aranha O, Glazyrin A, Chinni SR, Sarkar FH. Translocation of Bax to mitochondria induces apoptotic cell death in indole-3-carbinol (I3C) treated breast cancer cells. Oncogene. 2000 Nov 23;19(50):5764–71.

47. Dieli-Conwright CM, Orozco BZ. Exercise after breast cancer treatment: current perspectives. Breast Cancer. 2015 Oct 21;7:353–62.

48. Campbell KJ, Tait SWG. Targeting BCL-2 regulated apoptosis in cancer [Internet]. Vol. 8, Open Biology. 2018. p. 180002. Available from: http://dx.doi.org/10.1098/rsob.180002

49. Ming M, Ying M, Ling M. miRNA-125a-5p inhibits hepatocellular carcinoma cell proliferation and induces apoptosis by targeting TP53 regulated inhibitor of apoptosis 1 and Bcl-2-like-2 protein [Internet]. Experimental and Therapeutic Medicine. 2019. Available from: http://dx.doi.org/10.3892/etm.2019.7674

50. Li J, Wang Q, Wang Z, Cui N, Yang B, Niu W, et al. Tetrandrine inhibits colon carcinoma HT-29 cells growth via the Bcl-2/Caspase 3/PARP pathway and G1/S phase. Biosci Rep [Internet]. 2019 May 31;39(5). Available from: http://dx.doi.org/10.1042/BSR20182109

51. Irmawati A, Jasmin N, Sidarningsih. The effect of moderate exercise on the elevation of Bax/Bcl-2 ratio in oral squamous epithelial cells induced by benzopyrene [Internet]. Vol. 11, Veterinary World. 2018. p. 177–80. Available from: http://dx.doi.org/10.14202/vetworld.2018.177-180

52. Uth J, Fristrup B, Sørensen V, Helge EW, Christensen MK, Kjærgaard JB, et al. Exercise intensity and cardiovascular health outcomes after 12 months of football fitness training in women treated for stage I-III breast cancer: Results from the football fitness After Breast Cancer (ABC) randomized controlled trial. Prog Cardiovasc Dis. 2020 Nov;63(6):792–9.

53. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst. 1994 Sep 21;86(18):1403–8.

54. Fiegl H, Millinger S, Mueller-Holzner E, Marth C, Ensinger C, Berger A, et al. Circulating tumor-specific DNA: a marker for monitoring efficacy of adjuvant therapy in cancer patients. Cancer Res. 2005 Feb 15;65(4):1141–5.