COLON CANCER AND THE MOLECULAR DOCKING INTERACTION OF ENDOGENOUS GLUTATHIONE PEROXIDASE ON APOPTOTIC MARKER

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ABSTRACT

Background: In both men and women, colon tumor is the third highest cause of tumor death.. It is located at the digestive tracts lower end. Daily workout may prevent the tumor by inducing endogenous glutathione peroxidase. Nearly 1 million patients receive a diagnosis of colorectal tumor. Over 50,000 people die from this tumor annually.
Aim: To analyse the role of endogenous glutathione peroxidase on apoptotic markers through molecular docking interaction.
Materials and Methods: The molecular docking analysis is a bioinformatic study conducted in private dental college. Exercise induced endogenous glutathione peroxidase is used as target protein The interaction of glutathione peroxidase with protein relevant to colon tumor namely Bcl-2, Bcl-xl and 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 surface representation of glutathione with Bcl-2, Bcl-xl and Bax complex showed good shape complementarity. It shows the positive interaction between glutathione peroxidase with Bcl-2, Bcl-xl, Bax proteins and might have a protective role against colon tumor.
Conclusion: The results concluded that exercise-induced glutathione peroxidase endogenously has interaction with Bcl-xl, Bcl-2, Bax protein and might have a protective role against colon tumor. Exercise is good for both mental and physical health. Regular physical activity improves your overall health. It can improve memory and also reduce the risk factors of chronic diseases.

Keywords: colon tumor; exercise; Glutathione peroxidase; Bax, Bcl-xl; Bcl-2;Innovative method.

INTRODUCTION:

Colon tumor is also known as bowel tumor. Nearly 1 million patients receive a diagnosis of colorectal tumor (1). Risk factors that cause colon tumor include diet, obesity, smoking and lack of physical activities (2) It is located at the digestive tract lower end.. It causes many beneficial effects for health by increasing lifespan (3).

Physical activity that is both regular and vigorous has been scientifically shown. to have a preventive function against tumor, with the ability to cut the incidence by 40%. Breast tumor has the strongest effect (4). Exercise prescription has been shown to improve surgical success rates, reduce symptoms, manage radiation and chemotherapy adverse effects, maintain physical fitness, and improve psychological health.. Exercise actually increases survivorship by 50%-60% in tumor patients(5).

Aerobic exercise is a non pharmacological therapy. It improves systolic and diastolic function. Exercise aids in the regulation of hormone levels in the body. Increased amounts of some hormones raise your chances of getting tumor (5). Exercise hastens digestion, which may minimise the amount of time that a potentially dangerous drug remains in the body.. Some evidence suggests that people who are active their entire lives have the lowest risk of tumor. Exercise may help to fight tumor by changing the inner workings of certain immune cells(6). The experience from our previous studies (7) (8,9) (8)(10)(11)(12)(13)(11,13)(14)(15) (16) have led us to concentrate on the study.

Glutathione peroxidase (GPx-1) is the most important antioxidant enzymes in mammalian cells, inactivating hydrogen peroxidase and preventing oxidative damage. (17). It helps in maintaining the

cell membrane structure. In review they discussed that the effect of daily exercise increases the regulation of both antioxidant enzymes and glutathione antioxidant defence system. It reduces the risk of cellular injury, improves performance and delays muscle fatigue(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 study aims is to analyze the role of endogenous glutathione peroxidase on apoptotic markers through molecular docking interaction.

MATERIALS AND METHODS:

The molecular docking analysis is a computer based study conducted in private dental college. Endogenous glutathione peroxidase which is induced after the exercise is used as a target protein. The interaction of glutathione peroxidase with protein related to colon tumor namely Bcl-xl, Bax, Bcl-2 are included for docking analysis.

Retrieval of protein structure

In order to understand the interaction mechanisms among Glutathione peroxidase and Bcl-2, Bcl-xl, Bax proteins, These proteins' 3D crystallographic structures were procured from the Protein Data Bank. The 3D structures of proteins were gathered as follows BAX Glutathione peroxidase (Pdb id: 2I3Y), Bcl-2 (Pdb id: 4MAN), Bcl-xl (Pdb id:4QVF), Bax (Pdb id: 6EB6)(39).

Protein-Protein Docking

The Patchdock server was used to find out the interaction between Glutathione peroxidase and Bcl-2, Bcl-xl, Bax proteins. A molecular docking algorithm called Patch Dock (http://bioinfo3d.cs.tau.ac.il/PatchDock)(40,41) was used to study the interaction between SOD with Bcl-2, Bcl-xl, Bax proteins. The Patch Dock service calculates docked transformations that result in strong molecular dimension complementarity. The programme divides the Connolly dot surface representation of the molecules into concave, convex, and flat patches. 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. The result was retrieved from the e-mail address given during the docking process and downloaded. 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.

Using the academic version of the Pymol, the residual interactions between docked complexes were viewed. The intensity of colour for interactions was clearly noticeable here, and the results were exported for further analysis (42). Pdbsum was used to find out what kinds of interactions Glutathione Peroxidase has with Bcl-2, Bcl-xl, and Bax proteins.

Result:

In the present study, the interaction between Glutathione peroxidase and Bcl-2, Bcl-xl, Bax proteins were studied using the patch dock server. Based on the shape complementarity patch dock generated so many docked complexes, but based on the theme scoring system it ranked the complex and sent us the mail with the top 20 docked complexes. From that list the best complex was selected for each

complex. In order to identify the interacting amino acids residues, the selected complex was visualized using pymol.

The results showed that Glutathione peroxidase interacts with Bcl-2, Bcl-xl, Bax proteins. Some amino acids residues in Glutathione peroxidase like GLY-38, THR-39, ILE-40, TYR-41, ASP-42, GLU-44, ALA-45, ILE-46, LEU-48, ASN-48, LYS-50, TYR-53,VAL-54, SER-55, PHE-56, ASN-68, TYR-72 and LEU-82 predominantly involved to complex with Bcl-2, Bcl-xl, Bax proteins (fig 1,2,3). Results of this study used to understand the role of endogenous glutathione peroxidase in colon tumor.(Table 1)

Table 1: Molecular docking results of glutathione with Bcl-2, Bcl-xl, Bax proteins

S.NO	Protein name	score	Atomic binding energy
1	Bcl-2	17964	-270.22
2	Bcl-xl	11634	-331.96
3	Bax	12980	-259.22

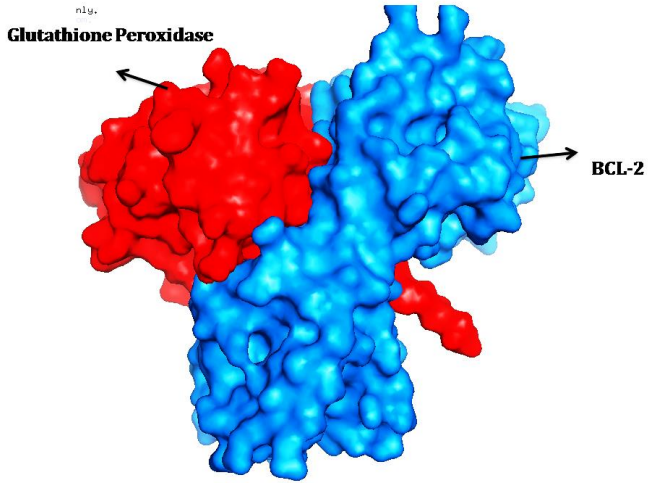

Fig 1: The figure represents the protein-protein interaction between Bcl-2 and glutathione peroxidase compounds

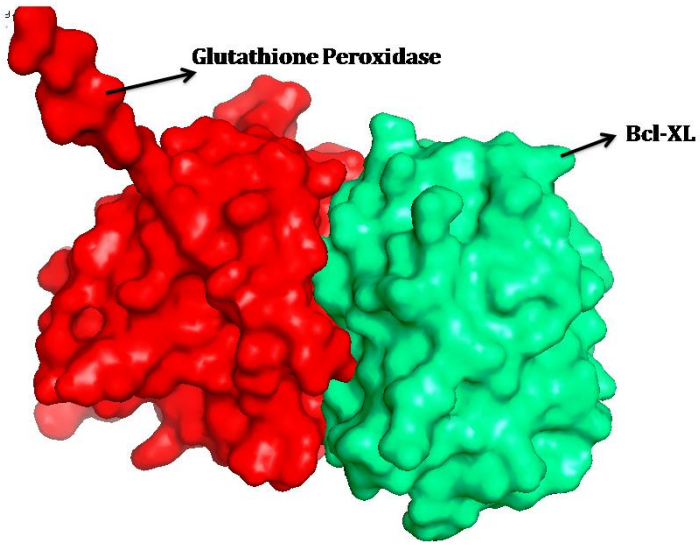

Fig 2: The figure represents the protein-protein interaction between Bcl-xl and glutathione peroxidase compound

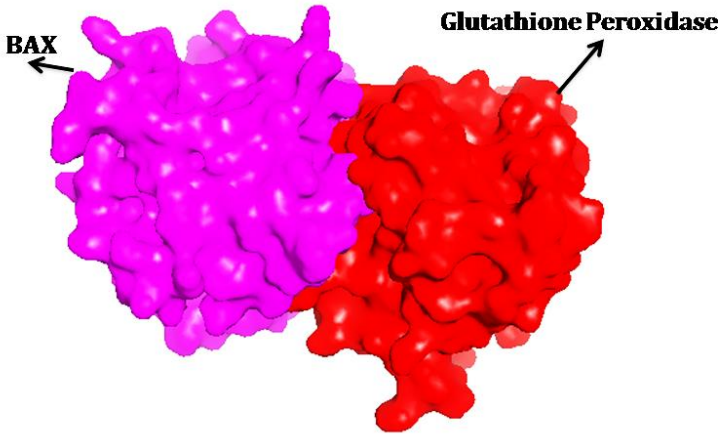

Fig 3: The figure represents the protein-protein interaction between Bax and glutathione peroxidase compound

DISCUSSION:

From the result of the docking study the surface representation of glutathione with Bcl-2, Bcl-xl, Bax proteins complex showed good shape complementarityEndogenous glutathione peroxidase, which is activated by exercise, may protect against colon tumor. We learned from this study that glutathione may play a role in the Bcl-2, Bcl-xl, and Bax signalling pathways in colon tumor.

Nearly all biochemical processes are the result of various types of protein-protein interactions in biological systems (PPIs). As for other biomolecules, proteins bind to themselves, such as nucleic acids, organic or inorganic cofactors, and so on. Thus, day by day, the concepts about PPIs are becoming important, and it has therefore become necessary to have a reasonable understanding of PPIs for biologists. Protein-protein interactions (PPIs) have been common therapeutic targets in the last couple of decades because PPIs are involved in effecting regulatory changes in response to

external stimuli. In tumor, metabolic diseases, neurological disorders, and several other diseases, various PPI targets have been implicated. There are numerous PPIs that detect both experimental and analytical methods developed by various laboratories. The above experimental instruments can yield exact results, but time is the biggest issue with them. These experimental approaches are procedures that are long. Besides that, these approaches are labour intensive and very expensive. A variety of computational algorithms have been developed in order to solve these problems. Patch dock software is the most widely used computational method. It is a molecular docking algorithm based on geometry. It is aimed at discovering transformations of docking that generate strong complementarity of molecular shape.

Glutathione peroxidase has a positive interaction with Bcl-2. Bcl-2 is a prototypic anti-apoptotic protein. Human health benefits from physical activity. Bcl-2 regulated autophagy produced by exercise is needed for muscle glucose homeostasis. Exercise is a newly recognized stimulus that causes autophagy in living cells (in vivo) (43). It prevents tumor from spreading and aids in the treatment of tumor. Bcl-2 is an antioxidant that scavenges peroxidase and N-acetylcysteine, and it suppresses most kinds of apoptotic cell death. Glutathione peroxidase, on the other hand, prevented apoptosis. (44).

Glutathione peroxidase has a positive interaction with Bcl-xl. According to a comparable study, Bcl-2 and Bcl-xl have 43 percent amino acid identical and share a sequence similarity region. It keeps cells from going into apoptosis in response to a variety of stimuli. Plays an important function in tumour growth and treatment resistance. (45). When compared to normal human bronchial epithelial cells, they discover two novel Bcl-xl inhibitors (BXI-61 and BXI-72) that have specific toxicity against lung tumor.(46).Glutathione peroxidase interacts positively with Bax. (47). It is a computer based study and it cannot be generalized. So further research need to be done in in-vitro study

CONCLUSION:

Exercise-induced glutathione peroxidase endogenously has interaction with Bcl-xl, Bcl-2, Bax protein and might have a protective role against colon tumor. Exercise is good for both mental and physical health. Regular physical activity improves your overall health. It can improve memory and also reduce the risk factors of chronic diseases.

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

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