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In Silico Techniques for the Identification of Novel Natural Compounds for Secreting Human Breast Milk

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Abstract

Low milk supply is an abounding problem endured by the pregnant women in every country. Many of them consume herbs and vegetables to stimulate the secretion of the breast milk. Some of the commercially available drugs that are used for the purpose are domperidone, metachlopromide (reglan) and many more. The main objective of the research work is to make out the chemical components enclosed within the natural galactogogues (milk stimulating products).? A total of 157 compounds were collected. Most of them were found in herbs such as alfalfa, fenugreek and other sources like ginger, onion, oats etc. In view of the project the prolactin receptor signaling pathway was taken into account since prolactin hormone is the chief hormone leading to lactation. For the purpose, the prolactin receptor complexed with prolactin hormone (3NPZ) was spotted as the targeted protein. The collected molecules were screened on the basis of Lipinski?s rule, and docking score. From the screened compounds the better interacting compounds were made out on the basis of their binding with the receptor through the Q-site finder. namely Sesamin, Quercetin, Kampferol, Trifoliol, Limonin were found to be the better interacting components that can be tabbed for the lead compound for stimulating the breast milk production.

Introduction

Remittent lactation in pregnant women is a common problem prevailing all over. It mortifies both the mother and the baby [1]. Depleted prolactin [2] secretion is the main factor responsible for this, accompanied with the new mother's stress level, nutrition, fluid intake, adequate nipple stimulation and baby's sucking technique all play a part in how much milk will be produced. Domperidone [3] are commercially available drug to alleviate the situation. Natural remedies incorporates consumption of galactagogues [4] including herbs like alfalfa[5], fenugreek [6]and other sources like onion, ginger, oats etc[7]

Human lactation is signaled through prolactin receptor pathway [8] associated with many other pathways. The prolactin receptor pathway is signaled with binding of the prolactin hormone to the receptor. Prolactin receptor is a cytokine receptor that triggers the second messenger JAK-STAT [9] pathway, important in the activation of the casein [10] gene during milk production. Dimerization of the prolactin receptor with the prolactin hormone activates the Janus kinase 2, a tyrosine kinase that initiates the JAK-STAT pathway through phosphorylation of JAK proteins activating the dormant kinase activity of the receptors. The activated receptors add a phosphate group to a tyrosine residue (Y) of a particular STAT protein (in this case, Stat5 [11]). This allows Stat5 to dimerize, be translocated into the nucleus, and bind to particular regions of DNA. In combination with other transcription factors (which presumably have been waiting for its arrival), the STAT protein activates transcription of the casein gene. GR is the glucocorticoid receptor, OCT1 [12] is a general transcription factor, and TBP is the set of proteins responsible for binding RNA polymerase.

Methods

Collection of Compounds????

The biochemical compounds found in the ordinarily used herbal and natural lactagogues were collected through the literature survey. These substances include phytoestrogen [13, 14], natural plant sedatives, plant sterols and saponins, and flavonoids, among others. These compounds were screened through Lipinski?s Rule of Five and their structures were downloaded in the SDF file format from the Chemical Database, PubChem [Fig 1.a, 1.b].

Energy Minimization

The screened biochemical compounds were energy minimized by using MarvinSketch, a powerful chemical editor for drawing chemical structures, queries and reactions. The energy minimized conformers were

further used for the docking purposes as ligands for the selected receptor molecule.

Fig 1.a 3Dimensional Structure of SESAMIN

Fig 1.b 3 Dimensional Structure of Domperidone

Selection of the receptor

In accordance with the literature studies? and the research to be undergone, the Prolactin Receptor (PRLR) complexed with the natural hormone Prolactin (PRL) [15],? was selected as the target receptor for the study and the structure was extracted from the Protein Data Bank, 3NPZ being the PDB ID for the protein molecule.

Docking of the Receptor with the Ligand

The energy minimized ligands and the chosen receptor protein was subjected to docking using the AutoDock tool and the compounds having the least binding affinity were sorted out. The tabbed compounds were then Hex docked with the target protein and the better interacting compounds were spotted on the basis of their well defined binding to the specific active sites of the target with the help of the Q Site Finder [Fig 2].

Fig 2. Binding site for sesamin

Toxicity Analysis

Toxicity analysis was carried out for the ligand molecules using the online toxicity testing tool, OpenTox. The human health effects such as the carcinogenicity, tendency to cause skin corrosiveness and eye irritation of the ligand molecules were evaluated and the molecules which showed negative results for these effects were eliminated.

Results

Sesamin, Trifoliol, Limonin, Queretin and Kaempferol were found out to be the ones that binds exactly to the 4th ,9th and 10th active sites on the target protein molecule. When docked, Sesamin[16] [Fig 2] bound directly with the 4th and 9th active site on the target, and the other four compounds namely Trifoliol, Limonin[17], Quercetin [18]and Kaempferol [19]fitted directly to the active pocket on the 10th site. The commercial galactagogue, Domperidone, when docked with the receptor was found to be binding with the 4th active site with precision. Thus, Sesamin was found to be in sync with Domperidone according to their affinity to the same active site on the molecule.

Discussion

The primary goal of the research is to make out the chemical components comprised within the galactogogues meant for stimulating the breast milk production.? In view of the project around 157 compounds were taken into account. The chemical components constituted within the tabbed galactogogues were then listed out. The prolactin receptor signaling pathway leading to the human lactation was taken into account. Prolactin receptor complexed with the prolactin hormone was spotted as the target protein. The molecules were screened and energy minimized and subjected for docking.

Fig 3. Graph Plot of the Compounds vs Commericial Drug

It was found out that from the 157 molecules selected from naturally occuring galactagogues, 5 compounds, namely, Sesamin, Trifoliol, Limonin, Quercetin and Kaempferol were found to be having the least docking score, low toxicity, and the best binding affinity to the specific, 4th, 9th and 10th active sites of the receptor [Fig 3]. Sesamin bound to the 4th (Lys, Thr, Val, Pro, Ile, Asp, Trp, Phe, Met) and the 9th site(Asp, Arg, Val, Lys, Thr, Tyr, Trp, His, Gly), while the other five molecules fitted to the 10th pocket on the target, Phe, Ile, Tyr, His, Arg, Val, Asp being the supporting amino acids on the 10th site.

Conclusion(s)

The insilico approach suggests novel target for milk production, and it proves the natural compound Sesamin, bark of *Fagara* plants and from sesame oil can act as a lead based molecule for more milk production by activating the prolactin receptor.

Illustrations

Illustration 1

Fig 1.a 3Dimensional Structure of SESAMIN

Illustration 2

Fig 1.b 3 Dimensional Structure of Domperidone

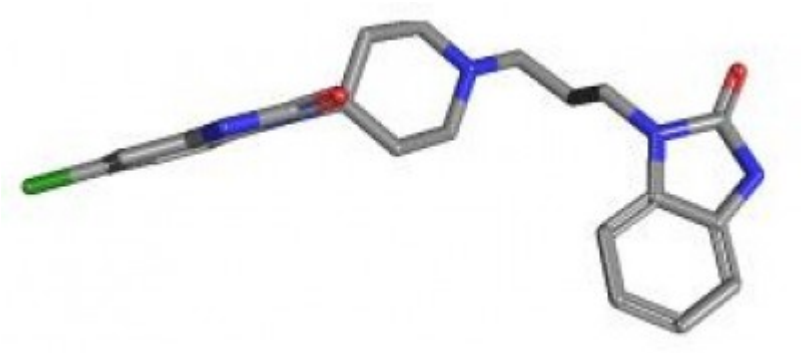


Illustration 3

Fig 2. Binding site for sesamin

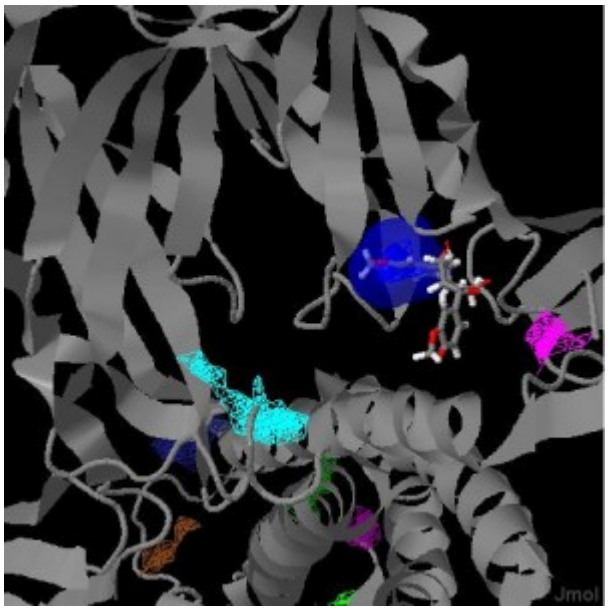
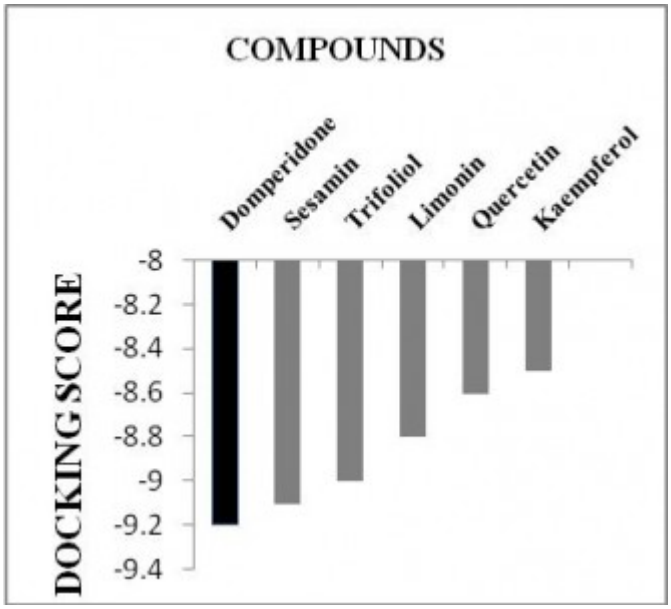


Illustration 4

Fig 3. Graph Plot of the Compounds vs Commericial Drug



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