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Influence of Mangifera Indica on Breast cancer: A Molecular docking approach

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Abstract

Cancer is the second disease with highest rate of mortality in India. Numerous types of cancers are observed in India like breast, prostrate, pancreatic and lung. Amongst the different types of cancer breast cancer is the most common in all age groups in India. Three types of breast cancer are prevalent amongst which triple negative breast cancer has the highest rate of mortality. Treatment methods for treating breast cancer are laser, chemotherapy and replacement. All these treatment methods are effective in treating this disease but they have a lot of side effects and they are too expensive.India has a tradition of Ayurveda since centuries. Numerous ayurvedic plants are used to treat a number of diseases like diabeties, inflammation and cancer. One such Ayurvedic plant used is *Mangifera Indica*. *Mangifera Indica* is a flowering plant and it belongs to family Anacardiaceae. It is used for treatment of diseases like skin disorders, gastric disorders etc. Here in we explored the different constituents present in *Mangifera Indica* against cancer using molecular docking and bioinformatic tools. So we have examined all phytochemicals in mango plant against breast cancer using numerous bioinformatic tools. Amongst all the phytochemicals, Mangiferin proves out to be the most promising candidate for breast cancer.

Keyword: Anticancer, Mangiferin, Phytochemical, Bioinformatic tools

Introduction

Cancer has been identified as the leading cause of non-communicable disease mortality globally, and is responsible for significant morbidity and costs to healthcare systems. Cancer incidence and mortality has been increasing at a greater rate than population growth alone could account for different types of cancer. Breast cancer is most commonly causing cancer among women, and it's impacting around 2.1 million women each year causing the greatest number of cancer-related deaths among women. Breast malignancy is an important medical issue and one of the primary reasons for tumor growth-related mortality in women. By far, most breast tumor growth results from the progression of the metastatic phenotype, which is described as malignant cells separating from the essential tumor and spreading to distal destinations in the body for example, the bone, brain, encompassing lymph hubs, liver, and lungs. Breast tumor metastasis is a complex and multistep process that incorporates morphological changes, separation from the cellular layer, expanded versatility and invasion into encompassing tissues, intravasation, flow, bond, extravasation, and development at distal destinations [1].Major depression is an important complication of breast cancer and has prevalence in this population of up to 9.3%. Within the first year after diagnosis, patients with breast cancer are at high risk for depression, particularly if they are premenopausal, are less than 65 years old, have a history of depression, or received chemotherapy. Unfortunately, major depression is a condition that is underrecognized and undertreated among patients with breast cancer. In addition, only 27% of these patients received antidepressant drugs or visited a mental health professional [2]. Evidence suggests that mangiferin could prove to be a beneficial, inexpensive compound for not only maintenance and improving health in the worried well, but also to meaningfully improve the outlook for those with certain cancers (e.g., breast cancer) and reduce the likelihood of developing cancer [3].

Fruits and vegetables have been shown to have anticancer potential owing to the presence of bioactive compounds [4].From that *Mangifera Indica*, (mango tree) is one of the flowering plant species belonging to the Anacardiaceae family. This family includes about 30 tropical fruiting trees with the genus Mangifera [5].From which *Mangifera Indica* which has been cultivated in India for over 4000 years. It is thought to have reached East Asia between the 4th and 5th century BC and cultivated in East Africa and thereafter in Brazil, West Indies, China, United States, Carribean and Mexico, where the climate is conducive for its growth. Among them the leading mango producer country in the world is India, with very little export as most of the produce is consumed within the country [6].

There are various application of all parts of the plant is based on the phytochemicals playing vital role towards proper health promotion, acting as antioxidant, stimulate the human system, in the liver inducing protective enzymes or inhibiting any kind of damage to genetic materials & also has various other activity like antiviral, anticancer, antidiabetic, immunomodulatory, and analgesic effect [5,7-10]. The phytochemicals in the plant include polyphenols, flavonoids, triterpenoids, Mangiferin(a xanthone glycoside), isomangiferin,

tannins and gallic acid derivatives. protocatechic acid, catechin, mangiferin are found in bark[5]. All of which are powerful antioxidant compounds and potential therapeutic agents [6].

Recently, several studies have documented the ability of natural compounds to increase the sensitivity of cancer cells to anticancer drugs by inhibiting efflux transporters. One of the promising natural compounds with anticancer activity and possible chemosensitizing activity is mangiferin [4]. It is now widely accepted that the antioxidant activity of plant-derived compounds is a good indicator of their potent anticancer ability although there is evidence to connect prooxidant activity with the anticancer ability of such compounds as well. Thus, the ability to influence production of reactive oxygen species is crucial to the chemopreventive effect of natural compounds. The potent antioxidant activity of mangiferin clearly indicates that more mechanistic studies need to be designed to fully elucidate its anti-cancer potential [6]. Mangiferin is a naturally occurring glucosylxanthone which is an effective anti-neoplastic agent in malignant cancer types including prostate cancer, nasophyrangeal cancer, breast cancer,lung cancer and ovarian cancer [11].

Mangiferin shows potential cytotoxicity effects on cancer cells and may even induce apoptosis by inhibiting and suppressing nuclear factor kappa B (NF-kB) and NF-κB-inducing kinase . Several literature also report Mangiferin-induced apoptosis, and tumorigenesis through altered gene expression, especially using Bcl-2 and Bax. Definitive activity of this bioactive phytochemical has also been documented on HL-60 cells programmed cell death, ascribed to suppression of Bcl-xL and XIAP expression and inhibition of the NF-kB pathway [12].Using a bioinformatics tool exploration of anticancer properties of mangiferin was done. Docking is a bioinformatic tool used to predict the conformations of the receptor with ligand, when it is in a bound state, forming more stable complex by providing the information about the binding energy, hydrogen bonding and the amino acid residues to which the ligand binds& its bond distance. As the conformation changes the binding affinity of the two molecules changes along with the amino acid residues to which it is binding. Docking, therefore, aids to predict the binding orientations of drug molecules with their target proteins[1]. So here the targeted protein used is PBcl-2so as, we aim to provide summarized account of the therapeutic potential of mangiferin against breast cancer.

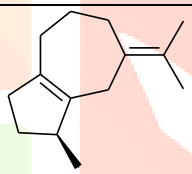
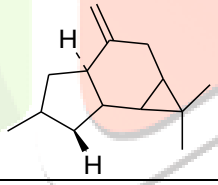
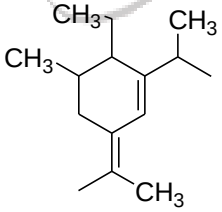
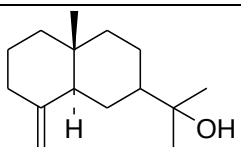
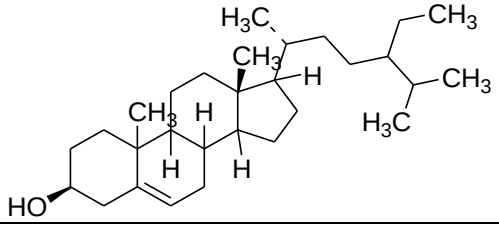
Materials and Methods

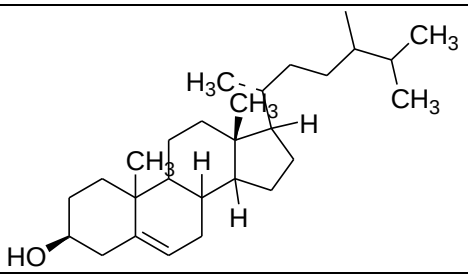
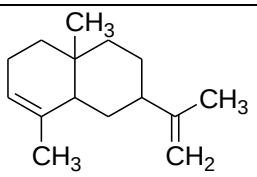
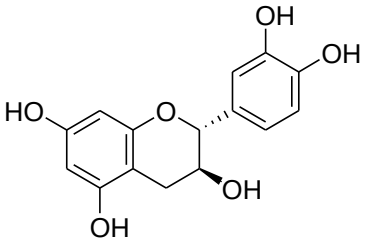
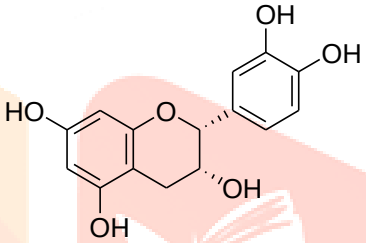
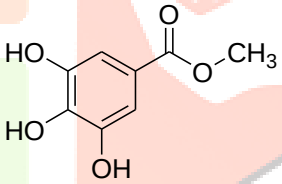
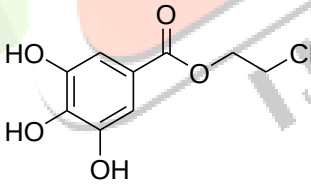
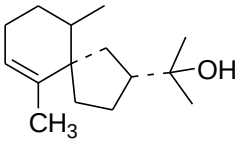
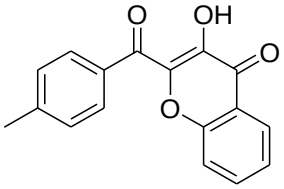
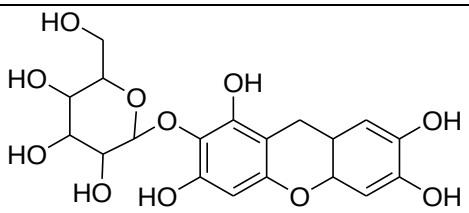
Molecular docking was performed using Autodock Vina software [13]. The different constituents of Mangiferin Indica were draw using Chemdraw software and smilie file was converted into PDB file using an online tool of 3D corina. The PDB files of different constituents were pasted in individual folders and they were further converted in PDBQT files by using MGL tools 1.5.4 software. The PDB file of Breast cancer protein BCL2 was obtained from the depository RCSPDB and cleaned in discovery studio. The cleaned PDB file was then converted into PDBQT file using MGL tools 1.5.4. Both the protein and ligand files were docked using Autodock vina software and an output file containing different conformations was generated. The output obtained was visualized from Pymol tool to obtain images of the ligand and protein.

Results and Discussion

Mangifera Indica is a tropical herb grown in almost every part of the country [14]. The herb is used in Ayurveda from centuries for treating skin and gastric disorders [15, 16]. This herb contains a lot of chemical constituents which altogether contribute for treating diseases. The different constituents have been isolated and reported in literature. Breast cancer is a second leading cause of death in India. Several proteins contribute for cause and migration of breast cancer. One such protein elevated in triple negative breast cancer is BCL2. BCL2 upregulation causes triple negative breast cancer and its inhibition could inhibit the cancer. Herein we have selected the protein of BCL2 and tried to explore the different constituents into its cavity. We have used these chemical structures and tried to put them in to triple negative breast cancer causing protein and elucidated there binding affinity and binding characteristics. The structures of all the constituents are tabulated in Table 1. The binding energy, number of hydrogen bonds and amino acid residues responsible for stabilizing the structure in the protein are tabulated in Table 2. From the results most of the constituents in mango plant inhibit BCL2 protein but amongst all M14 shows -6.0Kcal/mole and M13 shows -6.8 Kcal/mol.

Table 1. Different chemical constituents of Mangifera Indica

SR NO.	Code	Structure
1	M1(A- guanine)	
2	M2 (Aromandrene)	
3	M3 (B –Eleman)	
4	M4 (B –Eudesmpl)	
5	M5 (B- Sitosteroi)	

6	M6 (B-Campesterol)	
7	M7 (B-salinene)	
8	M8 (Catechin)	
9	M9 (Epicatechin)	
10	M10 (Gallic acid methyl ester)	
11	M11 (Gallic acid propyl ester)	
12	M12 (Hinesol)	
13	M13 (Hydroxychromone)	
14	M14 (Mangiferin)	

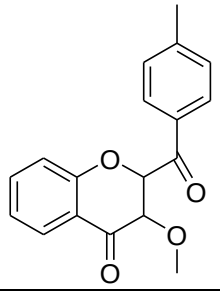
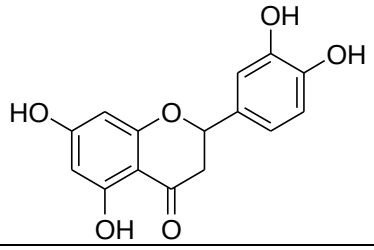
15	M15 (methoxy chromone)	
16	M16 (Quercetin)	

Table 2. Docking results of all the different chemical constituents of Mangifera Indica

Sr No.	Code	Binding energy	No. of hydrogen bonds	Amino acid with which H bond is made	Bond distance [Ă]
1	M1	-6.2	-	-	-
2	M2	-6.8	-	-	-
3	M3	-5.9	-	-	-
4	M4	-6.0	2	ASN58,PHE62	1.3,1.0
5	M5	-6.2	1	ARG67	2.9
6	M6	-6.7	1	ALA68	1.5
7	M7	-6.4	-	-	-
8	M8	-5.9	1	ASP191	2.1
9	M9	-5.5	2	ASP191,TYR180	2.0,2.4
10	M10	-4.4	2	ALA100,ARG107	2.3Ă,3.1
11	M11	-4.8	4	ARG107,TYR108,TYR63, PHE62	3.2,2.0,3.4,1.2
12	M12	-6.0	1	ALA100	2.8
13	M13	-6.8	6	ARG107,TYR63,TYR63,PHE62, TYR108,ASN58	3.2,3.4,2.9,1.4,3.3,1.1
14	M14	-6.0	3	THR187,THR187,THR187	2.0,2.4,2.6
15	M15	-6.5	2	ASN58,ALA57	3.1Aº,2.2
16	M16	-5.8	6	LEU55,GLY59,ILE65,PHE62,LEU66, LEU66	1.4,1.5,3.0,1.9,2.3,2.8

Conclusion

In the present study we have tried to investigate the different phytochemicals present in *Mangifera Indica* and elucidate their anticancer properties against breast cancer using molecular docking methods. There are 16 phytochemicals present in *Mangiferin Indica* and their average binding energy is -5.99 Kcal/mole. Amongst the 16 phytochemicals M2 and M13 show the highest binding energy in BCL2 protein i.e.-6.8 Kcal/mole. Mangiferin which is used in traditional medicines shows binding energy of -6.0 Kcal/mole. The high binding energy resembles stability of the phytochemical in the cavity of protein and its higher binding will show better inhibition of the protein. Hydrogen bonds present in the molecule help during the delivery of the molecule to the site of action and hence promote anticancer activity of the drug. Hydrogen bond distance also regulates the delivery mechanism the molecules with an average bond distance of 2.5-3.5 A show better stability during transport and the once with lower or higher bond distance get delivered at improper sites.

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