SUNITHA V.R

EXECUTIVE SUMMARY

A COMPARATIVE DOCKING STUDIES WITH A VIEW TO PREVENT THE GROWTH OF LEIOMYOMAS A UTERINE FIBROID USING A COMMERCIAL AND AN OPEN SOFTWARE

Uterine leiomyomas(Fibroids) are one of the common reason a hysterectomy is performed and the number one gynecological reasons behind hospital admissions. These are benign monoclonal tumor that arise from the smooth muscle walls of the uterus and is found in women of reproductive age. The exact cause of fibroids is unknown. Research and clinical experiences point to genetic, hormonal , growth factors, environmental exposures as factors contributing to the growth of fibroids. As surgery is the only definite treatment for fibroids and no medication without sideeffects is available , the potential of phytomolecules to prevent the growth has been investigated. Evidence points to the involvement of Transforming growth factor beta signaling in the development of leiomyoma and among the three isoforms, TGFB3 play a significant role in leiomyoma development by promoting cell growth and fibrogenic process. The investigation focussed on finding TGFB3 inhibitors from plant world against Uterine leiomyoma using molecular docking studies. The phyto molecules exhibiting antitumor properties were retrieved and studied using molecular docking. Pharmacogenomic approach , Proteomics, E-pharmachopore based screening and Qikprop were also conducted.

The influence of epigenetic, environmental and metagenomics factors in predicting the proneness to the growth of fibroids have been carried out. Among the epigenetic factors evolutionary history have been found to be the principal feature for DNA methylation for TGFB3 gene. Major disease causing SNPs rs398122984, rs587777617, rs796051885, rs796051886 have been identified as genetic signature towards the proneness of the disease. Proteomics were carried out to find the stable protein. Proteins of the corresponding gene were retrieved and characterization studies performed which resulted in protein having ID:1KTZ as the stablest one. A drug, Asoprisnil that targets TGFB3 were identified and selected as a reference molecule . E-pharmacophoric features of the reference molecules were obtained through docking studies . Two interactions, pi-pi interaction with the amino acid residue Arg25 and hydrogen bond with the residue Val33 were observed in the docking study. The docking results were then used to

find the structure based pharmacophoric features which helps to identify the best featured functional groups. The pharmacophoric features obtained were then further considered for the screening of phytomolecules. Among sixty, twenty three phyto molecules with pharmacophoric features similar to the reference ligand were obtained which were then further filtered based on their ADMET properties. Filtering the 23 molecules obtained after screening on the basis of Qikprop resulted in seven phyto molecules. These obtained compounds were then further docked against the selected protein target . Binding energy of the commercially available drug (-0.589 Kcal/mol)was used as reference to compare the binding energy of the phytomolecules. All the seven phytomolecules showed interaction with the aminoacid residue Arg25, indicating its significant role in the inhibition. Interaction of the protein with the phytomolecules also showed Hydrogen bonding as a common interaction showing its important role in structure and especially in inhibition of a complex. Docking scores of phytomolecules obtained from both the tools, Glide module of Schrodinger suit and Autodock exhibited docking values above -0.589Kcal/mol (reference drug molecule). These seven phytomolecules Quercetin, Ellagic acid, Luteolin, Apigenin, Genistein, Naringenin and Isoliquiritigenin emerged as promising candidates can be considered as good candidates as inhibitors to the protein TGFB3. Results suggest that all docking programs studied here do a reasonable job in docking and should aid significantly in the drug discovery process.