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MOLECULAR DOCKING OF PHYTOCHEMICALS AGAINST BREAST CANCER: A REVIEW

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ABSTRACT

There is a huge hike in the prevalence of cancer worldwide. Breast cancer is one of the widespread types of cancer and in terms of occurrence it has been ranked in the top first cancer types. Different cancer treatment methods cause high side effects in patients. A large number of isolated natural compounds have been reported to possess anticancer properties; the mechanisms of their action are not well understood. Different phytochemicals can be utilized for the treatment of breast cancer because of their wide safety nature and ability to target heterogeneous populations of cancer cells**.** Docking is a key tool in novel drug design and discovery. Inhibiting various receptors of breast cancer is an important therapeutic option. Protein target includes ERα, PR, EGFR, HER-2, etc. The 3D structures of these target proteins were obtained from the protein data bank. The **c**omplementarily of ligand and a protein target at the molecular level can be determined through *In silico* docking techniques. Protein-ligand docking concepts have applications such as structure-based drug design (SBDD), lead Optimization, evaluation of biochemical pathways and in De Novo drug design. Conclusion: In this review, an effort has been made to analyze the docking of potent phytochemicals against breast cancer target proteins.
Keywords : Molecular docking, Breast cancer, Docking score, Software, Phytochemicals.

Introduction

Cancer is one of the leading causes of mortality among humans and requires much attention to prevent its progression. Genetic change, environmental difference, and reversible change in cell properties are the consequence of phenotypic and functional heterogeneity among cancer cells within the same tumor (Meacham and Morrison, 2013). Even though various approaches such as vaccines and monoclonal antibodies (mAb's) are available, many of these methods are still showing toxicity (Purawarga Matada *et al*., 2021). It is important to know breast cancer-related pathways and biomarkers at the molecular level to develop safe effective agents that can reverse, reduce, or slow the growth of breast cancer (Rampogu *et al*., 2019; Purawarga Matada *et al*., 2021).

Presently employed clinical modalities in cancer treatment include surgical removal, radiotherapy, chemotherapy and hormone therapy. The therapeutic efficiency of these drugs is restricted as they cause hazards to healthy cells and tissues also (Mutazah *et al*., 2020), hence new anticancer drug is to be explored from different natural compounds such as xanthones, flavonoids, etc (Miladiyah *et al*., 2018; Moulishankar and 2020), that possess anticancer activities. Various researchers are conducting studies on the biological properties of several potential plants and herbs. Docking is one of the rational drug design methods, becoming an important tool in drug discovery over the last decade (Sanghani *et al*., 2012). In silico molecular docking studies give evidence on binding conformation, pattern and affinity when bio-active peptides or chemical drug molecules exert their action by binding with specific receptors (Rahman *et al*., 2020). To evaluate the binding tightness between the docked compound and target protein (receptor) computational methods using mathematical algorithms (the scoring function) are used. This review aims at establishing the efficacy of the phytochemicals against breast cancer through molecular docking.

1. Molecular Docking

New drug discovery is a difficult task. One of the most crucial strategies for drug discovery over the past few decades is targeted drug design. In complex and multifactorial diseases like cancer and diabetes, many sites might be required to target simultaneously, and hence targeting a single site did not work (Singh *et al*., 2014). In silico–chemico biological approach is mainly used in modern drug discovery. Prediction of the ligand conformation and posing within targeted binding sites is the important step of molecular docking. From the evaluation of interactions between compounds and potential targets, biological activity was predicted using scoring functions (Kitchen *et al*., 2004). Likewise in order to predict the affinity and activity of the drug, docking is often applied to forecast the binding orientation of drug candidates against protein targets. Computational molecular identification process and accomplishing an optimized conformation by reducing the free energy of an overall system is the main aim of molecular docking (Chaudhary and Mishra, 2016). The driving forces for the electrostatic and van der Waals energies depend on the complementarities between the shape and electrostatics of the binding site surfaces and the ligand or substrate (Pagadala

et al., 2017). The uses and applications of molecular docking in drug discovery include structure-activity studies, lead optimization, assisting X-ray crystallography in the fitting of substrates, etc (Morris and Lim-Wilby, 2008). AutoDock, Vina, MOE-Dock, FLexX and GOLD are some of the top software used for best scores in docking.

The docking process has complications including accurately predicting binding conformations, the limited resolution of crystallographic targets, inherent flexibility, induced fit or other conformational changes that occur on binding, and the participation of water molecules in protein-ligand interaction (Kitchen *et al*., 2004). Two important sections of molecular docking are search alogarithm and scoring function (Chaudhary and Mishra, 2016). Figure 2 shows different types of docking (Chaudhary and Mishra, 2016).

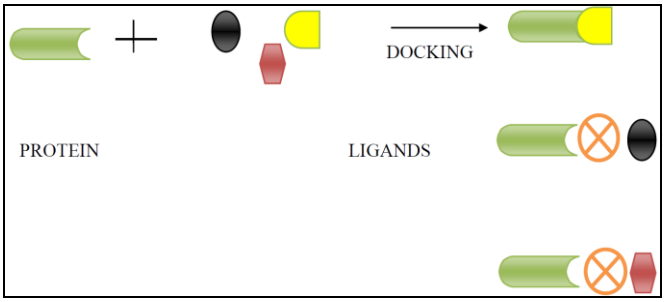

Fig. 1 : Schematic diagram of docking with different ligands to form a final steady compound.

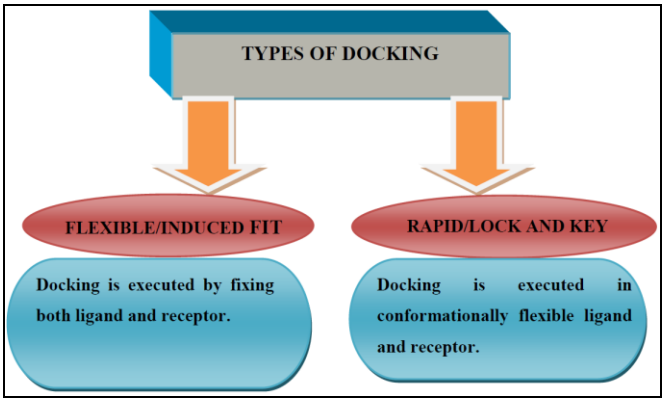

Fig. 2: Different types of Docking.

2. Breast Cancer

Breast cancer (BC) cause more death in women than all the other types of cancers, it is fast-growing cancer in women. Important ways of reducing the risk associated with the disease are to make more awareness of the sign and symptoms and more advances in the screening of drugs for the treatment. In order to stop and inhibit the growth of cancerous cells chemotherapy is commonly used. The main advantage of chemotherapy over radiation and surgery which treat cancer cells in a specific area is its ability to stop the growth of cancer cells that have spread to other places (Ismail *et al*., 2018). Triple-negative breast cancers (TNBC), constitute about 20% of all breast cancers and show a higher rate of reversion and poor survival rate in the metastatic situation compared to other types (Mehanna *et al*., 2019). The absence of overexpression of HER2 protein, lack of estrogen receptor (ER), and progesterone receptor expression (PR) are seen in TNBC (Ismail *et al*., 2010). Types of breast cancer are demonstrated in figure 3 (Dai *et al*., 2015).

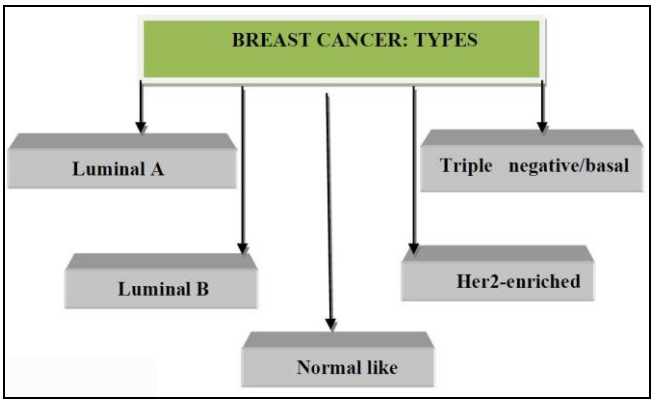

Fig. 3 : Types of Breast cancer.

2.1. Breast Cancer : Potential Targets

2.1.1 EGFR

It is a cell surface transmembrane glycoprotein, with an extracellular ligand-binding domain and cytoplasmic, intercellular tyrosine kinase (TK) domain. It can bind endogenous epidermal growth factor (EGF) and thereby activate various downstream pathways (STAT, MAPK, PI3K, AKT, PKC) that result in cell proliferation, cell growth, differentiation, and hence act as a crucial target in BC.

2.1.2 HER2

HER2 comprises four TK receptors such as HER1/EGFR, HER2, HER3, and finally HER4. Among this HER2 plays an important role in the development of normal as well as malignant breast tissue. Interaction of HER2 with insulin-like growth factor receptor-1(IGFR-1) and estrogen receptor initiates the cell signaling. HER2 act as an appropriate target for anti-cancer drug development.

2.1.3 Nf- κB

Nuclear factor-kappa B (NF- κB) is a transcriptional factor that can regulate the expression of genes that are involved in the proliferation of cells. NF- κB can hence contribute to the pathogenesis of breast tumors. In BC, NF-κB activation occurs downstream of EGFR signalling, especially in the ER-negative subtype. Activation of PI3K/Akt and induction of NF- κB (p50/p65) subunits are the results of the overexpression of HER-2 (Purawarga matada *et al*. 2021). Figure 4 shows some important targent proteins involved in BC.

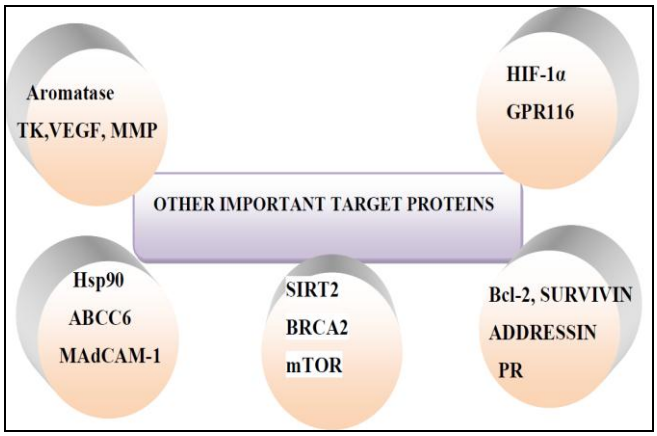

Fig. 4 : Other important targets of breast cancer.

3. Phytochemicals Against Breast Cancer

For the protection of chronic diseases such as cancers, hypertension, heart disease, and other diseases phytochemicals have been used. Due to their less toxic and safe nature, they are used for the treatment of cancer (Ismail *et al.*, 2018). There are continuous efforts of researchers worldwide to identify novel anticancer compounds. In vitro or in vivo anticancer evaluation of the number of compounds derived from medicinal plants shows cytotoxicity against several types of cancer cells (Hadisaputri *et al.*, 2020). Flavonoids are a large group of polyphenolic compounds, characterized by a benzo-4-pyrone structure which is extensively found in foodstuffs of plant origin, like vegetables and fruits (Moulishankar and Lakshmanan 2020).

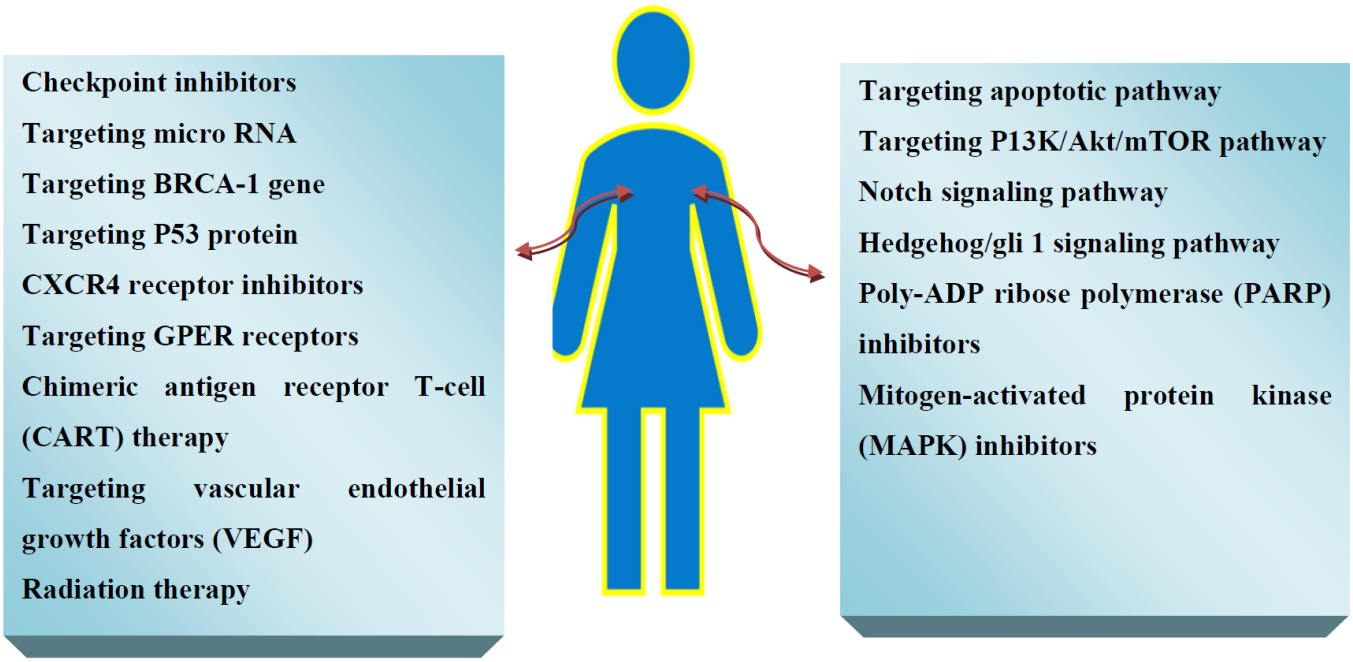

Fig. 5 : Diagram showing an overview of currently available treatment strategies of breast cancer (Singh *et al*. 2021).

Cheng *et al*. (2011) had reported some antioxidant xanthone derivatives that induce cell cycle arrest and apoptosis. In the clinical management of human cancers, multi drug resistance (MDR) is a major obstacle. Mechanisms such as decreased drug uptake, increased drug efflux, altered metabolism of drugs, and increased repair of drug-induced DNA damage are some of the biochemical mechanisms involved in the complex multifactorial phenomenon MDR. Overexpression of ABC-transporter proteins like MDR1/P-glycoprotein (MDR1/Pgp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2) is the best-known mechanism of MDR. The action of xanthones which shows action against sensitive and multidrug-resistant cancer cell lines was studied by Kuete *et al*. (2014). A commercially available drug and an antagonist of ER-α that binds with estrogen receptor and control its function, thereby preventing breast cancer is tamoxifen. It blocks the function of estrogen receptor and inhibits the function by binding with Arg394 (Ahmed *et al*., 2014; Farhad *et al*., 2016).

Dupuy *et al*. (2015) dictated the metastatic potential in breast cancer through PDK-1 (Pyruvate dehydrogenase kinase-1) dependant metabolic reprogramming. Several cancer-specific enzymes such as aromatase and sulfatase can be modulated by coumarin derivatives s (Thakur *et al*., 2015). A biological compound termed as herbal-marine compound (HES-A) of marine herbal origin comprises different organic and inorganic substances that are found to be an effective candidate against breast cancer (Wali *et al*., 2019). In a number of tumors including breast cancer, ornithine decarboxylase is overexpressed. In tumorigenesis models, flavonoids like quercetin and apigenin had been shown to prevent ornithine decarboxylase. Flavonoid quercetin was also found to be an effective inhibitor of phospholipase A2 which is an overexpressed gene in breast tumors as well as prostate tumor tissue (Cassidy and Setzer, 2010). Luteolin is a promising anticancer agents, that suppresses the expression of cancer-promoting proteins, reduce the tumor size, inhibit proliferation, and has a significant potential to suppress the expression of p-STAT3, p-EGFR, p-Akt, and p-Erk1/2 in MCF-7 breast cancer cells induced by EGF (Imran *et al*., 2019).

Chakravarti *et al*. (2019) studied the in vitro antibreast cancer activity of ethanolic extract of *Wrightia tomentosa* and found out 2 important constituent molecules, olenolic and urosolic acids that are responsible for anti-cancer activity. β-Sitosterol inhibits tumor cell growth and acts as an effective apoptosis-promoting agent (Awad *et al*., 2007). A naturally occurring minor secoiridoid isolated from extra virgin olive oil inhibit the proliferation, migration, and invasion of the epithelial human breast cancer cell lines (Elnagar *et al*., 2011). Anticancer activities are shown by flavonoids in the methanolic extract of fenugreek against KAIMRC1 breast cancer cell lines (Alghamdi *et al*., 2021). 95.7% (percent) cancer cell mortality has been observed at the concentration of 1600 µg/ml neem leaf extract with a pH 6.2 and found to be very effective against the human MDA-MB-231 breast cancer cell line (Ahammad *et al*., 2021).

Sulphur-containing compounds present in the leaves of *Clinacanthus nutans* show anticancer activity against breast cancer (Mutazah *et al*., 2020). Through the up-regulation of

p53 gene activation, aqueous extract of *Figonia creatica* has shown promising anticancer potential on MCF-7 breast cancer cell line (Riaz *et al.*, 2021). A flavonoid apigenin-7-O-rhamnosyl-6-C-glucoside was isolated for the first time from the aqueous methanol extract of *Erythrina crista-galli*. This plant shows high phytoestrogenic activities and the incidence of breast cancer is lower in Asian populations due to the high consumption of soy products which have a high phytoestrogens content (Ashmawy *et al*., 2016). In Asian Americans, the intake of green tea and risk of breast cancer have an inverse association (Thangapazham *et al*., 2007).

An essential oil compound, tetrahydroxy flavonone from *Angola vetiver* showed anticancer potential on human breast cancer cells (Javed *et al*., 2021). One of the green tea polyphenols, (−)-epigallocatechin (EGC) strongly inhibits the growth of breast cancer cell lines (MCF-7 and MDA-MB-231) but not that of normal breast epithelial cells (Vergote *et al*., 2002). One of the major carotenoid components found in tomatoes is lycopene which shows cell growth inhibition in breast, prostate and endometrial cancer cells by the modulation of cell-cycle-related genes (Preet *et al*., 2012). By inhibiting Wnt-TCF signalling lycopene also enhances the effect of quinacrine on breast cancer cells. A combination of PEITC (Phenethyl isothiocyanate) and paclitaxel synergistically improve the anti-proliferative role of paclitaxel on breast cancer cells (Ranjan *et al*., 2019).

A triterpenoid steroidal compound cucurbitacin B (CuB), inhibits the growth of various breast cancer cells with an IC_{50} ranging from 18-50nM after 48 and 72 h of treatment (Gupta *et al*., 2014). Genistein inhibit the proliferation of MCF-7 cells, by inducing cell apoptosis (Chen *et al*., 2015). Estrogen is a hormone that results in an increased risk of breast and other hormone-dependent cancers, the chemical structure of estrogen and isoflavones is similar. Isoflavones can decrease the health risks by competing with estrogen for the same receptor sites (Ferdous *et al*., 2013).

One of the key issues in chemoprevention with phytochemicals is to determine whether the activity and molecular mechanism(s) of the single active compound isolated and the extract are the same. Identifying and developing these isolated compounds is very expensive hence the extract may preferentially replace a single active compound when both active compound and extract are found to be similar.

4. Molecular docking of phytochemicals against breast cancer

Table 1: Phytochemicals as ligands from different plants docked with important targent proteins.

Proteins	Plants	Phytochemical with High Affinity	Docking Programme	Reference
ERα	*Ocimum sanctum*	Carvacrol	Glide of Schrödinger Maestro v 10.1	Farhad *et al*. (2016).
	Phyllanthus emblica	Isocorilagin	Glide of Schrödinger-Maestro v 10.1	Afrin *et al*. (2018).
	Terminalia bellerica	Anolignan B	Glide of Schrödinger-Maestro v 10.1	Majumder *et al*. (2017).
	Tacca integrifolia	quercetin-3-α- arabinoside	Glide of Schrödinger-Maestro v10.1	Ahmed *et al*. (2019).
	Psidium guajava	Guajadial and psidial A	Molegro virtual docker	Rizzo *et al*. (2014).
	Glycine max	Stigmasterol and Daidzein	Autodock 4.0	Kavitha and Gunavathy (2017).
	Asparagus racemosus	Compound 26 (rutin)	Quikprop software of maestro for ADME	Sharma and Jaitak (2020).
	Aloe vera	Beta-sitosterol	AutoDock Vina	Majumder *et al*. (2020).
HER-2	*Capparis zeylanica* Linn	α-Amyrin	AutoDock Vina	Warake *et al*. (2021).
	Ginkgo biloba	Cianidanol	PyRx, AutoDock Vina	Arannilewa *et al*. (2018).
NF-Kb	*Curcuma longa*	Curcumin	BSP-Slim server	Elengoe and Sundramoorthy (2020).
	Plumbago zeylanica	Plumbagin	Autodock 4.0	Dandawate *et al*. (2014).
SIRT2	*Ocimum basilicum*	Methyl Cinnamate and Eucalyptol	AutoDock	Bhura *et al*. (2019).
ABCC6	*Deprea subtriflora*	Subtrifloralactone G	AutoDock Vina	Pandya *et al*. (2020).
Bcl-2 and Survivin	*Annona muricata*	Coclaurine, coreximine and Synephrine	ArgusDock	Muthu and Durairaj (2016).

4.1 ERα, PR, EGFR and HER-2

Using molecular docking, identification of small molecular weight compounds that interact with binding pocket of EGFR, HER2, estrogen and NF- κB receptors can be determined. Candidates which are appropriate for receptor inhibition studies in BC were determined through in silico studies and from NPACT database (pristimerin, ixocarpalactone A, viscosalactone B and zhankuic acid A) which shows less toxic profile and were identified and found to be stable in computed environment (Purawarga Matada *et al*., 2021).

To discover the protein ligand connections and reasonable binding geometry phytochemicals are docked using different softwares and important docking engines. Using discovery studio, interaction study can be performed on the the highest negative binding energy, and various amino acid interactions and the distance can be ascertained.

Recently employed methods for the development of drug include QSAR, docking and pharmacokinetic studies. The important steps of pharmacokinetic phase of drug development are absorption, distribution, metabolism, excretion and toxicology (ADMET). Without violating any of the conditions of bioavailability the leading compounds gabridin and quercetin are in agreement with Lipinski rule of five, hence they are readily bioavailable. They show high binding affinity and have good pharmacokinetic parameters; hence they can be used in designing a highly effective anti breast cancer drug.

Human estrogen receptor 3D structure and structure of phytochemical can be retrieved from Protein data bank and Pubchem compound database respectively. With the help of Q-Site Finder and Computed Atlas of Surface Topography of proteins (CASTp) server the catalytic residue can be examined. Structural pockets and cavities having high affinity for candidate drugs are related with the binding and active sites of proteins. Inorder to locate the appropriate binding orientations and conformations of various inhibitors in the human estrogen receptor binding pocket automated dockings were performed by Ismail *et al*. (2018) using AutoDock4.0 a computational docking tool. Genistein, quercetin and daidzein show higher intermolecular interactions, binding affinity and docking score. They shares striking resemblance with the structure of estrogen and can act as the potential lead molecule for the inhibition of human estrogen. The most important residues for potential drug target are Leu346, Leu384, Leu387, Phe404 and Leu525. For designing therapeutic lead molecules these can be used (Ferdous *et al*. 2013).

Docking studies on two isoforms of the estrogen receptor, ERα and ERβ with 568 phytochemicals found in 17 of the most popular herbal supplements sold in the United State, selective estrogen receptor modulation are exhibited by almost all popular herbal supplements (Powers and Setzer 2015). Docking scores -6.456, 2.232, 1.985, -2.941 respectively were obtained when Carvacrol, palmitic acid, stearic acid, vicenin, the bioactive compounds from *Ocimum sanctum* were molecular docked against estrogen receptor alpha (ER-α) using Schrodinger. Among all the 4 compounds, carvacrol shows the best selective inhibition of estrogen receptor alpha (Farhad *et al*., 2016).

In number of cases estrogen receptor alpha over expression results in breast cancer. Compounds like 1, 1-diphenyl-2-picrylhydrazyl, isocorilagin, kaempferol, kaempferol 3-bita-D-glucopyranoside and quercetin isolated from Phyllanthus emblica when docked against ER-α by Schrodinger**,** isocorilagin possessed best value and hence chosen as the best compound for selective inhibition of estrogen receptor alpha (Afrin *et al*., 2018). Compounds Anolignan B, a bioactive compound from *Terminalia bellerica* showed best docking score towards estrogen receptor alpha and thereby selective inhibitors of estrogen receptor alpha (Majumder *et al*., 2017). Betulinic acid, catsanogenin and quercetin-3-α-arabinoside from *Tacca integrifolia* rhizome are allowed to interact with estrogen alpha receptor ligand binding domain. There is a strong ligand-protein complex formation by all the compounds. Among the 3 compounds quercetin-3-α-arabinoside showed highest docking score of –6.286 kcal/mol (Ahmed *et al*., 2019). One of the important therapeutic options for the treatment of breast cancer is to inhibit EGFR and HER2 targets. 3D PubChem structures of furanocoumarin compounds can dock with the 3D structures of ERα (Estrogen receptor), PR (Progesterone receptor), EGFR (Epidermal growth factor receptor) and mTOR (mammalian target of rapamycin) obtained from the protein data bank using FlexX. For docking of small ligands in binding sites of receptors and enzymes very flexible and fast FlexX alogarithm software is used, it also incorporates interactions between protein and ligand, ligand core placement, and complete ligand rebuilding.

The activation of ERα, PR, EGFR and HER-2 receptors initiate certain cellular downstream signaling pathways, thereby initiate and trigger the progression of breast cancer. PI3k, Akt, mTOR, PKB and Wnt/β-catenin are the major proteins involved in pathway, when appropriate *in-vitro* techniques like antagonist and inhibition assay of ERα, PR, EGFR and mTO R respectively has been performed the best docking score for breast cancer was found in xanthotoxol followed by bergapten, angelicin, psoralen and isoimperatorin (Acharya *et al*., 2019). In a study conducted by Prabhavati *et al*. (2020) to identify potential phytocompound inhibitors for EGFR and HER2 as anti-breast cancer agents, hit molecule panaxadiol with a low dock score for EGFR and HER2 targets were obtained. Hence it can be utilized for the development of a novel multi-target EGFR and HER2 target inhibitor with greater potential and lower toxicity. HSP90 co-chaperone and the human epidermal growth factor receptors EGFR and HER2/neu receptor expression level seems to be highly elevated in breast cancer. A study was conducted by Yousuf *et al*. (2017) on five multi-targeted compounds that have high binding energies against these target proteins that are involved in breast cancer. After tested through in vitro and in vivo studies these virtual hits can be utilized for the development of drugs. Phytochemicals such as rhinacanthin Q, subtrifloralacton D, and 7, 7″-dimethyllanaraflavone have high binding affinity to HER2 when docked to the ATP binding site of the HER2 kinase domain. Hence these compounds could be potential bioactive molecules to act as inhibitor of HER2 protein (Lamichhane *et al*., 2021). α-Amyrin followed by quercetin and β-carotene of *Capparis zeylanica* Linn. leaf extract shows highest binding affinity (− 8.4 Kcal/mol) when molecular docking studies were

conducted on HER2 protein using AutoDock Vina (Warake *et al*. 2021). An active compound in *Psidium guajava* shows similar physicochemical properties to estradiol and tamoxifen. When *in silico* molecular docking studies were conducted with guajadial and psidial A, they fit into the estrogen receptors ER-α and ER-β hence act as phytoestrogens (Rizzo *et al*., 2014).

When molecular docking of daidzein, stigmasterol, genistein, campesterol and sitosterol from *Glycine max* against breast cancer target estrogen receptor was conducted, stigmasterol and daidzein shows binding energy of -7.50 and -7.36 and have good binding mode and interaction energy (Kavitha and Gunavathy 2017). Pelargonidin, delphinidin, cyanidin,and hibiscetin from *Hibiscus sabdariffa* are more efficient than breast cancer drugs like tamoxifen and raloxifene, these compounds can act as estrogen receptor modulator molecules by few modifications (Laskar *et al*., 2021).

With a binding energy of -250.149 sanguiin H6, isolated from *Rubus coreanus* interact with ERα coactivator-binding site, and can act as a potential anti cancer agent against breast cancer (Trinh *et al*., 2019). With a lowest binding energy value of –5.9 Kcal/mol, corynan-17-ol,18,19-didehydro-10-methoxy from *Morinda tinctoria* fruit extract act as the efficient lead molecule against breast cancer protein ErBb2 (Praveena *et al*., 2019). Compound 26 (rutin) from *Asparagus racemosus* exhibited the remarkable binding affinity & docking score with estrogen receptor α than standard drug Bazedoxifene (Standard) (Sharma and Jaitak, 2020).

When molecular docking conducted with HER2+ and cianidanol from *Ginkgo biloba* a binding energy of -8.2kcal/mol was obtained. Cianidanol shows potential to inhibit HER2+ (Arannilewa *et al*., 2018). Molecular docking-based screening of compounds derived from *Carica papaya* using Schrödinger (Maestro 9.5) were done with therapeutic targets ERα, PR, HER2 Akt, PI3K for breast cancer therapy. Chlorogenic acid, caffeic acid, quinic acid, kaempferol, apigenin and hesperitin were identified as the most potential compounds for the development of anti-breast cancer agents (VL 2020). Compared to standard drug tamoxifen bioactive compounds like Aloe-emodin (8.8 Kcal/mol), 7-hydroxy-2,5 dimethylchromone (7.5 Kcal/mol), beta-sitosterol isolated from *Aloe vera* leaf have greater binding affinity toward estrogen alpha receptor when molecular docking studies were conducted (Majumder *et al*., 2020).

4.2 NF-κB

An important transcription factor reported to be overexpressed in breast cancer is a nuclear factor- kappa B (NF-kB) precursor protein p105, when nine phytochemicals namely boswellic acid, 1-caffeoylquinic acid, ellagic acid, emodin, genistein, guggulsterone, quercetin, resveratrol, and sylibinin obtained from different plants docked with this precursor protein quercetin and 1-caffeoylquinic acid showed binding energy of −12.11 and −11.50 Kcal/mol, respectively and hence both are very effective inhibitors against target molecule (Khan *et al*., 2013). Comparing with the parent plumbagin compound the novel plumbagin hydrazones exhibited high cytotoxicity, when docked into the protein cavity of p50-subunit of NF-κB (Nuclear factor-kappa B) protein. This novel compound inhibit NF-κb expression through its better fitting and better binding energies and can be utilized for the development of novel drug molecules against triple negative breast cancers (Dandawate *et al.*, 2014). Novel plumbagin hydrazonates with hydroxyl groups on plumbagin and hydrazonate side chain helps in the formation of additional hydrogen bonding interactions with amino acid residues in p50-subunit of NF- κB protein. Novel plumbagin hydrazonates exhibited superior inhibitory activity than the parent plumbagin compound (Dandawate *et al*., 2012). Using BSP-Slim server the breast cancer cell line proteins nuclear factor NF-kappa-B-p105 subunits, caspase 3, and MADCAM-1 (mucosal addressin cell adhesion molecule 1) were docked successfully with the curcumin. With the lowest energy value (3.165) nuclear factor NF-kappa-B-p105 bind strongly with curcumin compared with the other protein models hence curcumin can be used as a potential anti breast cancer agent (Elengoe and Sundramoorthy, 2020).

4.3 Other Important Target Sites:

4.3.1 GPR116

Using in silico approach drugable natural phytochemical ligands targeting GPR116 (G protein-coupled receptor 116) can be determined. GPR116 have a role in the progression of metastasis in triple-negative breast cancer (TNBC) one of the aggressive breast cancer found in young women, hence targeting GPR116 is a desirable way for the therapy (Muthiah *et al*. 2021).

4.3.2 HIF-1α

Molecular docking studies between genistein and HIF-1α (hypoxia inducible factor 1α) revealed that genistein binds to the FIH-1 binding site of HIF-1α protein (Mukund *et al*. 2019).

4.3.3 Aromatase

A critical target protein for treating hormone-dependent breast cancer is Aromatase enzyme (CYP19). Compounds like curcumin, capsaicin, rosmarinic acid, and 6-shogaol generated the highest dock scores when different phytochemicals with antioxidant potential have been assessed computationally with aromatase and these compounds can represent as valuable compounds to fight against the BC. Hence it can be concluded that antioxidant potential rich plant-derived compounds show excellent anticarcinogenic activities and can utilize to combat BC (Rampogu *et al*., 2019). Glide docking with 'extra precision (XP)', structure-based virtual screening (SBVS) followed by ligand-based virtual screening (LBVS) results revealed that *Artemisia annua*, *Zingibe officinale*, *Cicer arietinum*, *Annona muricata* and *Vitex agnus castus* are the top scoring plants (Dawood *et al*. 2018).

4.3.4 TK,VEGF and MMP

Seven phytochemicals (7-hydroxy-4′-methoxy-3,11-dehydrohomoisoflavanone, 4,4′-dihydroxy-2'-methoxychalcone,7,4′-dihydroxy-3,11-dehydrohomoiso-flavanone, luteolin, quercetin-3-methyl, kaempferol-3-O-β-d-xylopyranoside and kaempferol-3-O-α-lrhamnopyranosyl-(1 → 2)-β-D-xylopyranoside were isolated from young twigs and leaves of *Caesalpinia bonduc* and their interaction with cancer target proteins such as Tyrosine kinase (TK), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMP) were analyzed using molecular docking. They showed strong interactions with the proteins than their respective drug inhibitors (Iheagwam *et al*., 2019). Molecular docking of active constituents of *Cannabis indica*,

Azadirachta indica, and *Annona muricata* like cannabidiol, nimbin, and acetogenin respectively using autodock exhibits very high binding affinity to phosphatidylinositol 3-kinase (PI3K)/serine-theronine proteinkinase signalling molecules which plays an important role in cell survival, a progression which leads to different types of cancers including breast cancers (Mittal *et al.* 2018).

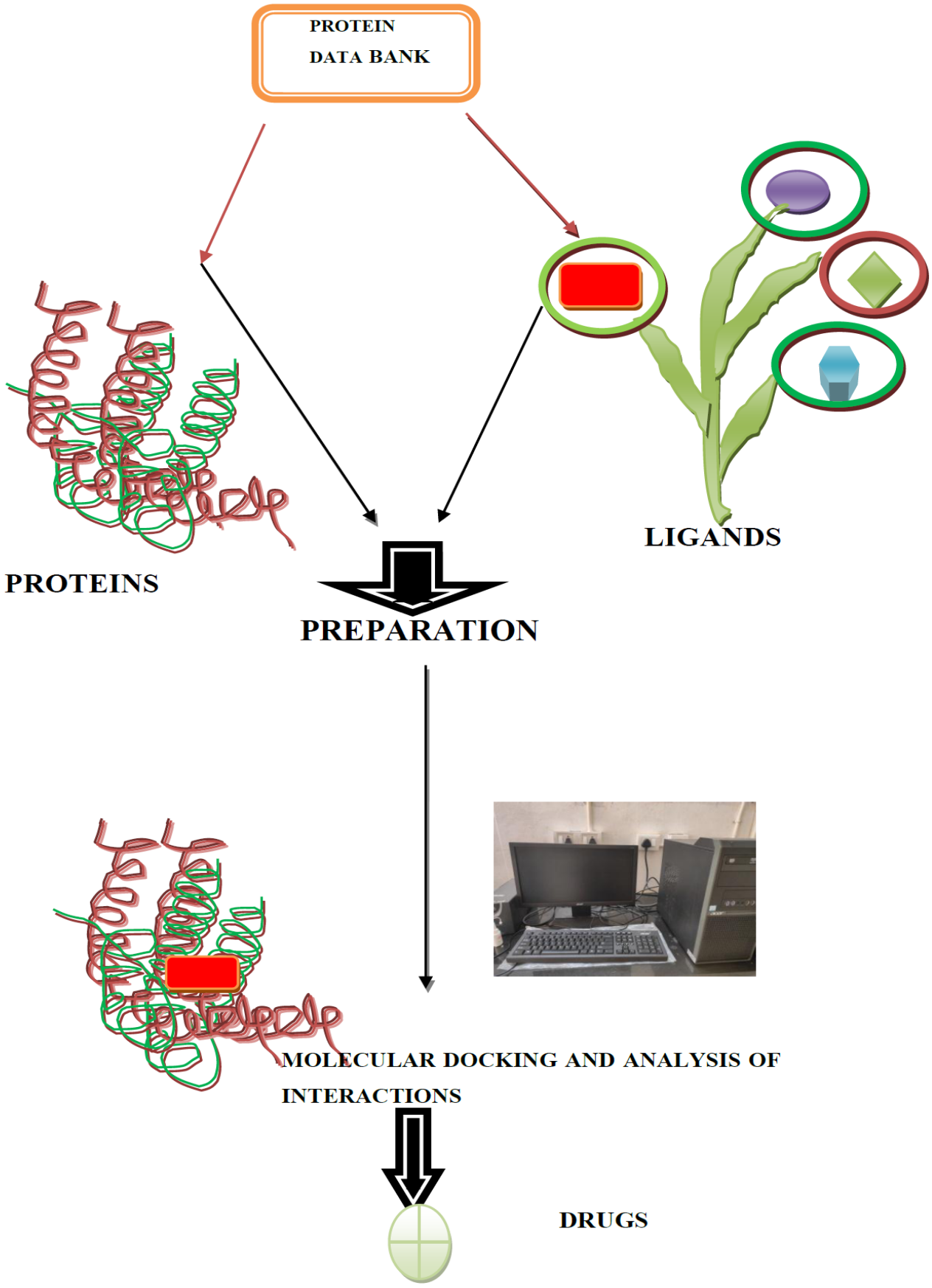

Fig. 6: Demonstartion of molecular docking: A summary

4.3.5 Hsp90

An emerging therapeutic strategy for the development of new drugs to treat breast cancer is Hsp90 inhibition. A structure-based pharmacophore model generated was utilized to screen inhibitors from natural compounds dataset of 3210 compounds and evaluated by molecular docking-based scoring with Genetic Optimisation for Ligand Docking (GOLD) program v5.2.2 (Rampogu *et al*. 2019).

4.3.6 SIRT2

SIRT2 (Sirtuin2, a class 3 histone deacetylase) has a role in the regulation of BC. Methyl Cinnamate and eucalyptol from *Ocimum basilicum* will bind to the active pocket of SIRT2 and shows binding energies -5.98 Kcal/mol and -6.06 Kcal/mol respectively. This shows the protective effects of phytochemicals from basil against breast cancer (Bhura *et al*., 2019).

4.3.7 ABCC6

In several cancer cells, a drug transporter protein ABCC6 is found dysregulated and thereby getting resistant to chemotherapeutic drugs. When this ABCC6 is docked with phytochemical subtrifloralactone G, a withanolide isolated from *Deprea subtriflora*, shows the highest binding energy. Subtrifloralactone G through ADMET analysis was found to be useful for the treatment of cancer especially Triple-negative breast cancer (TNBC) (Pandya *et al*., 2020).

4.3.8 Bcl-2 and SURVIVIN

Coclaurine, coreximine and synephrine isolated from *Annona muricata* will interact with Bcl-2 and survivin which plays an important role in the regulation of apoptosis in breast cancer cells. Amino acids located in the active sites of the Bcl-2 and survivin interacts with the phytochemical compounds, hence they can be utilized as therapeutic agents for cancer treatment. Docking simulations were done using ArgusDock (Muthu and Durairaj, 2016). Inhibition of survivin by an alkaloid piperine and some of its derivatives by binding to the BIR domain is been analyzed through molecular docking. Survivin can be used for the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated therapies for targeting triple-negative breast cancer (TNBC) cells (Hussain *et al*., 2019).

4.3.9 BRCA2

Selected compounds from *Tinospora cordifolia*, *Ocimum tenuiflorum*, *Podophyllum hexandrum*, *Andrographis paniculate*, and *Beta vulgaris* when allowed to interact with BRCA2 breast cancer tumor receptors, among the 63 compounds isolated isocolumbin have maximum negative binding energy against BRCA2 receptors (Bhatia *et al*., 2021).

4.3.10 ADDRESSIN

The binding energy of − 4.040, −5.127, and − 5.251 kcal/mol, respectively were obtained when local docking of glycyrrhizin with breast tumor cell proteins like p53 (a cellular cancer antigen), NF-kB (nuclear factor kappa B)-p105subunits, and addressin were conducted. ExPASy's ProtParam Proteomicsserver is used for assessing their physiochemical characteristics. BSP-SLIM server is used for docking the protein structure. Glycyrrhizin can be utilized as a potential drug candidate for cancer treatment (Supramaniam and Elengoe 2020).

SCOPE

For the development of target-based therapies, structure-based drug design techniques are used. The sophisticated molecular docking method plays a crucial role to identify ligands for targets of therapeutic interest. Only a few natural compounds have been explored for the treatment of BC. The molecular docking method can hence utilize to find out the aptest compound that can interact with different BC receptors, thereby further proceedings of development of drugs from natural compounds.

Conclusion

This review demonstrates the role of molecular docking in finding the phytochemicals from different plants as anticancer drugs of BC. Different phytochemicals are considered as ligands, the best-docked ligands with different target proteins are analyzed and thereby confirm the best anticancer agent. Interaction of Ligand receptors and their binding energies shows how to fit the ligand to the target molecule. Molecular docking of phytochemicals against breast cancer also gives structural features required to improve inhibitory activities. The role of molecular docking for a finding of novel anticancer drugs design and thereby the development of new pharmaceutical and therapeutic agents against breast cancer.

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