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A REVIEW OF TREATING BREAST CANCER BY INSILICO METHOD- NATURAL VS SYNTHETIC DRUGS

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ABSTRACT

Natural compounds are proper tools for inhibiting cancer cell proliferation. Hence, the search for these ligands of over expressed receptors in breast cancer has been a competitive challenge recently and opens new avenues for this drug discovery. In this review we have compared molecular interactions between natural products and synthetic drugs used for breast cancer using molecular docking. We have discussed the classification, signs and symptoms, stages and treatment of breast cancer and *in-silico* approaches of curcumin and flavonoids used in the treatment of breast cancer. We have concluded that using natural products like flavonoids and curcumin can be better option for the treatment of breast cancer in future as it is more safer to use than synthetic drugs as well as economically. Therefore, curcumin and flavanoids could be used as a anticancer agent for breast cancer.

KEYWORDS: Breast cancer, Curcumin, Flavonoids, Synthetic drugs, Docking.

INTRODUCTION[1,2]

Breast cancer is a known-recognized malignant tumor, causing the highest mortality rate among cancers in women. The reason is the lack of specific signs and symptoms at the early stage of this cancer and its aggressive nature. Currently, breast cancer treatments such as chemotherapy, surgery, and radiotherapy have not been effective. Moreover, these treatments have side effects such as liver, kidney, heart failure and mutation to healthy cells. Nowadays,

breast cancer is the most traditional cancers (Invasive) in women globally. Following lung cancer, breast cancer is the second major cause of cancer death in women. Breast cancer attributes to cancer which is beginning from breast tissue, most prevailing from the inner lining of milk ducts that supply ducts with milk1. According to the survey of august 2019, the chances of women decaying from breast cancer is all over 1 in 38 (2.6%). Almost 268600 women will obtain a diagnosis of intrusive breast cancer and almost 62930 people will obtain a diagnosis of non-invasive breast cancer in 2019 according to the ACS (American Cancer Society). In United States, the number of breast cancer survivors is about 3.1 million. Approximately there are 570.000 passing in 2015. Throughout the universe the number of women who are diagnosed with breast cancer every year is about 1.5 million. America was predicted that 30% of newer cancer cases (252,710) among women are completely breast cancer in 2017. Breast cancer is ecstatic cancer and can move to distant organs such as lung, liver, brain and bone. Early diagnosis of breast cancer can be a good prognosis which have high survival rate.

Breast cancer unfavorably affects women physical and physiological well-being. Almost 1.7 million newly [[determined cases and 521900 deaths appeared on a global span in 2012. It is necessary to identify a convenient biomarker that used to decrease the disease mortality.

Classification of breast cancer

Invasive breast cancer: It is the most common type of breast cancer where the cells break over the duct and lobular wall which occupy the surrounding fatty and connective tissues of breast. It can be interfere without being metastatic to other organs and to the lymph nodes.

Non-Invasive breast cancer: In this type of breast cancer, cells are restricted only to ducts and do not interfere surrounding fatty and connective tissues of breast. The most confirmed form (90%) of non-invasive breast cancer is Ductal carcinoma in situ (DCIS) and less confirmed is Lobular carcinoma in situ (LCIS) which is considered as an indicator for increased risk of breast cancer.

Ductal Carcinoma in situ (DCIS): It is the most accepted non-invasive breast cancer which is restricted to ducts of breast. Ductal comedocarcinoma is an example of such case.

Lobular Carcinoma in situ (LCIS, Lobular neoplasia): It is a point raise in the number of cells within lobules (milk glands) of the breast. The word "in situ" means which has not spread past the region where it initially developed.

Infiltrating Lobular Carcinoma (ILC): It popularly recognized as invasive lobular carcinoma which prepares in the lobules (milk ducts) though often metastatizes (escalation) to the another parts of the body and it accounts for 10-15 % of breast cancers.

Infiltrating Ductal Carcinoma (IDC): It is also recognized as invasive lobular carcinoma that prepares in the milk ducts and penetrates the surface of the duct, invading the tissues (fatty tissues) of breast and another region of the body. IDC (Infiltrating ductal carcinoma) is accounting for 80% of breast cancer diagnoses.

Tubular carcinoma: It is a special category of invasive breast carcinoma. Tubular carcinoma accounts for 2% of breast cancer diagnoses and mostly have better prognosis than other prevalent type of invasive carcinoma.

Medullary carcinoma: It is a special category of invasive breast carcinoma which forms a definite boundary between normal tissue and tumor tissue. Medullary carcinoma accounts for only 5% of breast cancer.

Mutinous carcinoma: It is an infrequent breast cancer developed by mucus-producing cancer cells. Colloidal carcinoma is another name for it. Women with this type of carcinoma have advance prognosis than any other types of invasive carcinoma.

Inflammatory breast cancer: It is an infrequent (about 1% of breast cancer) and excessively rapid growing cancer. There is appearance of aroused breasts (warm and red) with dimples or/and thick ridges produced by cancer cells that obstruct lymph arteries or channels in the breast skin.

Paget's diseases of the nipple: This category of cancer begins in milk ducts and develops to the skin of nipple and areola. It is an infrequent form and accounts for 1% of breast cancer.

Phylloides tumor: This perhaps either benign (Non-cancerous) or malignant (Cancerous). It develops in the connective tissues of the breast and can be treated by surgical removal.

Symptoms of breast cancer[3]

Inflammation of all part of a breast

Skin irritability or dimpling

Pain in breast or nipple

Nipple retraction

Redness or thickening, scaliness of nipple or breast skin

Discharge (Other than breast milk) from nipple.

Formation of lump.

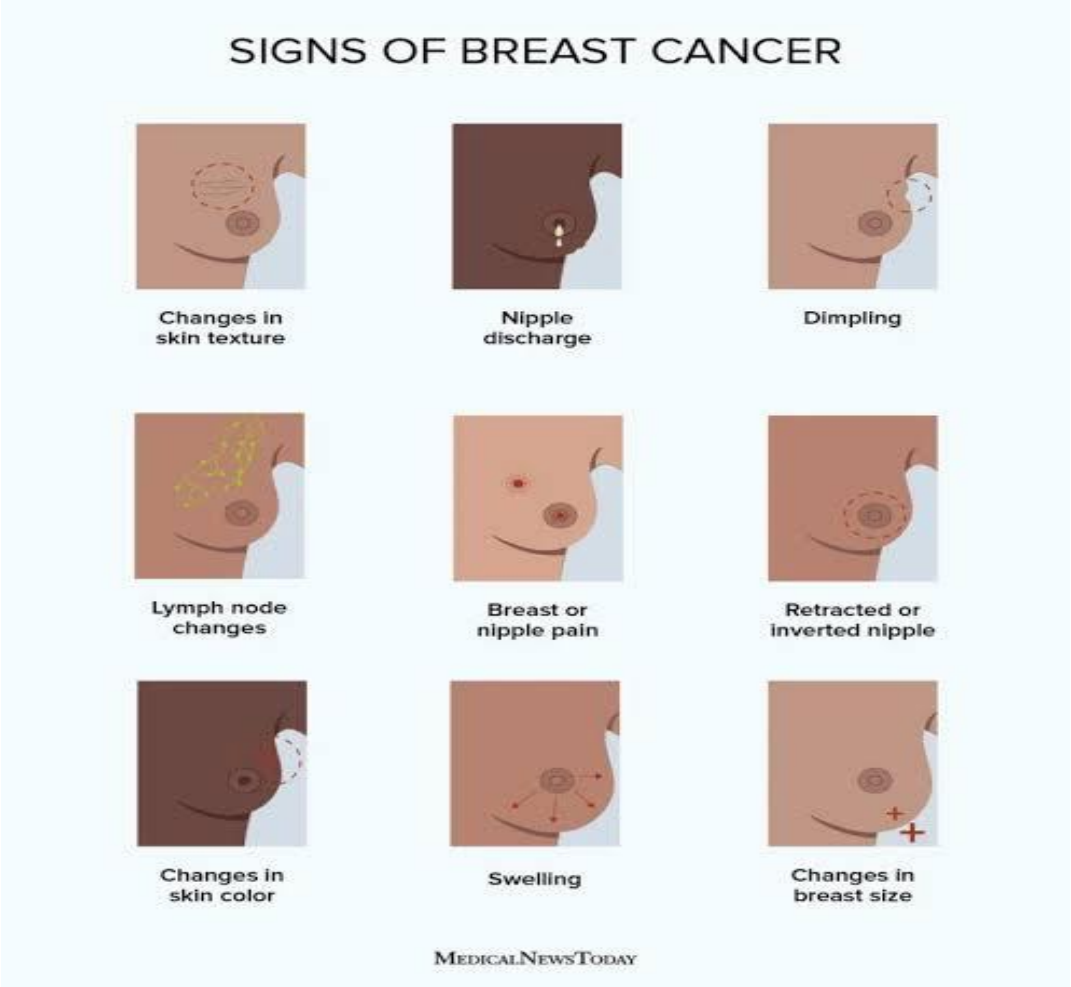

Figure 1: Signs of breast cancer.

Stages of breast cancer[4,5]

The stages of breast cancer, according to the American joint committee on cancer (AJCC), can be divided into the TNM system: T: size of the breast tumor, N: extent of tumor spread nearby lymph nodes and M: extend of tumor metastasis to other organs of the body. The earliest stage of breast cancer is called stage 0 or carcinoma in situ. In stage I, the tumor is

small and has not spread outside the patient's breast. Stage II cancer is less than 2cm in diameter and may also be found in some axillary lymph nodes. In stage III, the tumor found in breast may be of any size, but the axillary cancer will not be equivalent to stage II. Moreover, the cancer has also spread to the chest wall and /or to the skin of the breast, causing dimpling, inflammation or change of breast skin color. Finally, in breast cancer stage IV, the cancer has this disseminated to distant parts, such as the brain, lungs, plural or bone.

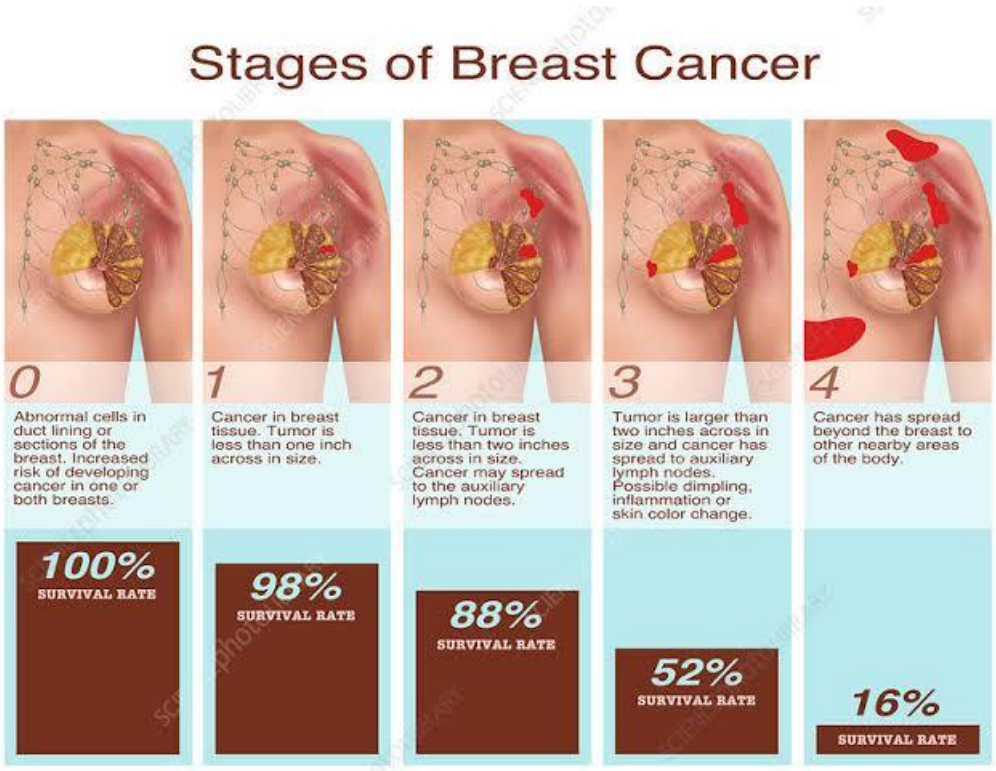

Figure 2: Stages of breast cancer.

Treatment of breast cancer

Most women with breast cancer in stages I, II or III are treated with surgery, often followed by radiation therapy. In general, the more the breast cancer has spread, the more treatment you will likely need. But other treatment options are affected by personnel preferences and other information about breast cancer, such as:

- If the cancer cells have hormone receptors. That is, if the cancer is estrogen receptor (ER)- positive or progesterone receptor (PR)-positive.
- If the cancer cells have large amounts of the HER2 protein (that is, if the cancer is HER2-positive).
- How fast the cancer is growing (measured by grade or Ki-67).
- Overall health.

- If you have gone through menopause or not.

Most women with breast cancer in stages I, II, or III will get some kind of systemic therapy as part of their treatment. This might include:

- Chemotherapy
- Hormone therapy
- Targeted drugs
- Immunotherapy

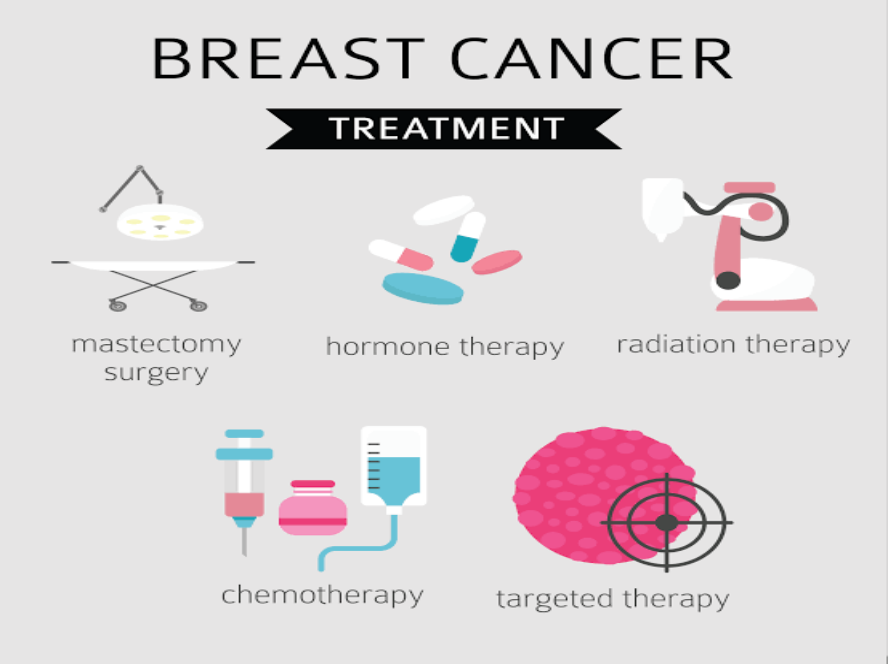

Figure 3: Treatment of breast cancer.

Treating stage i breast cancer

These breast cancers are still fairly small and either have not spread to the lymph nodes or have spread to only a tiny area in the sentinel lymph node (the lymph node to which cancer is likely to spread).

Local therapy (Surgery and Radiation therapy)

Surgery is the main treatment for stage I breast cancer. These cancers can be treated with either breast- conserving surgery. (BCS; sometimes called lumpectomy or partial mastectomy) or mastectomy.

If BCS is done, radiation therapy is usually given after surgery to lower the chance of the cancer coming back in the breast and to also help people live longer.

In a separate group, women who are at least 65 years old may consider BCS without radiation therapy. If all of the following are true:

- The tumor was 3cm (a little more than 1 inch) or less across and it has the removed completely.
- None of the lymph nodes removed contained cancer.
- The cancer is ER-positive or PR-positive, and hormone therapy will be given.

Treating stage 2 breast cancer

Stage II breast cancer are larger than stage I cancer and/or have spread to a few nearby lymph nodes.

Local therapy (Surgery and Radiation therapy)

Stage II cancers are treated with either breast conserving surgery (BCS; sometimes called lumpectomy or partial mastectomy) or mastectomy. The nearby lymph nodes will also be checked, either with a sentinel lymph node biopsy (SLNB) or an axillary lymph node dissection (ALND).

Women who have BCS treated with radiation therapy after surgery. Women who have mastectomy are typically treated with radiation if the cancer is found in the lymph nodes. Some patients who have SLNB that shows cancer in the few lymph nodes might not have rest of their lymph nodes removed to check for more cancer. In these patients, radiation may be discussed as a treatment options after mastectomy.

If chemotherapy is also needed after surgery, the radiation will be delayed until the chemo is done.

In some women, breast reconstruction can be done during the surgery to remove the cancer. But if you will need radiation after surgery, it is better to wait to get reconstruction until after the radiation is complete.

Treating stage iii breast cancer

Stage III breast cancer the tumor is large (More than 5cm or above 2inches across) or growing into nearby tissues (The skin over the breast or the muscle underneath)., or the cancer spread to many nearby lymph nodes.

Starting neoadjuvant therapy

Most often, these cancer treated with neoadjuvant (before surgery chemotherapy. For HER2-positive tumor. This may shrink the tumor enough for a women to have breast –conserving surgery (BCS). If the tumor does not shrink enough, a mastectomy is done. Nearby lymph nodes will also need to checked. A sentinel lymph node biopsy (SLNB) if is often not and option for stage III cancer, so an axillary lymph node dissection (ALND) is usually done.

Often, radiation therapy is needed after surgery. If breast reconstruction is planned is, it is usually delayed until after radiation therapy is done. For some, additional chemo is given after surgery as well.

Neoadjuvant treatment is preferable option for women with stage III TNBC or HER2-positive breast cancer because the treatment given after surgery is chosen depending on how much cancer is still in the breast and/or lymph nodes at the time of surgery. Some women with stage III cancer who get neoadjuvant treatment might live longer if the cancer goes away completely with that treatment.

Mechanism of breast cancer

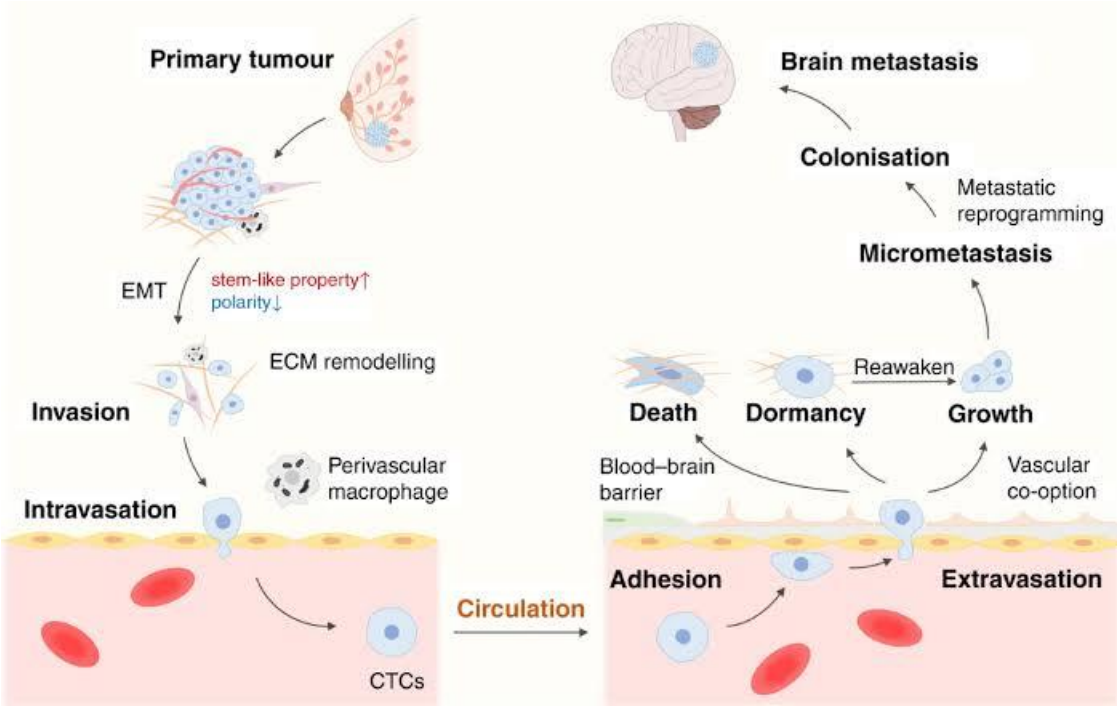

Figure 4: Mechanism of breast cancer.

The diverse histologic appearances of breast carcinomas and putative precursor lesions are the outward manifestation of the complex genetic and epigenetic changes that drive

carcinogenesis. As with other cancer, resident breast tissue stem cell have the hypothesized to be the cell of origin for all the breast cancer. Once the process is initiated in such cells by a driver mutation, there appear to be three major genetic pathway of carcinogenesis.

- ER-positive, HER2-negative cancers arise via the dominant pathway of breast cancer development, constituting 50% to 65% of cases. This is the most common subtype of breast cancer in individual who inherit germline mutation in BRCA2.They are often associate with gains of chromosomes 1q, losses of chromosome 16q, and activating mutation in PIK3CA, a gene that encodes phosphoinositide-3kinase(PI3K), which is an important component of signaling pathways downstream of growth factor receptors. These same genetic lesion are often found in flat epithelial atypia and atypical ductal hyperplasia, which are hypothesized to be a precursor lesion for this subtype of breast cancer. ER-positive cancer are termed "luminal" as these cancer most closely resemble normal breast luminal cells in terms of their mRNA expression pattern, which is dominated by genes that are regulated by estrogen.

- HER2-positive cancers arise through a pathway that is strongly associated with amplifications of the HER2 gene on chromosome 17q. They constitute approximately 20% of all breast cancers and may be either ER-positive or ER-negative. This is the most common subtype of breast cancer in patients with germline mutations in TP53 (Li-Fraumeni syndrome). These cancer have a distinct gene expression pattern that is dominated by genes related to proliferations that are regulated by signaling pathways lying downstream of the HER2 receptors tyrosine kinase.

- ER-negative, HER2-negative cancers arise through a distinct pathway that is independent of ER-mediated changes in gene expression and HER2 gene amplifications. As a result this is the least understood of the pathways. These tumors comprise about 15% of breast cancers overall, but are the most common tumor type observed in patients with germline PRCA1 mutations; they are occur with increased frequency in African American women. Sporadic tumors of this type often have loss-of-function mutations in TP53; mutations in BRCA1are uncommon, but BRCA1 may be silenced in sporadic tumors through epigenetic mechanisms. These tumors have a "basal-like" pattern of mRNA expression that includes many genes that are expressed in normal myo-epithelial cells.

Insilico approaches

In silico approaches with docking studies require at least two elements: a protein/drug database and a molecular docking algorithm. Protein and drug databases are a collection of the structures of proteins and drugs. The rapidly increasing number of structures has created big data, which over a wide range of biological and chemical information and are a recent opportunity to develop better knowledge of the relationships between drugs and targets (usually proteins), drugs and diseases, and targets and diseases. However, although the available data are often heterogeneous and incomplete, computational methods can exploit this knowledge to deepen these interaction. Given the cost and time consumption of experimental methods, high-performing computational algorithms for drug discovery processes are needed. The computational technique known as "docking" can predict the binding of drug–target complexes, as well as the conformation of the ligand upon binding to a protein target. The binding free energy of target–drug interactions establishes the affinity of an association and the conditions for forming a complex. Ranked binding free energies are not always precise, but they can be used to select new drugs such as small molecules to be experimentally tested in a virtual screening approach. Small molecules are promising new drugs with a low molecular weight, which allows them to penetrate cells easily. In addition, molecular docking can be also used for predicting the effects of a drug.

Curcumin

Curcumin is a hydrophobic polyphenol derived from turmeric, a traditional Indian spice. Curcumin has been used as an ethnic drug for the treatment of diverse diseases. Particularly, curcumin has been recognized as an effective anticancer agent that regulates multiple intracellular signaling pathways, including transcription factors (e.g., STAT3, NF-κB, and AP-1), receptors (e.g., IL-8, HER2, and CXCR4), kinases (e.g., EGFR, ERK, and JAK), cytokines (e.g., TNF, IL, and MIP), enzymes (e.g., MMP, iNOS, and GST), and growth factors (e.g., EGF, NGF, and HGF).[7] Yet, the discussions on curcumin's anticancer effects have only been available in the last few decades. Succeeded in treating colorectal cancer with curcumin in phase I, and used curcumin in the treatment of patients who were diagnosed with familial adenomatous polyposis. In an experimental investigation of mammary cancer induced by 7, 12-dimethylbenzanthracene (DMBA), curcumin significantly decreased the initiation of mammary adenocarcinoma on the fourth day after DMBA administration. Furthermore, a large number of studies on cancer prevention at different stages have

indicated curcumin as a favorable agent for cancer chemoprevention, used both alone and in combination with other drugs.

Flavonoids

Flavonoids are a class of natural substances that have phenolic structures in diverse forms and are found in plants. Flavones, flavanones, flavanols, flavonols, isoflavones, and anthocyanidins are the six subclasses of flavonoids. According to a study, flavonoids have anti-inflammatory, antiviral, anti-allergic, antioxidant, and anti-tumor properties. Flavonoids also inhibit tumor growth by causing death in cancer cells. Therefore, it is possible to treat breast cancer more safely than a dangerous method with side effects by inducing the death of cancer cells and receiving radiation treatment.

MATERIALS AND METHODS[9]

Protein preparation

Proteins were chosen on the basis of *invitro* studies that were performed on them and the structural data of the proteins were obtained from protein data bank (PDB). The protein was downloaded in the PDB format and saved as new file which was already created.

Import the protein file and the steps to be followed,

1. Delete the extra chains if the protein as more than one chain.
2. Remove the water molecules.
3. Add the hydrogen bond.
4. Click the calculation tools and select energy optimization and followed by geometry optimization.
5. Click the active site and select make a group from this residue and save the protein.

Ligand preparation

Ligand was downloaded from the pub chem or drug bank online and saved in mol. 2000 or SDF form.

Click the calculation tools and select energy optimization and followed by geometry optimization.

Click the active site and select make a ligand from this group residues.

Set docking data base and run docking calculations.

Active site prediction

The most significant step in molecular docking is to locate the ligand binding site on a protein. The protein-ligand binding site are located using the novel energy based method Q-Site Finder developed by Jackson, where the interaction energies of methyl prob with a protein are analysed. Using the software the active binding site of toxins were obtained. The binding sites which are more flexible were preferred for this analysis.

Protein ligand docking

After the compounds are screened, a virtual screening environment is created through an integrated tool Argus lab 4.0.1 and Auto dock tools 1.5.6. The tool affords the interactive interfaces to prepare both the binding site of the target protein and the screening compound library. Post screening, each compound in the library is docked into the binding site and there by generating the protein-compound interaction profile of electrostatic, Hydrogen bonding and Vander waals interaction.

RESULTS AND DISCUSSION

Table 1: Molecular docking of Flavonoids and Its binding energy.

S. No	Name of drugs	Target proteins	Binding energy (Kcal/mol)
1	Apigenin	2HBQ	-3.62
2	Categenin	2HBQ	-3.56
3	Chrysin	2HBQ	-3.25
4	Daidsein	2HBQ	-3.29
5	Genistein	2HBQ	-3.54
6	Quercetin	HER2	-9.96
7	Myricetin	HER2	-9.50
8	Genistein	HER2	-9.32
9	Chrysin	HER2	-11.01
10	Catechin	HER2	-9.05

Table 2: Molecular docking of curcumin and its binding energy.

S. No	Name of drugs	Target proteins	Binding energy (Kcal/mol)
1	Curcumin	HER2	-12.1
2		Estrogen receptor	-9.92
3		ERBB2	-8.30
4		Tyrosine kinase	-8.22
5		HSP90	-8.05
6		EGFR	-9.42
7		NF-Kb	-8.38
8	Bisdemethoxycurcumin	EGFR	-8.51
9	Diacetylcurcumin	EGFR	-10.72
10		NF-kB	-9.67

Table 3: Molecular docking of some synthetic drugs and its binding energy.

S. No	Name of drugs	Target protein	Binding Energy (kcal/mol)
1	Hesperidin	BCL-2	-8.0
2	Podototarin	BCL-W	-8.1
3	Theaflavin	MCL-1	-8.7
4	Hecogenin acetate	ERα	-8.6
5	Podototarin	BCL-2	- 7.8

CONCLUSION

The use of natural products can be useful for the therapeutic and nutritional purposes of humans. Numerous studies have shown that natural products are a good alternative to synthetic and chemical drugs because they have no side effects and are of natural origin. Based on the results of the above docking studies, we can also remark that natural compounds such as curcumin and flavonoids have the ability to become a unique and natural drug. Therefore, in order to achieve this promising goal, extensive *in vivo* and clinical studies are needed, although some researches have been started in this field. In the above review, we that have concluded that curcumin and flavonoids have the ability to kill the breastcancer cell lines than other synthetic drugs. Therefore phytotherapies may be an interesting and successful option in the treatment of breastcancer.

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