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Molecular Docking Study to Identify Natural Anti-Cancer Compounds as Possible Antagonist for Periostin Inhibition

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ABSTRACT

Background: Periostin, a matricellular protein, is the CNN family member protein which regulates various cancer stem cell maintenance, cancer progression and metastasis. It is also involved in cell invasion, inflammation, epithelial-mesenchymal transition, tumour growth and angiogenesis. To date, the molecular mechanisms associating periostin in relation to cancer in humans have not been fully illuminated.

Materials and Method: This study includes the identification of potential antagonist for cancer inhibition through bioinformatics technique. Around 151 phytochemicals were docked with periostin to check their effectiveness on the marker.

Results: Curcumin, luteolin and silibinin had the highest docking score, binding energy and glide gscore of the 151 phytochemicals selected to bind with periostin.

Conclusion: Molecular docking of periostin with natural compounds from various plants and vegetables provide insight into high binding affinity and molecular-level interactions to combat with different cancer targets.

Keywords: Periostin, oral cancer, bioinformatics, Molecular docking.

INTRODUCTION

World Health Organization has recognized oral cancer as the sixth most common cancer in males [1] and tenth most common in females.[2] But even after so many advances in treatment, the five-year survival rate of oral cancer patients still ranges between 40-50% only owing to the lack of early diagnosis.[3] This can be achieved by diagnosing molecular changes in tissues through various molecular biomarkers very early into the disease.

Periostin is one such biomarker that is expressed during molecular changes. It is one of the matricellular proteins that is found in stromal cells of tissues.[4] It is also called osteoblast-specific factor 2 as it was first found in an osteoblastic cell of a mouse in 1993 by Takeshita et al. Its structure is similar to a protein called Fasciclin 1 that is found in insect Drosophila.[5] Various studies have proved that periostin is increased in oral cancer patients and is associated with an increase in angiogenesis and metastasis.[6]

In the era of green evolution various studies are being carried out to find plants and vegetables that can help in treating cancer as they have very few side effects and can help in the prevention of

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disease as well. *In silico* analysis has become the new trend to assess the protein pathways in cancer [7]. It also gives the idea about the effect of various drugs, natural or artificial and how they can act on the proteins/genes to help in treating or preventing cancer.[8] Hence we carried out this *in silico* study to find the phytochemicals that can bind with periostin and can be used as a targeted therapy to treat oral cancer.

MATERIALS AND METHODS

Receptor-ligand selection and preparation

The three-dimensional structures of various edible vegetables, spices and plants were chosen for the molecular docking experiment. Total 151 phytochemicals were retrieved from Dr Duke's Phytochemical and Ethnobotanical Database (https://phytochem.nal.usda.gov/phytochem/search)[9] and prepared in Marvin Suite software followed by alignment, cleaning and energy minimization process with the help of Amber 03 force field and steepest descent method [10,11]. The crystal structure of periostin (PDB ID: 5yjg) was fetched from RCSB (https://www.rcsb.org/) which contains 628 amino acids length and 2.399 Å resolution. For docking study, all phytochemicals and protein were prepared in Schrodinger software which includes water removal, the addition of hydrogen bond and binding site identification.

Molecular docking

To perform molecular docking, binding site identification is necessary for every protein [12]. Due to the unavailability of the active site Schrodinger sitemap tool was used, which generated different sites based on its algorithm and site score function. The topmost scored site was selected as the active site, and 151 phytochemicals were docked on this site though glide tool with extra-precision (XP) method which relies on the below equation:

$$\text{XP GlideScore} = E_{coul} + E_{vdW} + E_{bind} + E_{penalty}$$

$$E_{bind} = E_{hyd\_enclosure} + E_{hb\_nn\_motif} + E_{hb\_cc\_motif} + E_{PI} + E_{hb\_pair} + E_{phobic\_pair}$$

$$E_{penalty} = E_{desolv} + E_{ligand\_strain}$$

The topmost docked phytochemicals were identified as a potential inhibitor of various cancer targets. The authentication of phytochemicals binding wasrelied on best binding energy and its interactions which were visualized by discovery studio visualizer. [7,13].

RESULTS

To identify the inhibitory mechanism of selected plant phytochemicals against receptor, molecular docking was performed using Maestro suite of Schrodinger software. Depending upon sampling methods and scoring functions extra-precision (XP) Glide was chosen for this experiment which ranks the ligand respected to the confirmation of the receptor. The top-ranked site from sitemap tool was implied as an active site, and 151 phytochemicals were docked in this site. Among them, top-most phytochemicals curcumin, luteolin and silibinin were considered as potential inhibitors for targeted protein. Table-1 represents the Docking score, binding energy, XP GScore, glide gscore and energy of selected phytochemicals. In this, glide score depicts the most prominent in the extra precision docking calculated in kcal/mol, where higher the negative energy means potential binding. Figure-1 to Figure-3 shows the binding of these phytochemicals with targeted protein (periostin) in three as well as two dimensions. The two-dimensional images illustrate various interactions that were generated with specific distance with proteins, amino acids which includes van Der Waals, hydrogen bond, Pi-alkyl, Pi-Cation, salt bridges, etc.

Table: 1 Molecular docking results of selected ligands

Sr. No.	Phytochemical name	docking score	XP GScore	glide gscore	glide energy
1	Curcumin	-6.56	-6.904	-6.904	-51.861
2	Silibinin	-6.152	-6.164	-6.164	-44.343
3	Luteolin	-5.565	-7.277	-7.277	-36.939

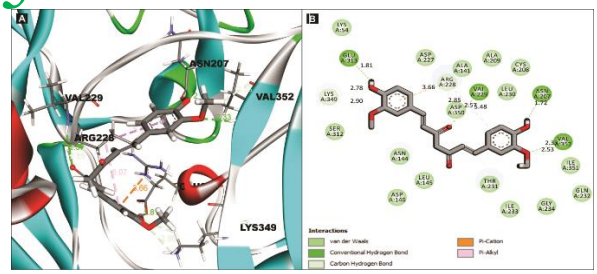

Fig1: (A) Binding pose of Curcumin with the crystal structure of Periostin (PDB ID: 5yjg) and (B) 2D representation of receptor-ligand interactions.

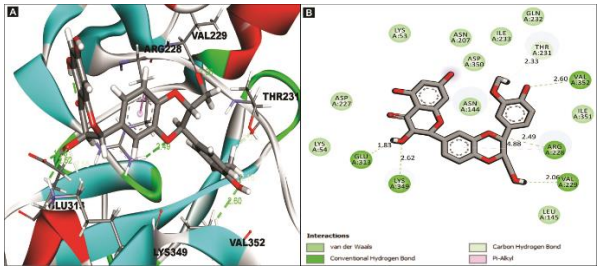

Fig2: (A) Binding pose of Silibilin with the crystal structure of Periostin (PDB ID: 5yjg) and (B) 2D representation of receptor-ligand interactions.

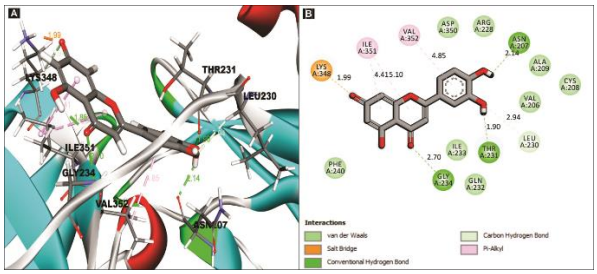

Fig3: (A) Binding pose of Luteolin with the crystal structure of Periostin (PDB ID: 5yjg) and (B) 2D representation of receptor-ligand interactions.

DISCUSSION

Periostin was first called osteoblast-specific factor 2 and was isolated from mouse cell lines by Takeshita et al. in 1993. It was later renamed as Periostin as it was expressed in abundance in periosteum surrounding the bone.[14,15] Its expression is low in tissues having less fibroblast content like the spleen and is more in tissues with high fibroblast content like skin and breast.[16] It also attaches to ECM proteins like fibronectin, tenascin C, collagen V to help in ECM remodeling.[14,17]

EMT is the basic step required for metastasis as it is responsible for detachment of primary tumour epithelial cells to distant organs.[14]Periostin causes expression of MMP 9, 10 & 13, which inturn leads to ECM degradation needed for local spread of tumour cells.[15] The microenvironment in which tumour exists is made of tumour cells, surrounding blood vessels, immune cells, cancer-associated fibroblasts (CAFs), ECM and signaling molecules.[18]Periostin binds to integrins αvβ3, αvβ5 and α6β4 leading to activation of PI3K/AKT and FAK signaling pathways by recruiting EGFR. These pathways promote all steps of tumour invasion like cell survival, migration, invasion, and angiogenesis.[19]

The lower the degree of tissue differentiation, the higher is the expression of periostin. Thus it predicts invasiveness of a lesion and is identified as an invasion promoting factor.[20] Expression of periostin is more in metastatic tumours as compared to primary ones.[16] New capillaries are required to provide nutrients and oxygen to solid tumours when they grow beyond 2-3 mm. Periostin is associated with an increase in blood vessel density in tumours and promotes capillary formation from endothelial cells of existing vessels.[21] Siriwardena et al. also proved that OSCC tumours showed more blood vessel density in periostin positive tumours as compared to periostin negative tumours.[21]

The *in silico*screening of selected anti-cancerous compounds were docked with periostin protein which identified the potential compound. Based on results, three compounds were chosen as anticancer inhibitors, curcumin, silibinin and luteolin with the glide binding energy of -6.904, -6.164 and -7.277 kcal/mol respectively. Curcumin possessed eight hydrogen bonds at Asn 207, Arg 228, Val 229, Glu 313, Lys 349 and Val 352 with 1.72, 2.85, 2.57, 1.81, 2.78, 2.90, 2.33 and 2.53 Å. It also bounded at Arg 228 with 3.66 and 5.48 Å through pi-cation and pi-alkyl bonds. Silibilin depicts six hydrogen bonds at Arg 228 (2.49 Å), Val 229 (2.06 Å), Thr 231 (2.33 Å), Glu 313 (1.83 Å), Lys 349 (2.62 Å), Val 352 (2.60 Å) and one pi-alkyl bond at Arg 228 with 4.88 Å distance. With respect to luteolin, three hydrogen bonds (Asn 207, Leu 230, Thr 231, Gly 234), one salt bridge (Lys 348) and three pi-alkyl bonds (Ile 351 and Val 352) were observed respectively. These results illustrate the inference of electrostatic and non-covalent interactions were most promising in the binding process as well as inhibition of the selected periostin protein.

CONCLUSION

Periostin is an important target enzyme in terms of controlling epithelial-mesenchymal transition. The bioinformatics analysis of periostin with natural compounds against cancer was performed with the most promising results through molecular docking analysis. Among 151 compounds curcumin, silibinin and luteolin were formed as potential promoters which can aid the periostin activity to inhibit the cancer targets. The hydrophobic properties of Asn 202, Asn 207, Val 229, Thr 231, Gly 234, Glu 313, Lys 348, Lys 349, Val 352, Val 353 conceded the binding affinity towards periostin assistance. Hence we can assume that curcumin, silibinin and luteolin compounds can be used as anticancer drugs.

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CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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