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Screening of Natural Inhibitors of Aromatase for the Treatment of Breast Cancer: An *Insilico* Approach

Pranav Tripathi[1], Devbrath Singh[1], Biplab Bhattacharjee[2] and Prachi Srivastava[*]

[1]Amity Institute of Biotechnology, AMITY University, Lucknow Campus, U.P., India
[2]Institute of Computational Biology, Bangalore, India
**Corresponding Author E-mail: p.srivastava2@gmail.com*

Abstract

Traditionally, drugs were discovered by testing compounds synthesized in time consuming multi-step processes against a system of *in vivo* biological screens. Promising compounds were then further studied in development, where their pharmacokinetic properties, metabolism and potential toxicity were investigated. In current course of work a study on herbal lead compounds are mentioned and further their potential binding affinity to the effectors molecules of major disease like Breast Cancer. Clinical studies demonstrate a positive correlation between the extent of production of estrogen from androstenediol after menopause and breast cancer through the release of epidermal growth factor (EGF). Therefore, identification of effective, well-tolerated aromatase inhibitors represents a rational chemo preventive strategy. Results investigated from the current study are showing the effects of naturally occurring non protein compounds propolis and curcumin that significantly inhibits aromatase. Although other four compounds have also been investigated as better inhibitors in comparison of various drugs available in market. Due to high ligand binding affinity of curcumin and propolis towards aromatase introduce the prospect for their use in chemopreventive applications in addition as they are freely available natural compounds that can be safely used to prevent breast cancer.

Introduction

The term "breast cancer" refers to a malignant tumor that has developed from cells in the breast.[1] Usually breast cancer either begins in the cells of the lobules, which are the milk-producing glands, or the ducts, the passages that drain milk from the lobules

to the nipple. Certain molecular changes at the level of DNA can change normal breast cells to cancer cell. Some inherited DNA changes (mutations) can increase the risk for developing cancer and cause the cancers that run in some families. For instance, BRCA1 and BRCA2[2] are tumor suppressor genes which in normal condition suppress the tumor formation.

Main cause of breast cancer is the activity of estrogen as it releases the heparin bound epidermal growth factor [3]. The two organs responsible for the production of this hormone are ovary and adrenal gland. One of the potent method to check the progression of Breast Cancer is the inhibition of aromatase enzyme. Although metabolically it happens after menopause, hence it can be the choice of target for cure of Breast Cancer in postmenopausal women. Aromatase inhibitors[4][5] are a class of drugs used in the treatment of breast cancer in postmenopausal women.

Materials and Methods

Databases and tools used

PubChem,, Marvin Sketch, Protein data bank, Argus Lab, QUANTUM 3.3.0 and ADME-T online software of pharma-algorithms.

Methodology: Collection of target molecule via literature study, collection of information regarding target molecule of breast cancer, searching of natural compounds using various data bases, journals & articles and searching for small molecule that is not commercialized is done through data mining and structure of target was retrieved through Protein Data Bank. Retrieved structures for the collected molecules through PubChem. Energy minimization of each selected ligand molecule was done by using Marvin Sketch. Docking of protein 3EQM[6] with natural compounds in QUANTUM3.3.0, ARGUS LAB AND HEX at default parameters. Similarly the drugs were docked with same protein. IC_{50} value of the lead compound was calculated by QUANTUM 3.3.0. The ADME-T analysis is done using the online software of pharma-algorithms.

Results

The compounds were screened firstly based on the Lipinski's rule of five. The final list of selected compounds is given in TABLE 1.

Table 1: Screened Natural Compounds

Natural Compound	Molecular weight	X-log value	H-bond acceptor	H-bond donor
1: Curcumin	368.3799	3.2	6	2
2: Catechin	290.26806	0.4	6	5
3: Matairesinol	358.38508	3.3	6	2
4: Piperine	285.33766	3.5	3	0
5: Propolis	438.42668	3.5	8	2

6: S-allylcysteine	161.22204	-2.1	3	2
7: Formononetin	268.26408	2.8	4	1
8: Secoisolariciresinol	362.41684	2.5	6	4
9: 3,3-diindolylmethane	246.30646	4.3	0	2
10: Genistein	270.236900	2.7	5	3

The quantum docking scores are given in Fig 2. These scores establish curcumin a better compound in comparison to various commercial drugs.

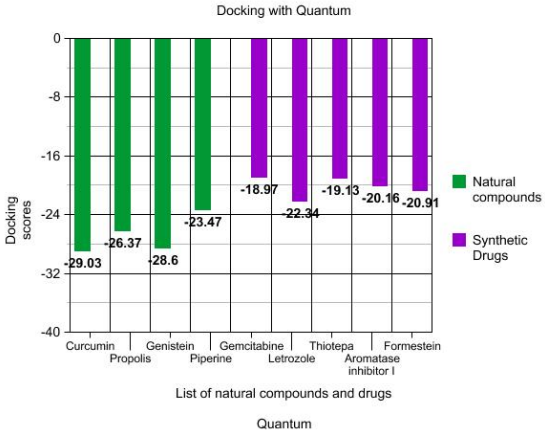

Figure 2: Docking scores of Quantum.

The docking scores of Argus Lab shows the best results for curcumin and curcumin is the only compound in the above mentioned list that gave an E_{total} value of -22.98 on rigid docking that is through Hex.

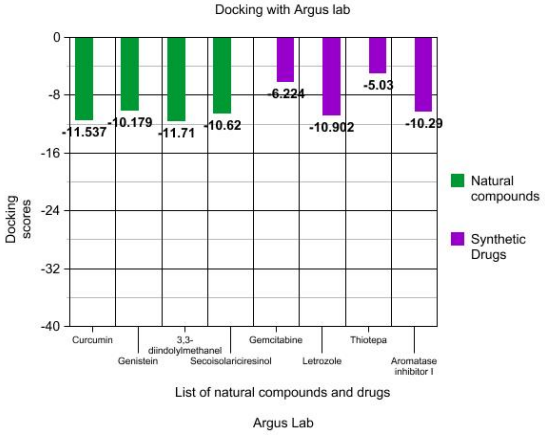

Figure 3: Docking scores of Argus Lab.

The IC50 calculation for curcumin was done using Quantum 3.3.0.

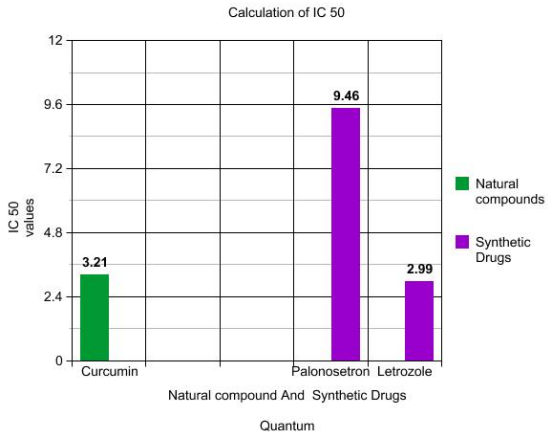

Figure 4: IC50 calculation for curcumin.

Discussions

The ADME properties retrieved using ADME-T online tool of pharma algorithm showed satisfactory results for the absorption, distribution, metabolism, excretion and toxicity of curcumin.

ADME TABLE for curcumin is given in TABLE 2.

Table 2: ADME VALUES from pharma-algorithms.

MOLECULE	ADME Properties				
	Oral bioavailability	Solubility	Drug binding to plasma protein	vd (volume of distribution)	AMES TEST
Curcumin	%F(Oral) > 30%: 0.231 %F(Oral) > 70%: 0.044	**-4.38**	**%PPB: 96.36% LogKaHSA: 4.13**	**0.67 L/kg**	**0.391**

Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent[7][8]. In addition to its use as a spice and pigment, turmeric has been used in India for medicinal purposes from centuries[8].To see the current significance of herbal compounds in current course of study we screened out some natural compounds inhibiting aromatase for the treatment of breast cancer like-curcumin, catechin[9], matairesinol[10], piperine[11], propolis[12], s-allylcysteine[13], formononetin[14], secoisolariciresinol[10], 3,3diindolylmethane[15] & genistein[16]. On the basis of results of docking score we can conclude that natural compound curcumin from *Curcuma longa* is found to be the best in comparison with synthetic drugs like

gemcitibine, letrozole, thiotepa and palonosetron. Further curcumin is showing better pharnmacokinetics and pharmacodynamics results and also reveals very good properties of acting as a natural aromatase inhibitor.Thus this compound can be considered a better compound against Breast Cancer.

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