ROLE OF ENDOGENOUS GLUTATHIONE AS REGULATOR OF WNT/BETA CATENIN SIGNALLING RELEVANT TO BREAST CANCER - A MOLECULAR DOCKING STUDY

[1]Prithiksha N [2]Lavanya Prathap [3]Dr. Selvaraj Jayaraman [3]Preetha. S

Running Title: Docking analysis of glutathione and Wnt/beta catenin signalling pathway.

Type of article: Original Research

Authors:

[1]Prithiksha N
Department of Anatomy
Saveetha Dental College and Hospitals
Saveetha Institute of medical and technical sciences
Saveetha university,
Chennai - 600077
Email: 152001085.sdc@saveetha.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
E Mail id: lavanyap.sdc@saveetha.com

[3]Selvaraj Jayaraman
Associate professor
Department of Biochemistry
Saveetha Dental college and Hospitals,
Saveetha Institute of Medical and Technical Sciences,
Saveetha university,
Chennai - 600077
Email: selvarajj.sdc@saveetha.com

[3]Preetha. S
Assistant Professor
Department of Physiology
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai - 600077
Email: preethas.sdc@saveetha.com

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 tumor is the most common tumor in women and the second leading cause of tumor death in women, after lung tumor. As people get older, their chances of developing breast tumor increase. Breast tumor is a major health concern in developed countries. Glutathione is an endogenous antioxidant that helps maintain quality of life and may help prevent breast tumor. The role of endogenous glutathione as a regulator of Wnt/beta catenin signalling in breast tumor will be studied using molecular docking.. **Materials and Methods**: The molecular docking analysis is a bio-informatic study executed in a dental college. The endogenous substance Glutathione which is secreted after exercise is used as a target protein. The interaction of glutathione with proteins relevant to breast tumor namely Beta catenin , MYC 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 surface representation of Glutathione with Beta-catenin,MYC complex showed good shape complementarity. The number of structurally aligned residues indicates anticipated binding free energy for the top-listed solutions. **Conclusion:** The findings suggest that exercise-induced endogenous glutathione may operate as a regulator of wnt/beta catenin signalling in breast tumor. The exercise may help maintain gene expression balance by modifying the Wnt/beta catenin signalling system, as well as operate as a protective factor in preventing, controlling, and aiding as an additional therapy for breast tumor with a favourable prognosis.

KEYWORDS: Beta-catenin; MYC; Breast tumor; Exercise; Glutathione; Innovative method

INTRODUCTION:

The most frequent tumour in women is a breast tumour. After lung cancer, breast cancer is the second most common cause of cancer death among women. Breast cancer risk rises as you become older.Breast tumor is a major health problem in developed countries. The chance that a woman will die from breast tumor is about 39(about 2.6%) From 2013 to 2019,the death rate decreased by 1% per year. Increase in the body weight contributes in the risk of developing number of tumors.. Glutathione is a natural antioxidant secreted endogenously post exercise that helps in maintaining the quality of life and may prevent breast tumor. Glutathione has its own vital role in the process of cell differentiation and proliferation. Any disturbances in the homeostasis of glutathione can lead to the

development of tumor. [1] Aerobic exercise training, circuit weight, combined training may modulate the GSH antioxidant system.[2,3]TP53 gene expression is a metastatic regulator in breast tumor. It may exhibit potent anti-tumor potential. [4] The GSH Oxidant system plays a key role in the dependent drug which can induce apoptosis. [5,6]Cells proliferate in the MYC variable so the transcription factors required for the gene expression in the breast tumor.[7] The exploration from our previous studies [8] [9,10] [91112131412,141516] [17] have led us to concentrate on the current study.

Glutathione is a crucial signal transduction pathway that controls cell differentiation, proliferation, apoptosis, ferroptosis, and immunological activities. Tumor development, progression, and treatment response have all been linked to molecular alterations and abnormalities . It elicits both protective and harmful responses. Exercise aids tumor patients in surviving and recovering after therapy. Long-term tumor survivors may benefit from exercise, which may help them live longer. Physical activity is beneficial to people with tumor of all types. [18]. Breast tumor symptoms, both acute and chronic, are influenced by regular exercise. [19]. Physical exercise promotion is a reasonably cost- effective technique to supplement current adjuvant therapy and perhaps aid in the prevention of breast tumor. [20]. Physical activity appears to have a greater impact on postmenopausal women, women of normal weight, and those without a family history of breast tumor.[21] Studies at molecular levels were performed by our team of researches which insisted us to proceed this study. [22–29],[30],[31],[32],[33,34],[35],[36],[37–41]Thus the present study attempted to analyse the role of endogenous glutathione as a regulator of Wnt/Beta catenine signalling relevant to breast tumor through a molecular docking study.

MATERIAL AND METHODS:

The molecular docking analysis is a computer based study. The endogenous substance Glutathione which is secreted after exercise is used as a target protein. The interaction of glutathione with proteins relevant to breast tumor namely Beta catenin , MYC are included for docking analysis.

Procedure:

Retrieval of Target proteins structures from Protein data bank:

In order to study the mechanism of interaction between Glutathione with Beta-catenin,MYC proteins, the three dimensional structures were downloaded from

Protein Data Bank using the respective Pdb ids(Pdb ids: Glutathione -1PKW; Beta-catenin-4DJS; MYC-6G6K)

Protein-Protein Docking:

Patch Dock (http://bioinfo3d.cs.tau.ac.il/PatchDock), a molecular docking approach based on geometry, was used to investigate the interaction of Glutathione with Beta-catenin and MYC proteins. The Patch Dock service generates docked transformations with high molecular shape compatibility. The computer divides the Connolly dot surface representation of the molecules into concave, convex, and flat regions. To achieve a variety of transformations, the patches were coupled according to their complementarity. Clustering was done with a default value of 4, and duplicated solutions were removed using RMSD clustering. The geometric score, desolvation energy, interface area scale, and actual rigid transformation of the solutions are all generated by the Patch Dock output. There are twenty solutions for each complicated were developed, and one complex was chosen for further examination based on the geometric shape scoring of both complexes.

Visualization of Protein – Protein interactions:

The remaining interactions between docked complexes were examined using the Pymol academic version. For the results, the colour intensity of interactions was displayed and exported [4]. Pdbsum was used to figure out what kinds of interactions Glutathione has with Beta-catenin and MYC proteins.

RESULTS

The surface representation of the Glutathione with Beta-catenin, MYC complex showed strong shape complementarity and was docked using Patch dock server (http://bioinfo3d.cs.tau.ac.il/PatchDock) to understand the level of interaction between these proteins. (Figure 1,2The number of structurally aligned residues expressed within the distance cut-off of 4, and the number of hot-spot left overs in the protein and protein interface were analysed using grades representing assumed binding free energy for the top-listed solutions, the number of structurally aligned residues expressed within the distance cut-off of 4, and the number of hot-spot left overs in the protein and protein interface. (Table1). The number of hydrogen bonds, hydrophobic, and non-bonded contacts is calculated using the PDBSUM software.. Mainly the amino acidsTYR-9, ALA-12, PHE-10, GLY-14, ARG-13, ARG-15, GLU-17, SER-18, LEU-41, ARG-45, PHE-52, GLN-54, THR-68, VAL-55. PRO-66, of glutathione plays a major to form the interaction with Beta-

catenin, MYC proteins. These amino acids residues act as a hot –spot for interaction among these proteins.

Table 1: Molecular docking results of Glutathione with Beta-catenine,MYC proteins.

Protein Name	**Score**	**ACE(Atomic contact energy)**
Beta Catenin	16312	-191.62
MYC Protein	13824	-475.19

fig1: The figure represents the Structure for Protein Glutathione

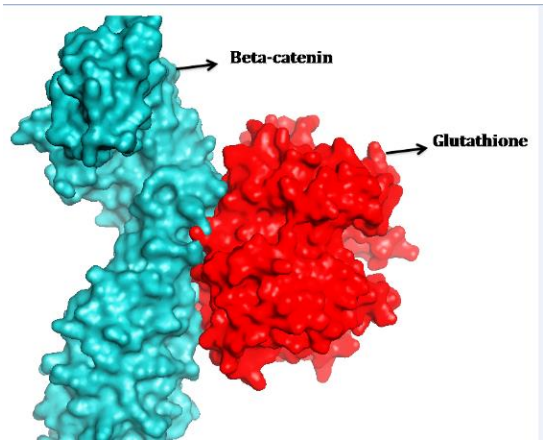

Fig 2: The figure represents the protein- protein interaction between beta-catenin and Glutathione protein compounds

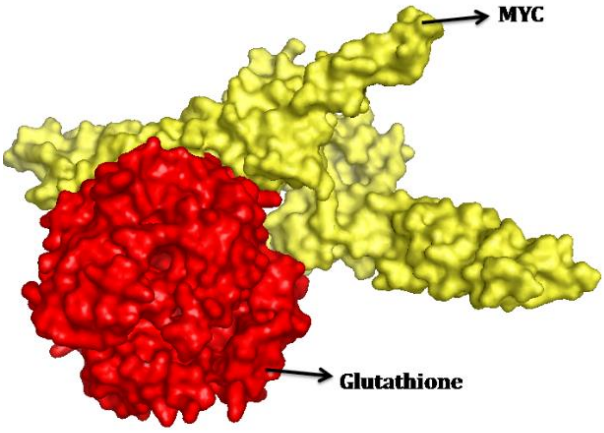

Fig 3: The figure represents the protein- protein interaction between MYC and Glutathione protein compounds

DISCUSSION:

The docking study's findings could add to the growing body of data indicating exercise-induced endogenous glutathione may be a protective molecule against breast tumor cell development. It was possible to create more selective and effective inhibitors by understanding these types of interactions. We confirmed that glutathione may operate as a regulator for the Wnt/beta catenine signalling pathway in breast tumor in this work..

Protein-protein connections comprise much of the cellular processes (PPIs). Therefore, accurate information about the residues of amino acid present in PPIs must be gathered. The numerous PPIs that describe experimental techniques seem to be available. Though very reliable, these experimental approaches are consuming more time, intense labour, and very costly. Various laboratories have built various bioinformatics parameters to create different numbers of bioinformatic technical tools to forecast PPIs in order to solve the existing challenges. For the prediction of three-dimensional structures of proteins as well as protein complexes, bioinformatic algorithms have been used. These days, numerous machine learning algorithms were used for the purpose of PPI analysis.. The methods of docking can be classified widely as rigid body and flexible system of docking, Patch Dock is a database for molecular protein-protein docking.

Aerobic exercise prevents breast tumor. Protein protein connection is a cellular process and the molecular docking used to produce 3D Structures in the Protein Data Bank(PDB). Oxidised glutathione will reduce the glutathione bound together

by the sulfur atoms. Endogenous oxygen and the nitrogen species will reduce the oxidative stress in the Beta catenin.[42,43] 83g/d of almonds increases the glutathione in the smokers which will decrease 16% of DNA damage.In meditation practitioners 20% of glutathione level is reported to get increased. GSH oxidant system plays a key role in MYC dependent drugs which will induce the apoptosis and the transcription factors required in MYC for gene expression in breast tumor to proliferate the cells. Glutathione with MYC Protein may prevent breast tumor through wnt/beta catenin pathway as discovered by Nusse and Varmus. Wnt/beta catenin signalling,a highly conserved pathway through evolution and the key cellular function will include the cell proliferation, differentiation, migrates, stem cell renewal, gene stability, apoptosis. [42]

WNT's translated products of WNT genes are cysteine rich glycoproteins which are secreted by the cells into the extracellular matrix. The Wnt family's signalling is secreted by glycoproteins via beta catenin, a transcriptional co-activator that regulates embryonic development and adult homeostasis. The expression of beta catenin in triple negative breast tumor was linked to poor overall survival and disease-specific survival.. [2]

Glutathione helps to maintain the stem cell phenotype by promoting glutathione synthesis and keeping the body's redox balance in check. It restored the redox equilibrium in the stress response, which is critical for physiological cellular processes and survival. Glutathione has pleiotropic functions in protecting damage from external, internal, and intracellular stressors. The GSH homeostasis is maintained in cells that have been exposed to genotoxic stress. Genotoxic stress is essential for the maintenance of normal cellular function, transcriptional activity, and metabolism. At the promoters of numerous genes in the GSH metabolism cascade, beta catenin forms a complex.. [44,45]

Exercise training has evolved the new approach. Effectiveness of the exercise training programmes was demonstrated to have a significant impact in breast tumor prevention and progression.[46] The scope of this study was to assess the impact of the aerobic exercise training as assessed by the changes in the GSH oxidant system.[47-52]. Antioxidant mechanisms include enhanced expressions of the molecules which can control the ROS accumulation by both the enzymatic and non-enzymatic interactions. Wnt/beta catenin signaling has a major role in development and diseases and it can start by the action of the FZ(frizzled receptors) whose co.receptors is LDL receptors related to the tumor protein. Wnt/beta catenin signaling is crucially involved in the pattern of axial in the vertebrates embryogenesis.[44,53-57]

Encapsulating through the molecular docking study can act as preliminary evidence to understand the interacting mechanism between the target protein endogenous glutathione and the proteins expressed in breast carcinoma beta catenin and MYC. The interactions make the concept evident that exercise induced glutathione can act as a regulator in modulating the expression of beta catenin and MYC proteins in controlling breast carcinoma. Future research could include more protein interactions in human and animal models as part of a large-scale investigation to better understand the context.

CONCLUSION:

From the results of the analysis it can be concluded that the role endogenous glutathione induced by exercise may act as the regulator of wnt/beta catenin signaling in breast carcinoma. By regulating the Wnt/beta catenin signalling pathway, the exercise may assist maintain 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.

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 following agencies.

- Saveetha Dental College
- Saveetha Institute of Medical and Technical Sciences (SIMATS)
- Saveetha University
- Jyothi gas agency

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

REFERENCES:

1. Traverso N, Ricciarelli R, Nitti M, Marengo B, Furfaro AL, Pronzato MA, et al. Role of glutathione in tumor progression and chemoresistance. Oxid Med Cell Longev. 2013 May 20;2013:972913.

2. Geng Y, Ju Y, Ren F, Qiu Y, Tomita Y, Tomoeda M, et al. Insulin Receptor Substrate 1/2 (IRS1/2) Regulates Wnt/β-Catenin Signaling through Blocking Autophagic Degradation of Dishevelled2 [Internet]. Vol. 289, Journal of Biological Chemistry. 2014. p. 11230–41. Available from:

http://dx.doi.org/10.1074/jbc.m113.544999

3. Csiszár J, Horváth E, Bela K, Gallé Á. Glutathione-Related Enzyme System: Glutathione Reductase (GR), Glutathione Transferases (GSTs) and Glutathione Peroxidases (GPXs) [Internet]. Redox State as a Central Regulator of Plant-Cell Stress Responses. 2016. p. 137–58. Available from: http://dx.doi.org/10.1007/978-3-319-44081-1_7

4. Oakley A, Parker M. Human glutathione S-transferase P1-1, complex with glutathione [Internet]. 1998. Available from: http://dx.doi.org/10.2210/pdb8gss/pdb

5. Tars K, Olin B, Mannervik B. Glutathione transferase A2-2 in complex with glutathione [Internet]. 2008. Available from: http://dx.doi.org/10.2210/pdb2vcr/pdb

6. Hayes JD, Pickett CB, Mantle TJ. Glutathione S-transferases and Drug Resistance. Taylor & Francis Group; 1990. 459 p.

7. Bae B, Nair SK. c-Myc DNA Unwinding Element Binding Protein [Internet]. 2007. Available from: http://dx.doi.org/10.2210/pdb2okv/pdb

8. 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

9. 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

10. 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

11. Prathap L, Suganthirababu P, Ganesan D. Fluctuating Asymmetry of Dermatoglyphics and DNA Polymorphism in Breast Tumor 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

12. 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.

13. Prathap L, Jagadeesan V. Association of quantitative and qualitative dermatoglyphic variable and DNA polymorphism in female breast tumor 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_Tumor_Population/links/5a28c8f1a6fdcc8e8671c0cd/Association-of-Quantitative-and-Qualitative-Dermatoglyphic-Variable-and-DNA-Polymorphism-in-Female-Breast-Tumor-Population.pdf

14. Lavanya J, Kumar VJ, Sudhakar N, Prathap S. Analysis of DNA repair genetic polymorphism in breast tumor 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

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

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

17. 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/

18. Rajarajeswaran P, Vishnupriya R. Exercise in tumor [Internet]. Vol. 30, Indian Journal of Medical and Paediatric Oncology. 2009. p. 61. Available from: http://dx.doi.org/10.4103/0971-5851.60050

19. Adraskela K, Veisaki E, Koutsilieris M, Philippou A. Physical Exercise Positively Influences Breast Tumor Evolution. Clin Breast Tumor. 2017 Oct;17(6):408–17.

20. McTiernan A. Physical Activity, Weight, Diet, and Breast Tumor Risk

Reduction [Internet]. Vol. 170, Archives of Internal Medicine. 2010. Available from: http://dx.doi.org/10.1001/archinternmed.2010.416

21. Lynch BM, Neilson HK, Friedenreich CM. Physical Activity and Breast Tumor Prevention [Internet]. Physical Activity and Tumor. 2010. p. 13–42. Available from: http://dx.doi.org/10.1007/978-3-642-04231-7_2

22. Sekar D, Lakshmanan G, Mani P, Biruntha M. Methylation-dependent circulating microRNA 510 in preeclampsia patients. Hypertens Res. 2019 Oct;42(10):1647–8.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. 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

34. 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

35. 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

36. 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.

37. 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.

38. 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

39. 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.

40. 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.

41. 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.

42. Wu D-M, Han X-R, Wen X, Wang S, Fan S-H, Zhuang J, et al. Salidroside Protection Against Oxidative Stress Injury Through the Wnt/β-Catenin Signaling Pathway in Rats with Parkinson's Disease [Internet]. Vol. 46, Cellular Physiology and Biochemistry. 2018. p. 1793–806. Available from: http://dx.doi.org/10.1159/000489365

43. Zhang Y, Wang F, Han L, Wu Y, Li S, Yang X, et al. GABARAPL1 Negatively Regulates Wnt/β-catenin Signaling by Mediating Dvl2 Degradation through the Autophagy Pathway [Internet]. Vol. 27, Cellular Physiology and Biochemistry. 2011. p. 503–12. Available from: http://dx.doi.org/10.1159/000329952

44. Ikeda S. Axin, a negative regulator of the Wnt signaling pathway, forms a complex with GSK-3beta and beta -catenin and promotes GSK-3beta -dependent phosphorylation of beta -catenin [Internet]. Vol. 17, The EMBO Journal. 1998. p. 1371–84. Available from: http://dx.doi.org/10.1093/emboj/17.5.1371

45. Fishell G. Faculty Opinions recommendation of Beta-catenin-mediated Wnt signaling regulates neurogenesis in the ventral telencephalon [Internet]. Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature. 2009. Available from: http://dx.doi.org/10.3410/f.1157012.617095

46. Schiffer C, Platen P. A MULTIVITAMIN-MULTIMINERAL SUPPLEMENTATION DOES NOT AFFECT ENDURANCE EXERCISE INDUCED GLUTATHIONE ALTERATIONS IN FEMALE SPORT STUDENTS [Internet]. Vol. 34, Medicine & Science in Sports & Exercise. 2002. p. S233. Available from: http://dx.doi.org/10.1097/00005768-200205001-01308

47. Larson D, Atalay M, Niskanen L, Hänninen O, Sen CK. EXERCISE INDUCED BLOOD GLUTATHIONE AND PLASMA SUPEROXIDE DISMUTASE RESPONSE IN YOUNG DIABETIC MEN [Internet]. Vol. 27, Medicine & Science in Sports & Exercise. 1995. p. S81. Available from: http://dx.doi.org/10.1249/00005768-199505001-00459

48. Madhanraj P., Nadimuthu, N., Panneerselvam A.. Mycoecology in the Soil of a Casuarina Bioshield Plantation along Southeast Coast of India. Asian J. Pharm. Res. 1(2): April-June 2011; Page 37-41.

49. Ravindra B. Saudagar, Nachiket S. Dighe, Deepak S. Musmade , Vinayak M. Gaware, D. A. Jain. SERM's in Treatment of Breast Tumor. Asian J. Pharm. Res. 1(4): Oct. - Dec. 2011; Page 81-86.

50. Inhibitory Effects of Successive Solvant Extracts of Barleria gibsoni Dalz. on the Proliferation of MDA MB 4355 (Human Breast Tumor) and Hep G2 (Liver Tumor Cell line). Asian J. Pharm. Res. 5(4): 2015; 183-185.

51. V. N. Dange, S. J. Shid, C.S. Magdum, S.K. Mohite. A Review on Breast tumor: An Overview. Asian J. Pharm. Res. 2017; 7(1): 49-51.

52. Akshay R. Yadav, Shrinivas K. Mohite. Tumor- A Silent Killer: An Overview. Asian J. Pharm. Res. 2020; 10(3):213-216.

53. Borkar Sudarshan, Shende Vikas, Chatap Viveknand, Sawant Vilas, R Suresh, Dama Ganesh. Tamoxifen Citrate Loaded Solid Lipid Nanoparticles- A Novel Approach In The Treatment of ER+ Breast Tumor. Research J. Pharma. Dosage Forms and Tech. 2009; 1(2): 143-149.

54. Akshay R. Yadav, Shrinivas K. Mohite. Antitumor Activity of Psidium guajava Leaf Extracts on Breast Tumor Cell Line. Res. J. Pharma. Dosage Forms and Tech.2020; 12(4):298-300.

55. Sarav A. Desai , Prakash S. Sukhramani, Maulik P. Suthar, Vipul P. Patel. Biological Cytotoxicity Evaluation of Sulfonamide Derivatives as Anti-Lung and Anti-Breast Tumor Activity. Asian J. Research Chem. 4(4): April, 2011; Page 671-677.

56. Subramaniam Sivakumar, Sangeetha. D. Identification of New Inhibitor against Mycobacterium tuberculosis using structure based Drug Designing and Docking Studies. Res. J. Pharmacognosy and Phytochem. 2017; 9(3): 173-176.

57. Anjali Soni, Patel Femida, Preeti Sharma. In-vitro Cytotoxic Activity of Plant Saponin Extracts on Breast Tumor Cell-Line. Res. J. Pharmacognosy and Phytochem. 2017; 9(1): 17-22.