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A comprehensive review: Breast cancer and the role of natural products in its treatment via in silico approach

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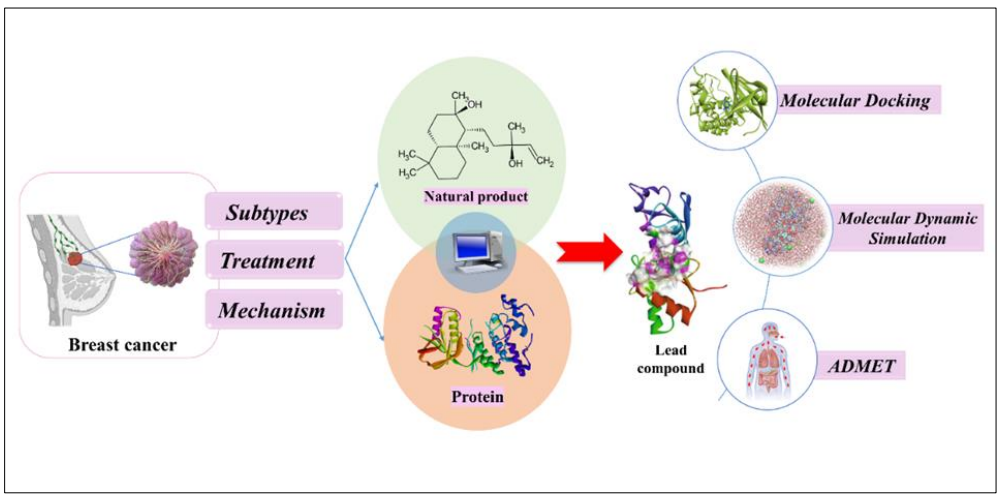
Abstract

Breast cancer is the most frequent malignancy and a leading cause of cancer-related death among women, thus representing a global health challenge linked to its high heterogeneity. However, there has been major progress in breast cancer diagnosis and therapy, still it remains a heavy burden with high incidence and death rate majorly in females. This review provides a comprehensive exploration of breast cancer, mechanism pathways and treatment options and highlights the potency of significant alkaloids, flavonoids, and other natural compounds, emphasizing their potential as therapeutic agents. Moreover, the present study employs an approach focusing on computational methods including molecular docking, molecular dynamics simulation, and Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) to investigate the potential of natural products in breast cancer treatment. Furthermore, this review concludes by the discussion of recent studies which outlines the role of natural products via in silico approach for breast cancer treatment.

Keywords: Breast Cancer; Natural Products; In Silico Approach; Therapeutic Agents; Treatment

Graphical Abstract



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1. Introduction

Breast Cancer (BC) is the highly heterogeneous and the most frequently diagnosed cancer which is now the leading cause of death among women. Breast cancer is a type of carcinoma that develops from breast cells with an uncontrolled growth; some have found to begin in the ducts, while others beginning in lobules. Appearance of lump in the breast or abnormal nipple discharge is the first sign of BC. The fact that BC is most commonly found in women and people assigned female at birth (AFAB) at the age of 50, males or even younger women can also develop the disease[1]. Internationally, breast cancer is a major public health concern due to its high incidence (second most common cancer diagnosed) and the highest rate of mortality among women worldwide[2]. In 2020, an estimated global number of new cases (2.3 million) were observed and the disease accounted for around 11.7% of all cancer cases worldwide which made breast as a major cause of incidence overtaking lung and prostate cancer. According to epidemiological studies, global breast cancer burden is expected to exceed over 2 million by the year of 2030. In India, between 1965 - 1985, the onset rate was almost about an alarming figure of approximately 50%[3]. Figure 1A and 1B shows that according to the GLOBOCAN data 2022, breast cancer is made up (192,020) of all new cancer cases and (98,337) of all mortality cases in females in the age group range (0 – 85+) years in India.

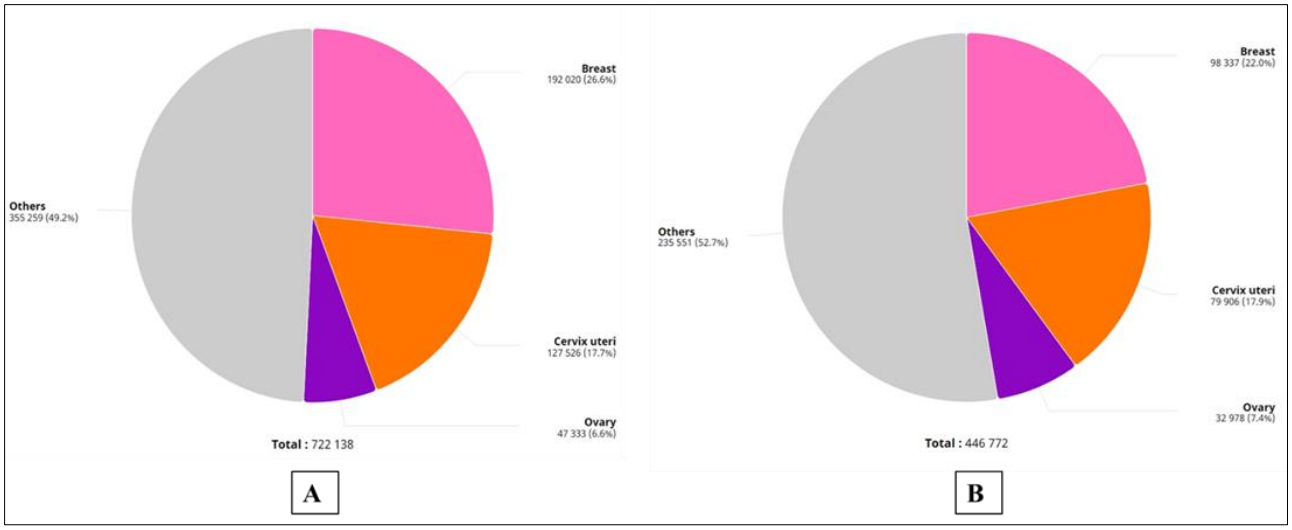


Figure 1 Statistics of breast cancer cases (A) No. of incident breast cancer cases in females (B) No. of mortality of breast cancer cases in females in India (data adapted from https://gco.iarc.fr/en)

Nowadays, breast cancer has become a major threat by growing risk factors. The causes of cancer are complex and derive from environmental factors such as tobacco, chemical and radiation exposures, and infectious agents, as well as excess alcohol consumption, significant overweight or obese, genetic and non-genetic risk factors, internal causes including genetic mutations, hormone exposures, immune and metabolic dysfunctions, and gene alterations. Traditional treatments like surgery, hormonal therapy, radiotherapy or radiation therapy, chemotherapy, and small-molecule targeted therapy routinely fail to meet the complexity and heterogeneity of certain subtypes of breast cancer. Inadequate treatment sometimes leads to resistance to the drug and progression of metastatic disease. Furthermore, the main reason behind drug resistance is due to high inconstancy and adaptive mechanisms employed by cancer cells, resulting in failure of treatment[4] [5]. Therefore, finding effective therapeutic targets and agents is necessary. Considering their low toxicity and wide variety, natural products and their analogues have increasingly been seen as potential sources for small-molecule anticancer drugs[6] [7]. Natural products (NPs) hold significant importance in the treatment of a disease, including cancerous diseases. Natural products originate from the internal chemical characteristics of plant extracts. These extracts are flavonoids, alkaloids, polysaccharides, quinonoids, terpenoids, coumarins, and saponins. Overall, it has been well established that natural products originating from plants have many properties and medicinal activities such as anti- inflammatory, anti-viral, antioxidant, neuroprotective, and cardioprotective actions. Additionally, natural products, originating from medicinal plants, are found all over the world[8,9].

2. Molecular subtypes of BC

The molecular subtypes are important for grading cancer and identifying the most effective treatment strategies against the disease. The expression of hormone receptors is one of the key factor in deciding the type of therapy required[10].

With biomarkers like progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), breast cancer is divided into several subtypes i.e. Luminal A, Luminal B, basal-like and HER2-positive (HER2+). Certain cases of basal-like breast cancer are also considered as Triple-negative breast cancer (TNBC) because TNBC is defined as being negative for these three biomarkers[11,12]. The molecular subtypes of BC are described in detail in Figure 2.

2.1. ER/PR receptors

The Estrogen receptor (ER) plays a vital role in diagnosis. About 70–75% of invasive breast carcinomas show high levels of ER. The Progesterone receptor (PR) shows up in over half of ER-positive patients. It is rare to find PR in those with ER-negative breast cancer. PR expression is regulated by ER. Both ER and PR are expressed often in BC and are considered as biomarkers of BC[13,14].

2.2. Luminal A breast cancer

This subtype represents about 50-60% of all breast cancers. It is characterized by the activation of genes which are controlled by the ER transcription factor with low levels of Ki-67 and best prognosis. The standard treatment for this subtype mainly consists of hormonal therapy. It has been defined as ER+/HER2- and low Ki-67[15,16].

2.3. Luminal B breast cancer

This subtype consists about 10-20% of all breast cancers. It shows ER positive and HER2 negative, and presents high levels of Ki-67 or ER+/HER2+. As the growth of Luminal B is faster than luminal A, they have slightly worse prognosis. About 6% of Luminal B tumors are clinically ER-/HER2-)[15]. Luminal A and B both these subtypes show same gene expression of ER, but in comparison, the prognosis of Luminal B is very different. The biological distinct between these two subtypes is an overexpression of cell proliferation genes, such as MKI67, cyclin B1 in Luminal B which mainly expresses EGFR and HER2[17] [15].

2.4. HER-2 enriched breast cancer

HER2 expression represents 15–25% of breast cancers. HER2 overexpression is among the first events that occur in the development of breast cancer. They usually have worse prognosis. HER2 increases the recognition rate of metastatic BC by 50% and sometimes even 80%. HER2 amplification leads to increased overactivation of proto-oncogenic signaling pathways, leading to uncontrolled cancer cell growth, which results in worse clinical outcomes in HER2+ cases[13,18,19]. HER2 tumors are characterized by high proliferation rates, including 75% having high histological grade and over 40% having p53 mutations[15], [20]

2.5. Triple-negative / basal-like breast cancer (TNBC)

TNBC subtype accounts for about 20% of all breast cancers[21–25]. It shows ER-negative, PR-negative and HER2-negative as discussed in the Figure 2.

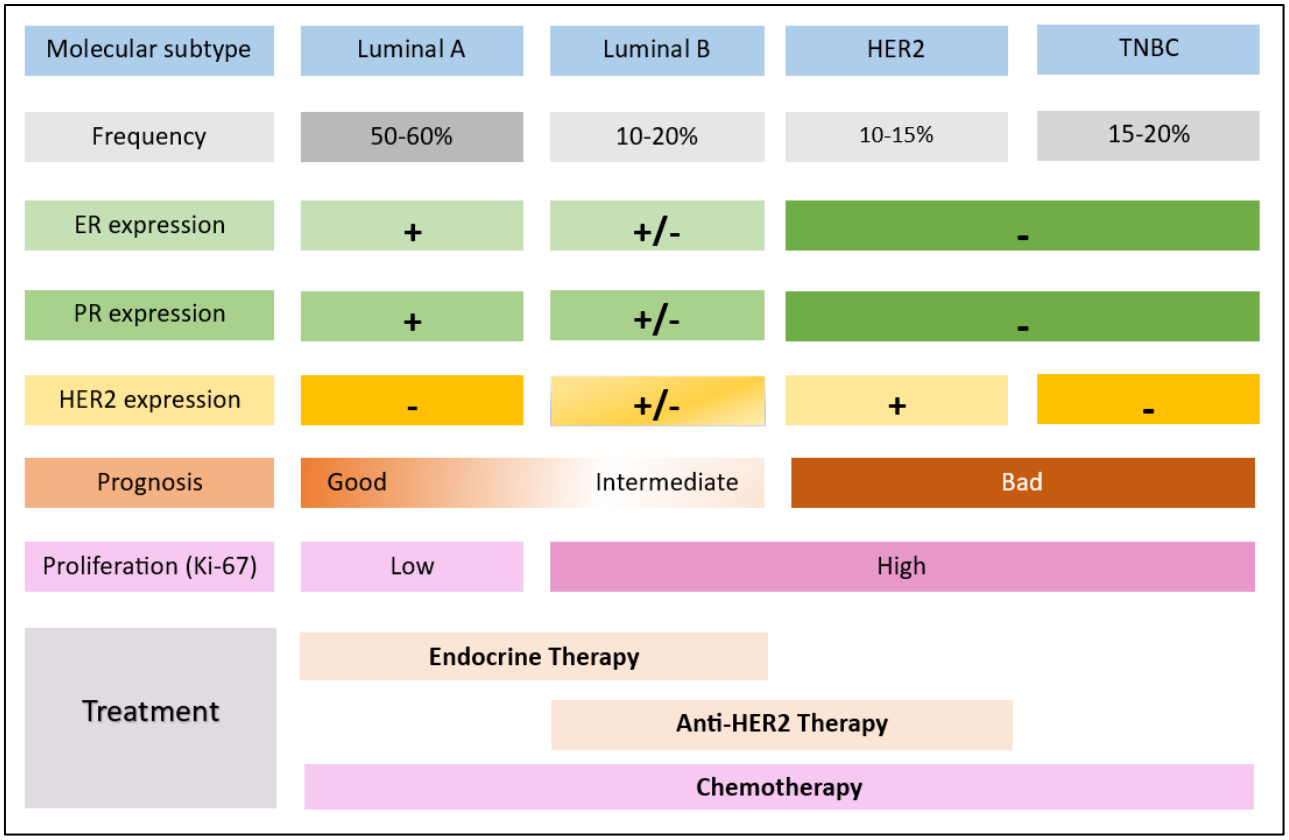


Figure 2 Subtypes, Characteristics and Types of treatment of Breast cancer [15]

3. Mechanism and Treatment of breast cancer

3.1. Mechanism pathway of BC

To study the mechanism pathway of BC, it is important to know that cellular functions are carried out by set of molecules, usually enzymes that produces multiple chemical reactions (signals), and certain molecules that results in the formation of a response and a "pathway" which might be further altered by some factors[26]. Efforts were made by the researchers in past few decades to categorize or distinguish BC based on their molecular or intrinsic biology. They inspected the signaling pathways that regulates the mechanism of formation, maintenance, and expansion of tumor as well as promotion of cell survival[15] [27]. The receptors on cellular membranes and ion channels respond to several environmental factors, these include, but are not limited to, hormones, neurotransmitters, antibodies, cytokines, growth factors, and ions that modulate cell communication. Those stimuli will act on their receptors or ion channels to activate intracellular pathways like MAPK, PI3K/AKT, and Ca2+ release as shown in Figure 3. The cross-talks of the different signaling processes increases the complexity of signaling cascades of BC, and as a result, makes the treatment process very difficult [28] [29]. Various signaling pathways such ER signaling pathway, HER2 signaling pathway, P13K/AKT/mTOR signaling pathway, RAS/MAPK/ERK signaling pathway, Wnt / β-catenin signaling pathway etc. are discussed in Figure 3.

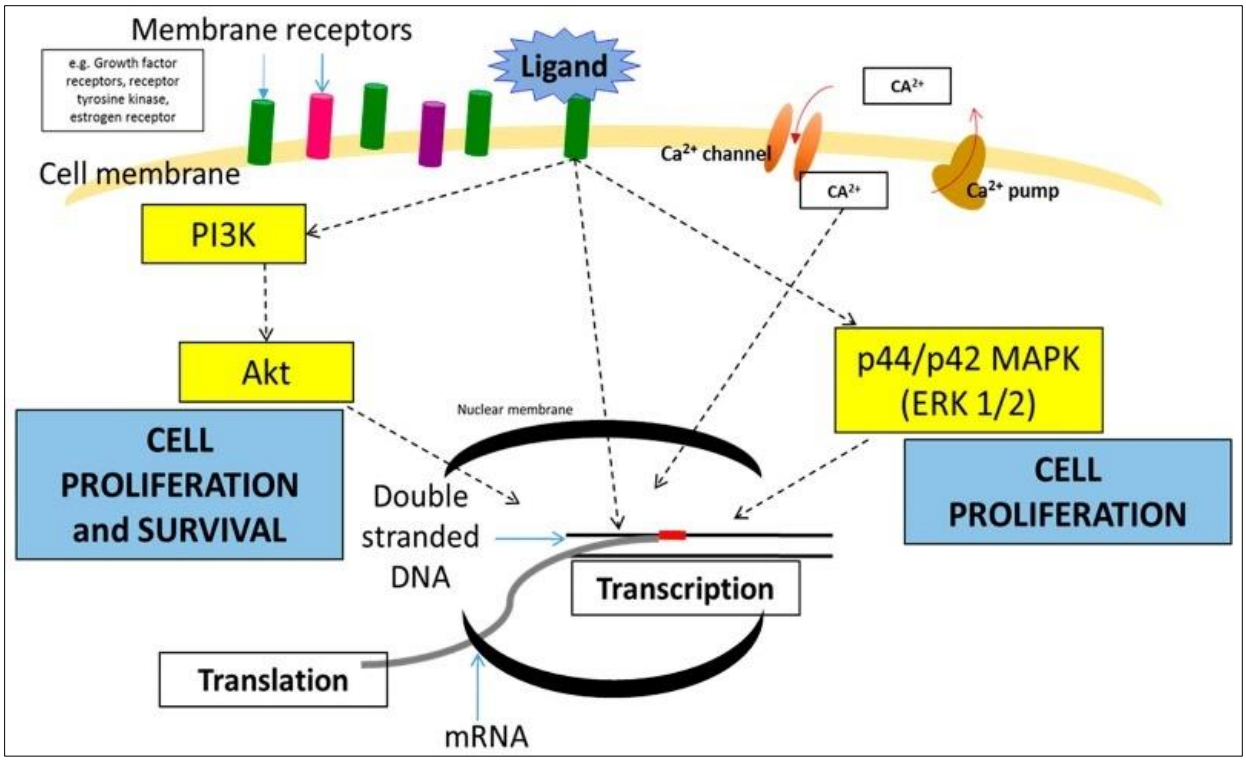


Figure 3 Common signaling pathways of breast cancer leading to proliferation and survival of BC cells. Adapted with the permission of ref[28]

3.1.1. ER signaling pathway

Estrogen receptors comprise of membrane estrogen receptors (G protein-coupled receptors) and nuclear estrogen receptors (ER-alpha ER-beta). BC cells typically show high expression of ER-alpha and low expression of ER-beta receptors. These two receptors forms homo- or heterodimers when binded to a ligand and further proceeds into the nucleus to perform the main function of the ER i.e. for transcriptional regulation[21].

3.1.2. HER-2 signaling pathway

HER-2 pathway is a de-regulation pathway which results in proliferative signaling. HER-2 receptor belongs to the human epidermal receptor (HER) family[15].

3.1.3. P13K/AKT/mTOR signaling pathway

This is a downstream oncogenic signaling pathway which shows cellular functions like cell proliferation, survival, metabolism, division, apoptosis and migration ability[15]. HER receptors are responsible for the activation of this pathway and is linked with resistance to endocrine therapy against breast cancer[26] [30].

3.1.4. RAS/MAPK/ERK signaling pathway

As mentioned above, this pathway is also a downstream signaling pathway which is activated by hormone receptors, growth factors which are in linkage with resistance to anti-breast cancer drugs[26] [31].

3.1.5. Canonical Wnt / β-catenin signaling pathway

This pathway plays an important role in processes like biological and pathological processes such as development of mammary gland, breast tumorigenesis[21] [32].

3.2. Common types of treatment of BC

Breast cancer is a type of cancer which progresses from breast cells with an uncontrolled growth; some have been found to begin in the ducts, while others initiate in lobules. The risk of getting breast cancer increases at any age from puberty onwards. As the molecular / intrinsic subtypes of Breast cancer is classified on the basis of gene expression, the characteristics itself decides the selection of treatment. Surgery, Radiotherapy, and Chemotherapy are the most

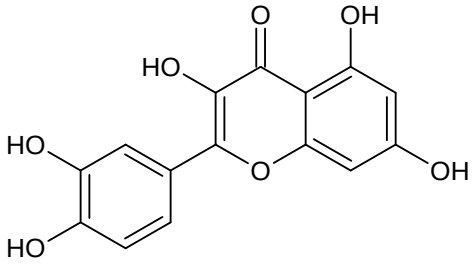
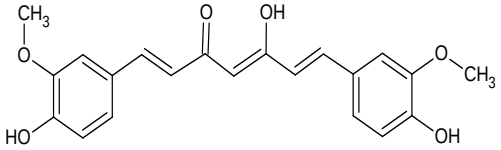
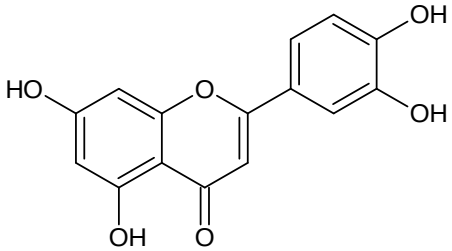
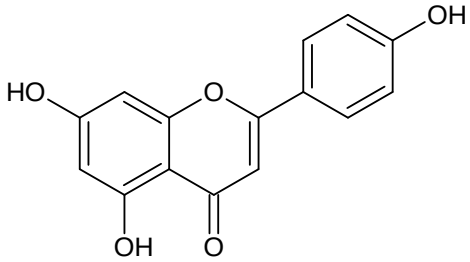
common therapies used in treatment for all subtypes of BC as depicted in Figure 2[33], [34]. As the history of radiotherapy (RT) starts when W. C. Rontgen discovered X-rays in 1895, RT is used to treat all BC subtypes. Radiotherapy has more importance in TNBC as it is the only subtype of BC with no personalized therapy[33]. One of the main limitations of traditional treatment methods is that they increase the risk of attacking non-targeted areas and exceeding high chances of damage to the healthy cells[35]. Normally, in breast surgery mostly mastectomy (removal of breast) proceeding by the breast reformation, or lumpectomy (breast-conserving surgery)[33]. Depending on the type, stage and size of tumor the type of surgery is decided. After breast surgery, sometimes chemotherapy and radiation therapy are given to some patients as this reduces the risk of getting cancer back. Detection at an initial stage and proper diagnosis of breast cancer leads to better standard of life for women[35]. Treatments like chemotherapy along with chemotherapeutic drugs like anthracyclines and taxanes helps in fighting breast cancer[26] [36].

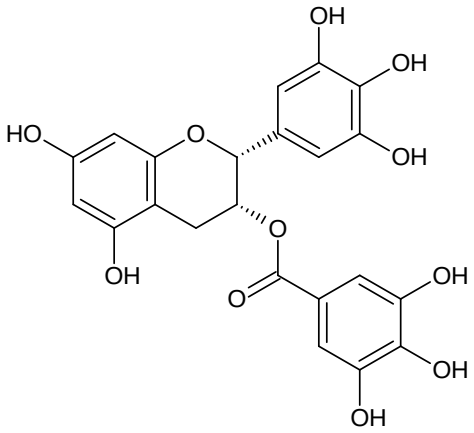
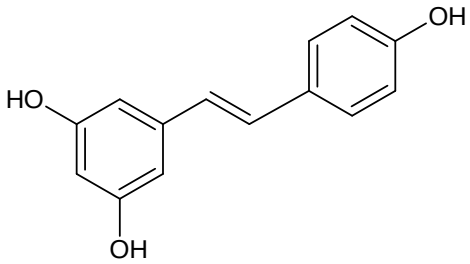
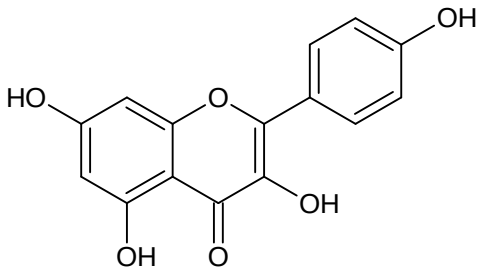
Tamoxifen, raloxifene etc. that target estrogen receptor and aromatase inhibitors like anastrozole, letrozole and exemestane which have been used to prevent breast cancer in postmenopausal women above 35 years of age decrease its risk[26] . Nanocarriers like liposomes, polymeric micelles, quantum dots, nanoparticles and dendrimers have been found to enhance the therapeutic potential of anticancer treatment[35]. A total of 207 drugs have been approved by FDA for cancer treatment out of which 39 are specifically approved for breast cancer or adjuvant breast cancer treatment[37]. Earlier Methotrexate was the first and most used cytotoxic drug approved by FDA for BC. In 1977, Estrogen receptor modulators came into attention in the medical field as Tamoxifen emerged as a precise medicine for cancer. Then in 1998, the advent of Trastuzumab, a humanized monoclonal antibody directed against the receptor tyrosine kinase HER2 became another milestone in the treatment of breast cancer. Subsequently, another variant of hormone therapeutic drugs such as Anastrozole, Letrozole were incorporated in the first line treatment of ER positive type of BC[37] [38]. Generally, combination therapy i.e. combination of drug with the natural products is the more effective approach in the treatment of breast cancer surge in as some of the natural products incidentally have antitumor activity.

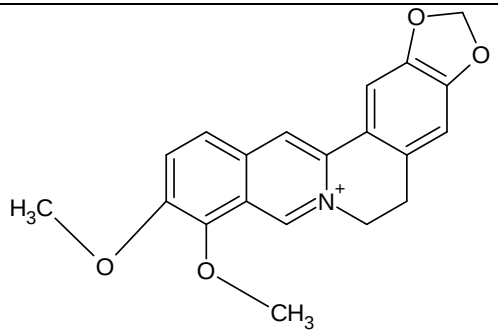
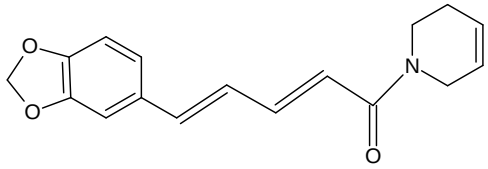
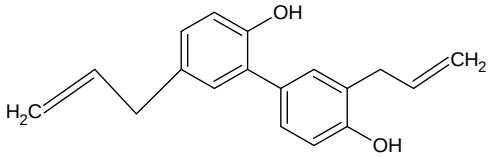
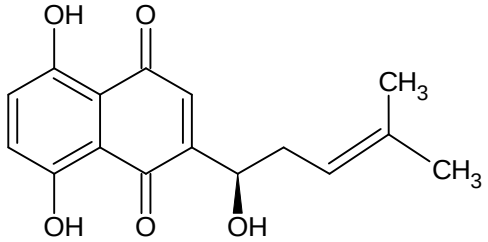
4. Role of Natural products in BC treatment

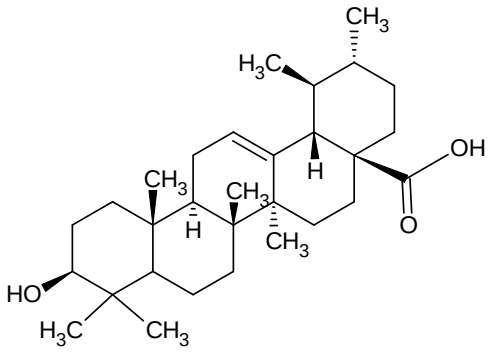
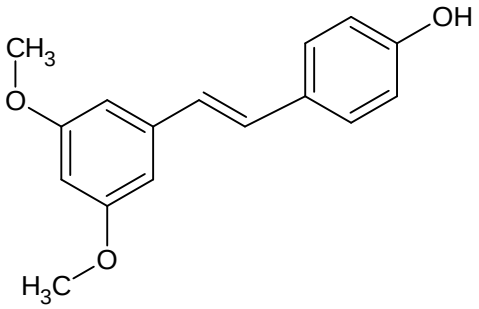
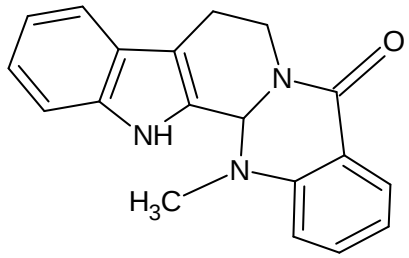
In contrast to pharmacological chemotherapeutics that serve as treatment options, natural products have been consumed by humans for a long time and typically have low systemic toxicity. Many NPs with distinct mechanisms have preclinical efficacy[39] . From past many decades, natural products derived from plants and animals are benefitting humans in various aspects. Most of the researchers find natural products useful in design and discovery of novel drug compounds with less toxicity and exhibit anticancer potentials. NPs extracted from plants sources (such as alkaloids, terpenes, quinones, polysaccharides) have verified anti-tumor properties. Many NPs are also derived from various animals, micro-organisms, and marine organisms. For e.g. Paclitaxel (diterpene alkaloid) extracted from the Pacific yew, is helpful in the treatment of breast cancer, ovarian cancer, and non-small cell lung cancer[6] . NPs are used majorly in numerous therapeutic properties such as anti-inflammatory, antioxidant and anti-cancer properties[40]. Examples of NPs used as anti-breast cancer agents are listed in Table 1.

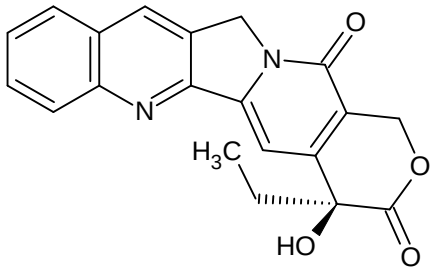
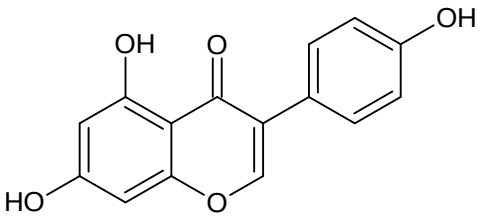
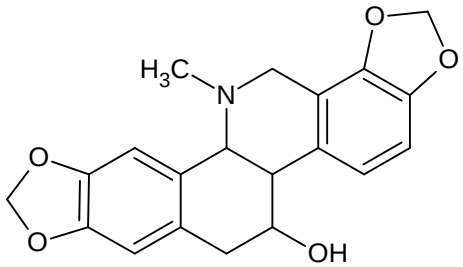
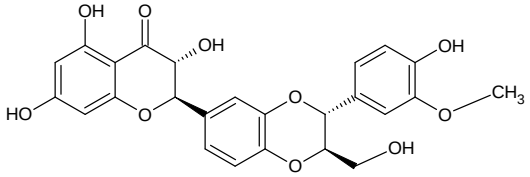
Table 1 Natural products and their derivatives, properties used in treatment of breast cancer

Sr. no.	Name of natural products	Structure of NP	Function	Class of NP	Ref.
1.	Quercetin		Inhibits the growth and cell survival of TNBC cells	Flavonoid	[6,41]
2.	Curcumin		Inhibits cell proliferation Induces cell apoptosis	Flavonoid	[22][23]
3.	Luteolin		Induce apoptosis Inhibit tumor metastasis Anti-inflammatory	Flavonoid	[45–48]
4.	Apigenin		Inhibits ER-positive breast cancer cell proliferation Induce cell apoptosis	Flavonoid	[49–51]

5.	Epigallocatechin gallate		Inhibit proliferation Induce apoptosis	Polyphenol	[52,53]
6.	Resveratrol		Induce apoptosis and autophagy	Polyphenol	[51,54]
7.	Kaempferol		Induce apoptosis	Polyphenol	[48,55], [42]
8.	Berberine		Inhibit proliferation and metastasis Induce autophagy, apoptosis, cell cycle arrest and DNA damage	Alkaloid	[56–58]

					
9.	Piperine		Induce apoptosis and cell cycle arrest Inhibit proliferation	Alkaloid	[51,59]
10.	Lycopene		Inhibit proliferation and metastasis and apoptosis	Tetraterpenoids	[60–63]
11.	Honokiol		Inhibits tumor cell proliferation, and programmed cell death	Biphenols	[64,65]
12.	Shikonin		Inhibits estrogen-encouraged cell production	Naphthoquinone	[66–68]

13.	Ursolic acid		Apoptosis Anti-metastasis	Triterpenoid	[69,70]
14.	Sulforaphane		Induce cell apoptosis	Isothiocyanate	[71–73]
15.	Pterostilbene		Apoptosis Anti-proliferation	Stilbenoid	[70,74]
16.	Evodiamine		Induces apoptosis Inhibits metastasis	Alkaloid	[75–79]

17.	Camptothecin		Induce apoptosis DNA damage	Alkaloid	[80,81]
18.	Genistein		Induces cell proliferation Induces autophagy	Flavonoid	[82,82,83]
19.	Chelidonine		Anti-proliferative activity	Alkaloid	[82,84]
20.	Silibinin		Induces autophagy	Flavonoid	[69,85,86]

4.1. In-silico study by using natural products

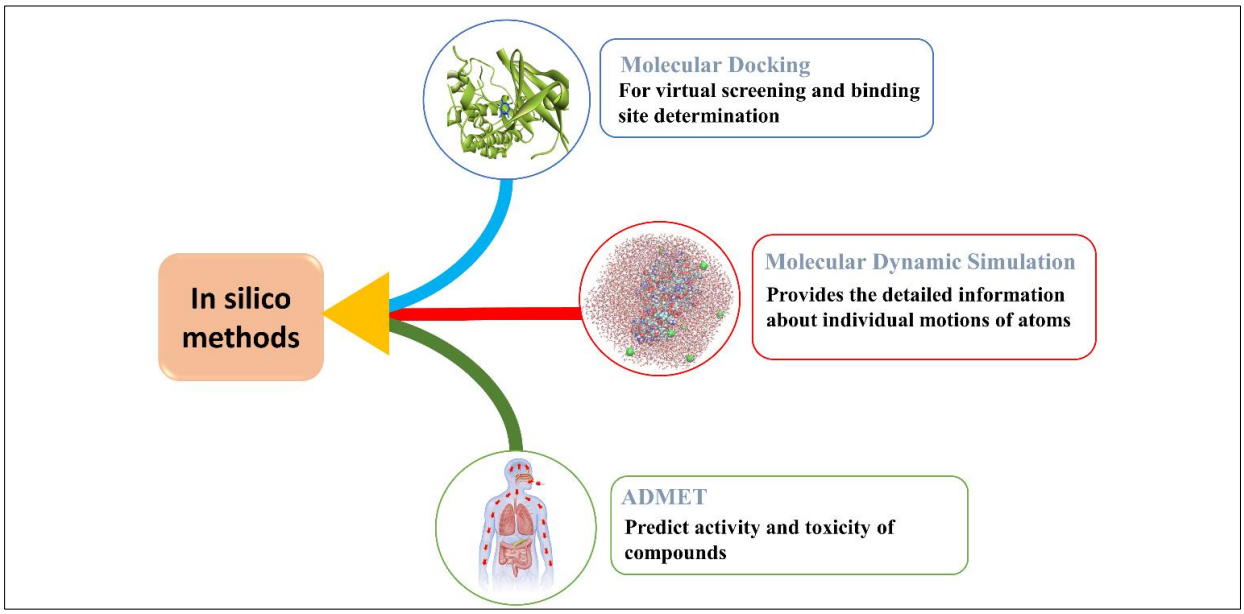


Figure 4 In silico methods - Molecular Docking, Molecular Dynamic simulation, ADMET

Usually, the process of drug discovery through traditional method is very labor-intensive and time consuming. Because, it takes a long period of time (years) and hundreds of millions to design and discover a novel compound and to reach its clinical (final) phase. So, to avoid wastage of time, cost of preclinical trials, other resources, and to overcome these parameters during the drug development, In-silico method is used. Computational methods which involve the following: Molecular Docking – for binding site determination, Absorption Distribution Metabolism Excretion and Toxicity (ADMET) - to predict activity and toxicity, Molecular Dynamics Simulation (MDS) – provides the detailed information about individual motion of atoms. In silico approach (computational methods) is a key factor in the identification, development, and discovery of drugs Figure 4[87,88], [89]. The drug development process can be notably speed-up by computational modelling, which also improves efficiency. It is important to validate the findings of the computational research through experimental testing. This in silico approach has significant potential for creating a new and effective cancer treatments, as it integrates drug modelling with experimental validation[90].

4.1.1. Molecular Docking

Types of In silico study have been classified namely Structure-based drug design (SBDD) and Ligand-based drug design (LBDD). In structure-based type, lead identification is carried out by taking into account the active site of macromolecules, the existence of particular amino acid residues at binding pockets and how strong the interactions are with corresponding species. In contrast, Ligand-based drug design (LBDD) is used when the receptor (protein) information is not available in the database. In-silico approaches such as molecular docking are commonly used in Computer aided drug design (CADD). Structure and ligand-based techniques depends on the availability of crystallized 3D protein (receptor) structures in the Protein Data Bank (PDB) (https://www.rcsb.org/)[91] [92]. Examples of recent studies published in this area that used molecular docking to identify the plant-based compounds as leads are listed and are discussed in detail in Table 7.

Case 1

In this case, they selected 131 phytocompounds from 51 plant families, out of 131 phytocompounds only 42 of them showed drug like properties which were further used for docking and dynamic studies. The phytocompounds were retrieved from PubChem. 3D structure of EGFR (PDB id: 1M17) and HER2 (PDB id: 3RCD) receptors as targets which were retrieved from the Protein Data Bank (PDB) database. The molecular docking study was carried out using Autodock Vina in PyRx docking tool. They also used commercial drugs – Erlotinib, Neratinib and TAK-285 which were docked with the same target proteins. The docking analysis was carried out using Discovery Studio v19.1.0.18287 Biovia for the best docked poses result. As 40 NPs were compared with reference drugs, 38 compounds showed lowest binding energy. Out of those 3 compounds (Camptothecin, Panaxadiol, Ursolic acid) showed lowest binding energy when compared with ref. drugs when docked with EGFR (1M17). Similarly, with HER2 (3RCD) only 3 phytocompounds (Emetine, Alpha-Peltatin, Panaxadiol) showed lowest binding energy (kcal/mol) than reference drugs. This analysis

specifies an idea of efficacy of phytocompounds over clinically approved reference drugs. The detailed binding affinities of the hit compounds and the drugs are reported in Table 2,3[93].

Table 2 Binding energies of compounds when docked with EGFR (1M17)[93]

Sr. no.	Phytocompounds/ PubChem Id	Binding energy (kcal/mol)
1.	Camptothecin (24360)	-8.9
2.	**Panaxadiol (73498)**	**-9.4**
3.	Ursolic acid (64945)	-9.1
4.	Erlotinib (ref. drug) or (EGFR) (176870)	-7.0

Table 3 Binding energies of compounds when docked with HER2 (3RCD)[93]

Sr. no.	Phytocompounds/ PubChem Id	Binding energy (kcal/mol)
1.	Emetine (10219)	-9.5
2.	**Alpha-peltatin (92129)**	**-9.7**
3.	**Panaxadiol (73498)**	**-9.7**
4.	Neratinib (ref. drug) (9915743)	-9.5
5.	TAK-285 (ref. drug) (11620908)	-9.7

Overall, Panaxadiol showed binding energy (-9.4 kcal/mol) when docked with EGFR (1M17). This led to identification of Panaxadiol as the best inhibitor of EGFR. Also, Panaxadiol and Alpha-peltanin represented the lowest binding energy of -9.7 kcal/mol. This study concludes that Panaxadiol has the ability to inhibit both the receptors of BC i.e. EGFR and HER2[93].

Case 2

In this case, they downloaded approved phytochemicals for BC from PubChem in 3D sdf file format. The 3D crystal structure of proteins including BRCA1 (4Y2G), BRCA2 (3EU7), and MDR1 (6C0V) were collected from Protein Data Bank (PDB) database. (BRCA1: Breast tumor suppressor gene 1, BRCA2: Breast tumor suppressor gene 2, MDR1: Multiple drug resistance 1. Active binding sites were analyzed using Drug Discovery Studio version v.20.1.0.19295 and 3D Ligand Site Virtual tool. Among the 16 phytochemicals, only 10 NPs showed best binding energy and among them Sclareol generated highest binding energy of -9.8 kcal/mol when docked with BRCA1 (4Y2G). In case of BRCA2 (3EU7) protein, only 11 NPs showed up with the best binding energy but among them only alpha-Hederin generated highest binding energy of -11.0 kcal/mol. Similarly, in case of MDR1 (6C0V) protein, only 11 NPs showed up with best docking results but among them only andrographolide exhibited significantly improved binding energy of -9.2 kcal/mol as compared to the other compounds. As some of the natural products showed best binding energies but from the study of noncovalent bond interaction compared to other compounds, they claimed that alpha-hederin, andrographolide, auricularic acid, asiatic acid, sinularin and apigenin will be the best phytocompounds for BRCA1, BRCA2, and MDR1-cancer for the upcoming research. The detailed binding affinities of the compounds and the target proteins are reported in Table 4[94].

Table 4 Docking results showing binding energies[94]

Sr. no.	Natural Products	BRCA1 (4Y2G)	BRCA2 (3EU7)	MDR1 (6C0V)
1.	Sclareol	**-9.8**	-7.2	-
2.	Hispolon	-7.8	-6.7	-7.4
3.	Citrinin	-7.5	-7.6	-7.6

4.	Curcumin	-7.2	-6.7	-8.3
5.	Alpha-Hederin	-6.9	**-11.0**	-8.3
6.	Andrographolide	-6.2	-8.2	**-9.2**
7.	Apigenin	-5.8	-7.7	-9.0
8.	Auricularic acid	-6.2	-7.8	-8.5
9.	Sinularin	-6.8	-9.0	-8.4
10.	Asiatic acid	-6.5	-8.9	-8.1
11.	5-Fluorouracil	-4.5	-5.0	-5.2

Case 3

In this case, they used an open-source software i.e. CB-Dock2 (GUI version of Auto Dock Vina) for screening of phytochemicals. They also used PyMol 2.5.2 molecular graphic system software for active site prediction[95]. selected P53 (Uniprot ID- P04637) and NOTCH (1-4) as target proteins and 4 herbal compounds (Epigallocatechin gallate, Piperine, Gingerol, Thymoquinone) were selected. In this, the complexes that made more no. of hydrogen bonds showed the strong binding affinities. For visualization, they used PyMol visualizer tool. Proteins were retrieved from UniProt (https://www.uniprot.org). The docking results showed that among all 4 natural compounds Epigallocatechin gallate (Green tea) showed the highest Vina score of -9.2 with more no. of hydrogens and hydrophobic interactions, when docked with P53 protein. The docking results are represented in the Table 5[95]. This protein-ligand complex with strong binding affinity and the best docking results were taken into consideration for further analysis.

Table 5 Docking results of CB-dock of Epigallocatechin gallate (green tea) ligand with target proteins[95]

Sr. no.	**Target**	**Ligand**	**Binding energy (kcal/mol)**
1.	**P53**	**Green tea**	**-9.2**
2.	NOTCH 1	Green tea	-8.1
3.	NOTCH 2	Green tea	-8.1
4.	NOTCH 3	Green tea	-9.4
5.	NOTCH 4	Green tea	-7.5

Case 4

In this case, they selected 40 phytocompounds from Foeniculum vulgare Mill for molecular docking and the 3D structures were downloaded from PubChem database (www.pubchem.com). The target protein Estrogen Receptor Y537S (PDB ID: 6CHZ) were selected and the 3D structure was downloaded from PDB database (http://www.rscb.org/pdb). To study the interactions of protein-ligand interactions Discovery Studio (https://discover.3ds.com/d) was used. From all the selected phytocompounds, alpha-pinene and D-limonene showed the best binding energy amongst all the 40 phytoconstituents. Docking was carried out by using AutoDock vina software. Alpha-pinene showed binding energy of -6.0 kcal/mol and D-limonene showed binding energy of -5.9 kcal/mol when docked with 6CHZ. From these results, alpha-pinene and D-limonene can be considered as the lead compounds against breast cancer. Figure 5 represents the 3D interaction of docked complexes: (A) D-limonene with 6CHZ and (B) alpha-pinene in which purple shows the target protein, green represents hydrophobic interactions, and the red shows the ligand[96].

Case 5

In another case, selected 95 gene targets from screening out of total 143 compounds of Scutellaria baicalensis from the TCMSP (http://tcmspw.com/tcmsp.php) database. Analysis of the interactions between the target and the active site was done by using AutoDockTools-1.5.6, Discovery Studio 4.5 Client, and PyMOL software. The top five compounds were then selected for docking studies: (5,2-dihydroxy-6,7,8-trimethoxyflavone, moslosooflavone, stig masterol, coptisine, and 9-cedranone). The protein structures were retrieved from PDB database having PDB id: AKT1 (PDB ID: 4EJN), IL6 (PDB ID: 4O9H), TNF (PDB ID: 2AZ5), TP53 (PDB ID: 7BWN), ESR1 (PDB ID: 1A52), JUN (PDB ID: 5T01), VEGFA (PDB ID: 1VPF), FOS (PDB ID: 1A02) and HIF1A (PDB ID: 1H2K), PTGS2 (PDB ID: 5F19). Amongst all, only 3

complexes showed best binding energies including: coptisine–AKT1, stigmasterol–AKT1, and coptisine–PTGS2. Table 6 represents the complexes resulted in best binding energies.

Table 6 Binding energy of docked complexes[97]

Target protein ↓	Stigmasterol	Coptisine
AKT1	-11.1	-11.1
PTGS2	-8.6	-11.0

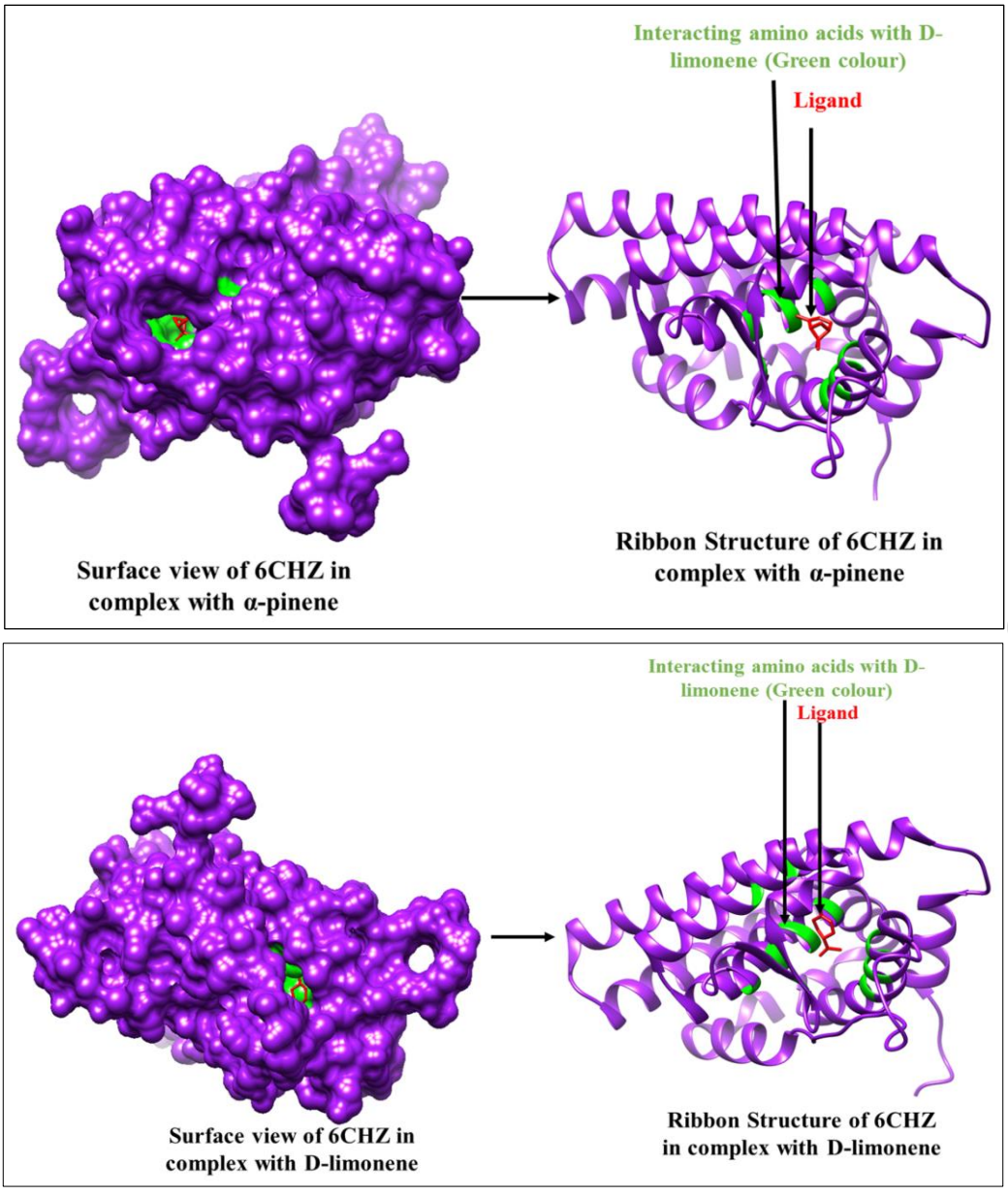


Figure 5 (A) Docking poses of the compounds showing best binding energy – 6CHZ with D-limonene (-5.9 kcal/mol) (B) 6CHZ with α-pinene (-6.0 kcal/mol) Purple shows the target protein, green represents hydrophobic interactions, and the red shows the ligand. Adapted with permission of ref[96]

Table 7 List of phytochemicals as ligands from different plants docked with important target proteins

Sr. no.	Proteins	Natural products (PubChem ID)	Phytochemicals with high affinity (kcal/mol)	Docking programme	Ref.
1.	EGFR (1M17)	Panaxadiol (73498)	-9.4	AutoDock Vina in PyRx	[93]
2.	HER2 (3RCD)	Alpha-peltatin (92129)	-9.7	Autodock Vina in PyRx	[93]
		Panaxadiol (73498)			
3.	P53	Epigallocatechin gallate (Green tea)	-9.2	CB-Dock2 (GUI version of Auto Dock Vina)	[95]
4.	6CHZ	D-limonene	-5.9	Auto Dock Vina	[96]
5.	6CHZ	Alpha-pinene	-6.0	Auto Dock Vina	[96]
6.	AKT1	Stigmasterol	-11.1	AutoDockTools-1.5.6	[97]
		Coptisine	-11.1		
7.	PTGS2	Stigmasterol	-8.6	AutoDockTools-1.5.6	[97]
		Coptisine	-11.0		

Table 7 includes natural products showing best binding energies from molecular docking studies – Stigmasterol when docked with AKT1 shows binding energy = -11.1 kcal/mol, Coptisine when docked with AKT1 shows binding energy = -11.1 kcal/mol, Coptisine when docked with PTGS2 shows binding energy = -11.0 kcal/mol, Alpha-Hederin when docked with BRCA2 (3EU7) shows binding energy = -11.0 kcal/mol. Overall, these natural products can be considered as lead compounds against breast cancer.

4.1.2. Molecular Dynamic simulation (MDS)

As the biomolecules present in the human body are in constant motion, it is essential to understand the dynamic molecular structures of receptors in order to promote more efficient methods of drug development[91] [98]. Molecular Dynamic Simulation (MDS) study helps in studying the stability of the protein-ligand interactions. It helps to examine the molecular and structural variations of the biomolecules which undergoes during the simulation period[91] [99]. In MDS study, significant terms such as Root Mean Square Deviation (RMSD), Radius of Gyration (Rg), and Root Mean Square Fluctuation (RMSF) are measured. The most significant metric of the MDS is RMSD; Lower the RMSD value more the stability of the biomolecular system. As the RMSD do not show the results of small variations that occur in the residues of the complex during simulation period hence, RMSF metric is used. RMSF metric is considered as the gold standard for the residue stability study; Higher the RMSF value, lesser the stability of residues. In some cases, another metric such as Radius of gyration (Rg) is calculated as a function of time; Higher Rg values indicate more flexibility, less stability[100]. As hydrogen bonds plays an important role in protein-ligand complex, it is also considered in MDS study.

Case 1

As discussed above in Case 1 of molecular docking, set of triplicates MDS of 100ns duration were performed for both EGFR and HER2 docked complexes by using Desmond Maestro v11.3. Triplicates of EGFR (1M17): [1M17- Panaxadiol (73498), 1M17 - APO, and 1M17- Erlotinib (ERL)]. The average of the RMSD plot was consistent. The RMSF plot of average triplicates resulted in minimum fluctuations. EGFR-ligand complex 1M17-73498 showed lower flexibility as compared to the reference ligand 1M17-APO and 1M17-ERL. In contrast, Molecular Mechanics with Generalized Born and Surface area solvation (MMGBSA) method was performed to calculate the strength of the interactions between ligand and receptors. It is the most common method used to calculated binding free energy of the protein ligand complex using Discovery Studio 3.5 (Accelrys Software Inc.). MMGBSA results showed that the binding free energy affinity for 1M17-73498 complex is less than reference drug complex i.e. 1M17-ERL which indicates the efficiency of 1M17-73498. Similarly, MDS study for HER2(3RCD) docked complex were performed using Desmond Maestro v11.3 in triplicates i.e. (3RCD-APO, 3RCD–TAK, and 3RCD-73498). The RMSD plot was consistent for the average triplicates. After that the RMSF plot was calculated which resulted in lower stability of 3RCD-73498 when compared to the reference ligand 3RCD-TAK, 3RCD-APO. Lower flexibility by 3RCD-73498 showed higher stability at the binding site. Further studies like Hydrogen bond interaction of MD simulation of stabilized effect shown by 3RCD-73498 was analyzed resulting in the solidity of protein-ligand complex 3RCD-73498. At the end of 100ns period MDS, binding free energy of HER2 was

calculated by MMGBSA method. Hence, the outcomes were: Binding energy affinity for 3RCD-TAK is less than that of 3RCD-73498 which signifies that binding function of 3RCD 73498 complex relatively closer to the binding energy of 3RCD-TAK. Overall, Panaxadiol can be considered as a good inhibitor of EGFR and HER2 according to hydrogen bond analysis performed in this study.

Case 2

In this study, they selected 40 phytochemicals of Foeniculum vulgare for the docking studies with Estrogen Receptor Y537S (PDB ID: 6CHZ) as a target protein. As they performed the molecular docking, and the toxicity, on the basis of these results alpha-pinene and D-limonene were found to be the good inhibitors for BC. Thus, both the complexes alpha-pinene and D-limonene with target protein 6CHZ were selected for MDS study by using the Amber18 tool. To check the dynamic flexibility of these complexes, 100-ns at 300K, MDS was performed. This MDS study validated alpha-pinene as the potent inhibitor for the treatment of BC. The D-limonene complex with 6CHZ C-alpha initially showed stable RMSDs from the beginning of the simulation up to 40ns (3Å). Later, it showed low turbulence between 40-50ns (which was acceptable) and then it was stable at a level of 2.9Å Figure 6A until 100ns. On the other hand, alpha-pinene in complex with 6CHZ, the RMSDs of C-alpha stayed at a constant level between 30-100ns at 2.7Å for the rest of the simulation as shown in Figure 6B[96] . The Figure 7 represents Root Mean Square Fluctuation (RMSF) graphs of the 6CHZ protein D-limonene and alpha-pinene also showed lower residual atomic displacements of the secondary structure elements of proteins[96].

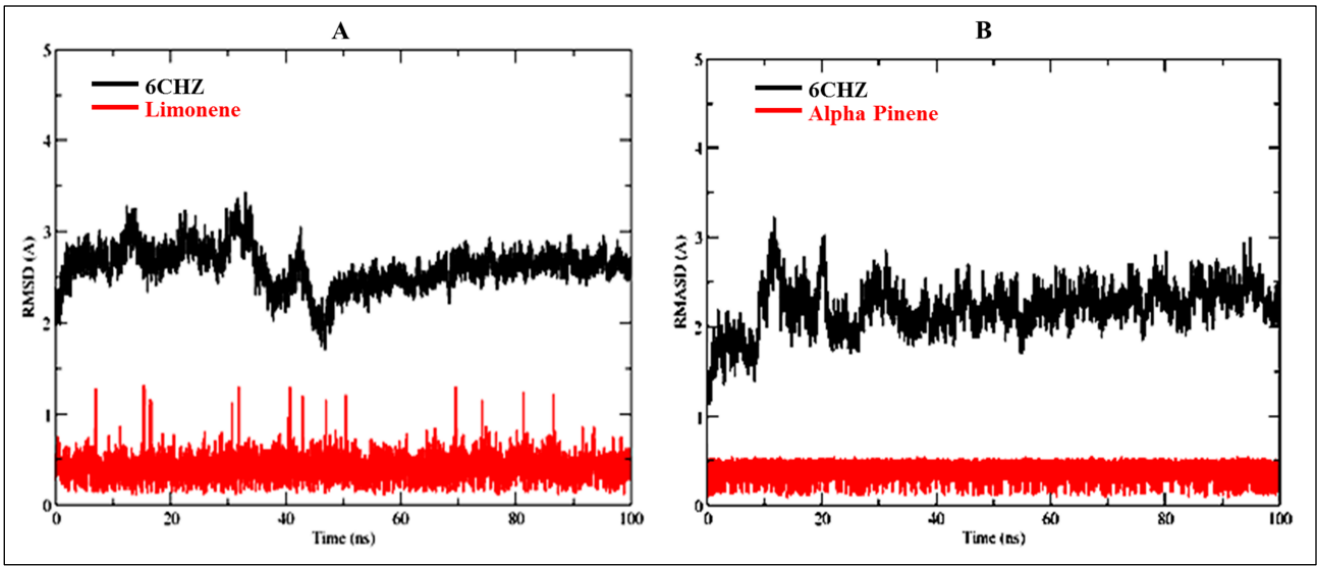


Figure 6 RMSDs of protein-ligand complexes: (A) D-limonene with 6CHZ and (B) Alpha-pinene with 6CHZ[96]

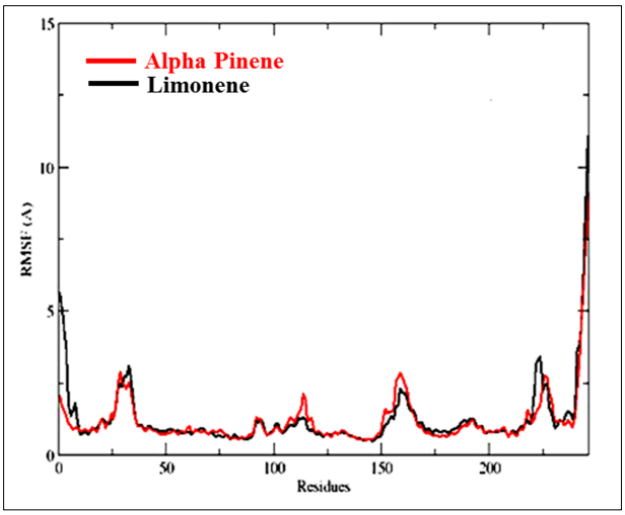


Figure 7 RMSF plots of D-limonene and alpha-pinene complexes with 6CHZ. Adapted with permission of ref [96]

Case 3

In this case, the top two complexes with the lowest binding energy (coptisine–AKT1 and stigmasterol AKT1) were taken for the molecular dynamic simulation study. A MDS study of 300ns was performed for analysis. RMSD curves were calculated which resulted in relatively stable fluctuations in protein. Hydrophilic bond interaction with strong hydrophilicity was observed between sites of stigmasterol–AKT1 and coptisine–AKT1 as shown in Figure 8(a, b). Also, the formation of hydrogen and pi-bonds are observed which helps in preserving the stability between the complexes.

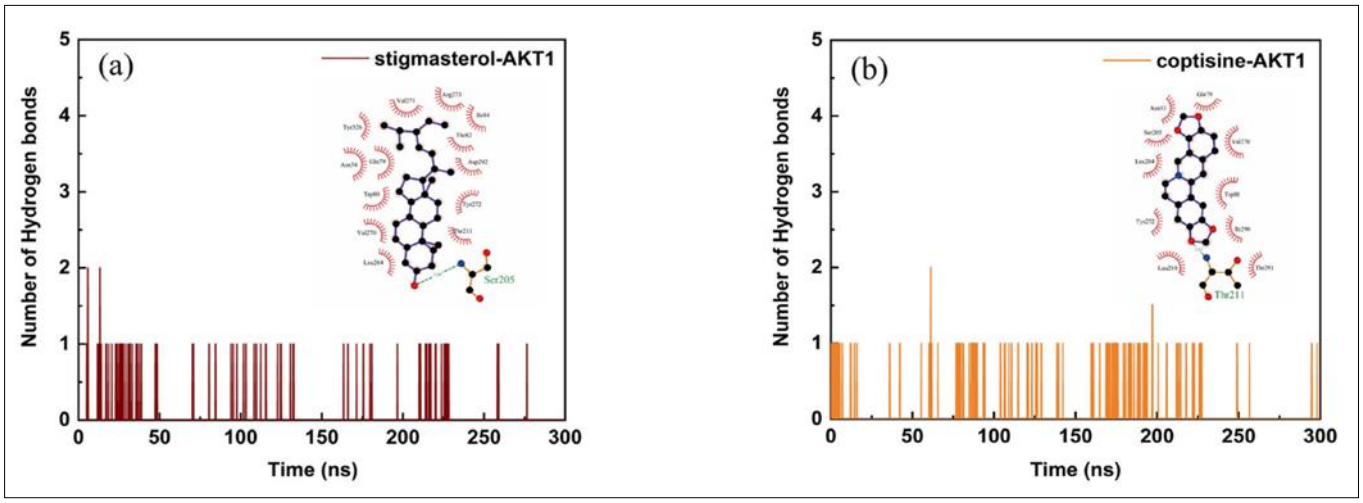


Figure 8 Number of hydrogen bonds between the (a) stigmasterol AKT1 and (b) coptisine–AKT1 complexes with 2D interaction diagrams plotted inside the figures. Complexes with 2D interaction diagrams plotted inside the figure. Adapted with permission of ref [97]

4.1.3. ADMET study

ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) is referred as the important part of the computational methods. It is basically the replacement for the in vivo and in vitro studies. Swiss ADME and ADMETSAR tools are used to study the drug likeness and other pharmacokinetic study of molecules. In this, various characteristics such as Molecular weight, Hydrogen Bond Acceptor and Donor Count, log P, log D, log S, Molar Volume, Dissociation Constant, Total Polar Surface Area (TPSA), Number of violations of Lipinski's Rule of Five, Log P, Log D, Log S and other properties were computed. Depending on the toxicity and pharmacokinetic qualities the drug is approved for further tests. ADME studies is the replacement of traditional in vitro and in vivo experiments[93]. The optimal range for these properties: lipophilicity – XLogP3 (-0.7 AND +5.0) size, Molecular weight (MW) should be 150 to 500g/mol, Total Polar Surface Area (TPSA) should be in the range of 20 to 130 $Å^2$, Solubility Log S should not be higher than 6, Saturation should be fraction of carbons in the sp3 hybridization not less than 0.25, flexibility: no more than 9 rotatable bonds. Toxicity is the most important part or concern of the drug development. SwissADME is an easy-to-use, fast and robust web tool with free access to a pool of specialized, multi-task prediction of ADME-related properties used for drug-likeness evaluation such as the BOILED-Egg [a predictive model of 2 major methods of ADME property i.e. gastrointestinal Absorption (HIA) and Blood Brain Barrier (BBB)], iLogP and Bioavailability radar. The pink area in the Figure 9 signifies the optimal range of the properties mentioned: Lipophilicity - between −0.7 and +5.0, Molecular weight MW – between 150 and 500g/mol, TPSA should be between 20 and 130 Å2, Log S should not be greater than 6, in saturation - the fraction of carbons (sp3 hybridization) should not be <0.25, and flexibility should not be more than 9 rotatable bonds. In this example, the compound is predicted not orally bioavailable, because it is too flexible and too polar[89] [101].

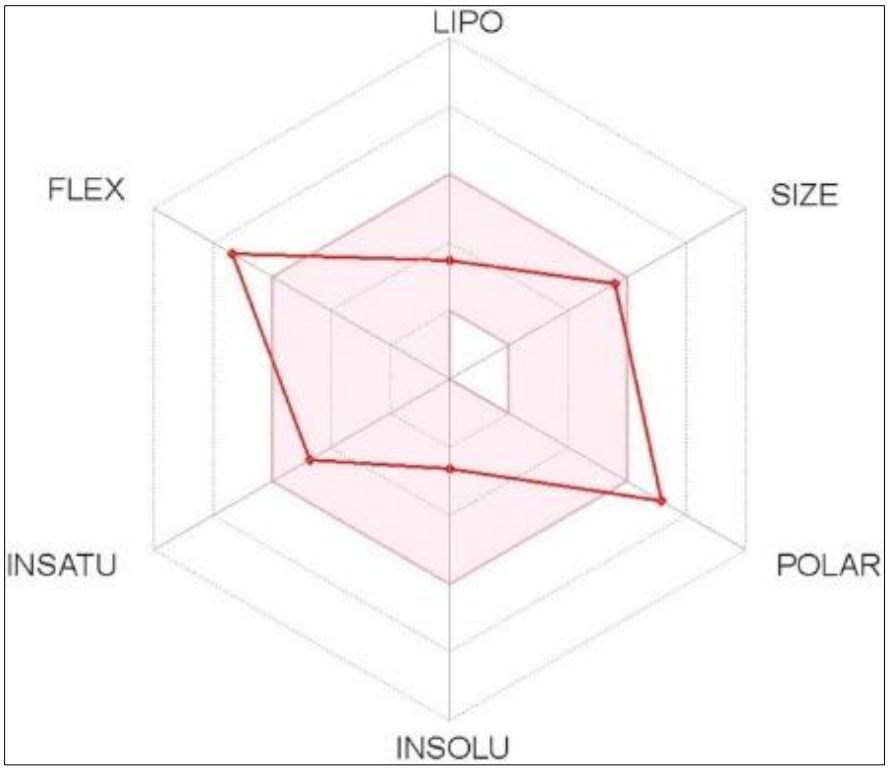


Figure 9 Bioavailability radar showing drug-likeness of molecule. Adapted with permission of ref[89]

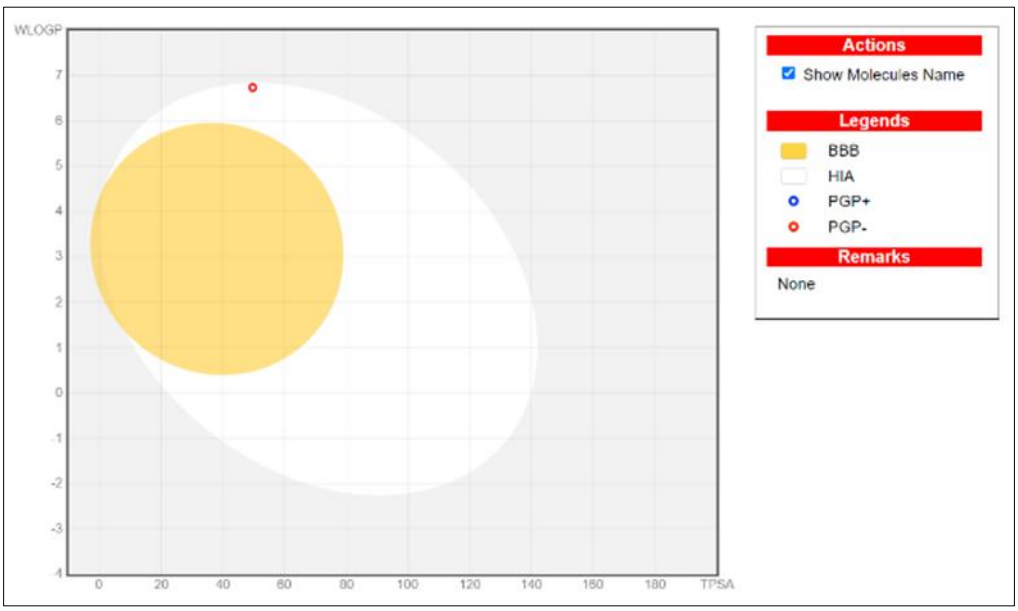


Figure 10 BOILED-Egg model of NP- Panaxadiol (data adapted from Swiss ADME (http://www.swissadme.ch/ on 11/12/2024)

The white region in Figure 10 signifies greater passive absorption of the molecule by the gastrointestinal tract (GI tract), and the yellow region (yolk) signifies Brain permeability[89]. In this example, Panaxadiol is predicted as non-brain penetrant (outside the Egg) and molecules located inside the egg white are predicted to be passively absorbed by the GI tract.

The studies below are the discussion of ADMET analyses of NPs with anti-breast cancer effects.

As discussed above, Case 1 of molecular docking represented Panaxadiol as the common inhibitor for both EGFR and HER2 target receptor. ADMET profiling of Panaxadiol was done using ADMETSAR prediction tool (http://lmmd.ecust.edu.cn:8000/)[93]. ADMET results showed Panaxadiol positive for BBB and it penetrates into brain after absorption. The toxicity results showed that Panaxadiol is a weak inhibitor of hERG, non-cancerous, non-toxic for oral toxicity. It also showed high solubility (high LogS) as depicted in Table 8. The overall study indicates that, Panaxadiol can be taken forward for further experimental validation.

Table 8 Predicted ADMET profile of Panaxadiol [93]

ADMET	Results	Probability
BBB	BBB+	0.8730
HIA	HIA+	1.0000
Caco-2	Caco-2+	0.7036
P-gp substrate	Substrate	0.7342
P-gp Inhibitor	Inhibitor	0.6135
ROC transporter	Non-inhibitor	0.8758
CYP IP (inhibitory promiscuity)	Low	0.9121
hERG (Human ether-a-go-go-related gene)	Weak Inhibitor	0.9669
AMES toxicity	Non toxic	0.7725
Carcinogen	Non-Carcinogen	0.9148
Biodegradation	Not readily biodegradable	0.9968
Acute oral toxicity	III	0.5097
Aqueous solubility (logS)	–4.3062	

In another case 2 of MDS, the molecular properties and drug-likeness of the phytochemicals and the standards were evaluated by using Molinspiration web server[96]. Out of the selected phytochemicals many of them exhibited drug likeness properties and also approved the criteria of it. Based on docking results discussed above, alpha-pinene and D-limonene with zero number of violations and zero polar surface area, can be considered as the good drug candidates for BC. The study of toxicity of the phytocompounds selected was performed using Protox II online tool[96]. Toxicity results also showed that alpha-pinene and D-limonene are the best drug candidates with Inactive- hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity.

In case 5 of molecular docking, reported 14 parameters of ADMET by using Swiss ADME web server (https://www.swissadme.ch/). For the physicochemical and pharmacokinetic predictions of the active compounds they used pkCSM website[102]. Stigmasterol (phytoconstituent derived from A. precatorius) showed best binding energy of -9.9 kcal/mol in comparison with Ertolinib (reference drug) (binding energy: -6.8 kcal/mol). Amongst all the phytoconstituents selected, Stigmasterol distinguished itself as a potent drug compound for breast cancer with the best intestinal absorption, good permeability, and intermediate BBB permeability as discussed in the Table

Table 9 ADMET properties[102]

ADMET properties ↓	Abrin	Abrusoside A	Glycyrrhizin	Stigmasterol	Ertolinib (ref. drug)
Water solubility (Log mol/L)	-2.171	-3.263	-2.892	-6.682	-4.403
$CaCO_2$ permeability (LogP in 10^{-6} cm/s)	0.664	-0.39	-0.812	1.213	1.238

Intestinal absorption (%)	100	41.123	0	94.97	95.549
VDss (log L/kg)	-1.782	-1.502	-0.615	0.178	-0.053
BBB Permeability(Log BBB)	-0.23	-1.191	-1.494	0.771	-0.67
CYP2D6 substrate	No	No	No	No	No
CYP3A4 substrate	No	Yes	Yes	Yes	Yes
CYP1A2Inhibitor	No	No	No	No	Yes
CYP2C19 Inhibitor	No	No	Yes	No	Yes
Renal OCT2 Substrate	No	No	No	No	No
Total clearance	0.781	0.174	-0.304	0.618	0.591
AMES toxicity	No	No	No	No	No
Max. dosage tolerance (human) (log mg/kg/day)	0.694	-0.372	0.389	-0.664	-0.002
hERG I Inhibitor	No	No	No	No	No
hERG II Inhibitor	No	No	No	Yes	Yes

From the overall case studies of ADMET, we can conclude that phytoconstituents like Stigmasterol, alpha-pinene, and D-limonene can be considered as potent compounds showing anti-breast cancer properties.

Abbreviations

- BC: Breast Cancer
- AFAB: Assigned Female at birth
- PR: Progesterone receptor
- HER2: Human Epidermal Growth Receptor 2
- TNBC: Triple Negative Breast Cancer
- NP: Natural Products
- RT: Radiotherapy
- FDA: Food and Drug Administration
- ADMET: Absorption Distribution Metabolism Excretion and Toxicity
- MDS: Molecular Dynamics Simulation
- CADD: Computer-aided drug design
- SBDD: Structure-based drug design
- LBDD: Ligand-based drug design
- PDB: Protein Data Bank
- RMSD: Root Mean Square Deviation
- RMSF: Root Mean Square Fluctuation
- Rg: Radius of gyration
- MMGBSA: Molecular Mechanics with Generalized Born and Surface Area Solvation
- TPSA: Total Polar Surface Area
- BBB: Blood-Brain Barrier
- BRCA1: Breast tumor suppressor gene 1
- BRCA2: Breast tumor suppressor gene 2
- MDR1: Multiple drug resistance 1
- GI: Gastrointestinal tract
- P13K: Phosphoinositide 3-Kinase
- mTOR: Mechanistic target of rapamycin
- RAS: Rat sarcoma
- MAPK: Mitogen-activated protein kinase

5. Conclusion

Breast cancer research is increasingly adapting computational strategies to explore the potential of natural products for prevention and efficient treatment. In the recent years, several computational methods like Molecular docking, Molecular Dynamics Simulation (MDS), pharmacophore modelling, Absorption Distribution Metabolism Excretion and Toxicity (ADMET) are in demand due to its cost effectiveness, time-saving, and labor intensiveness. These methods speed up the identification and optimization of bioactive compounds, leading to promising therapeutic options. Despite the promise of computational methods, challenges remain in applying these findings in clinical settings, which necessitates further research and validation. As the advanced machine learning algorithms and AI tools are integrated, achievement of greater precision is expected giving rise to the discovery of lead compounds from natural products. In summary, this review emphasizes the significant potential of natural products as a source of anti-cancer agents in breast cancer treatment. This review also provides databases and web servers available publicly which gives information about phytocompounds, useful in further drug discovery. In addition to this, the overall discussion of recent studies helps in identifying the anti-cancer properties which target the cellular activities such as cell proliferation, apoptosis etc. Therefore, it is expected, that this review will be helpful for further research studies in the scientific community worldwide.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.No conflict of interest exists.

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