INFORMATICS JOURNALS

Review Article

Journal of Natural Remedies
DOI: 10.18311/jnr/2026/49938

eISSN: 2320-3358 | Vol 26(2), 2026 | pp. 283-302

# Immunomodulatory Effects of Natural Products in Breast Cancer: From Molecular Mechanisms to Clinical Translation

**Pooja Dave[1*], Anirudh Mehta[2], Brahmdutta Raval[3] and M. K. Mohan Maruga Raja[4]**

[1]Department of Pharmaceutics, RK University, Rajkot - 360020, Gujarat, India; poojadave.pharma@gmail.com

[2]Manufacturing science and Technology, Moderna Therapeutics, Norwood - 02062, Massachusetts, USA

[3]Northeastern University, Boston - 02115, Massachusetts, USA

[4]Department of Pharmacognosy, East Point College of Pharmacy, Bengaluru - 560049, Karnataka, India

## Abstract

Breast Cancer (BC) is the most common type of cancer and the second most common cause of death from cancer. Triple negative breast cancer is substantial risk breast cancer as compared to other subtype cancer. Researchers are looking for the more productive drugs which can be used in prevention and treatment of breast cancer, because chemotherapeutic agents are highly toxic, resistance and have more side effects. To overcome these concerns, medicinal plants could be the best alternative to treat breast cancer cells as compared to chemotherapeutic drugs. Moreover, nanoparticulate drug delivery systems enhance drug delivery, drug circulation time in blood, controlled drug release and reduction in the apoptosis of breast cancer cells. In this review, medicinal plant derived drugs used in breast cancer with its name, source, mechanism of action, activity, efficiency, immune modulatory effects; *in-vitro* and *in-vivo* studies were discussed. Future aspects of natural products are the new era in breast cancer treatment and play cardinal role in patient survival rates.

**Major Findings:** Plant-derived compounds (*e.g.*, curcumin, resveratrol, genistein, quercetin, EGCG) exhibit anticancer, anti-inflammatory, antioxidant, and pro-apoptotic effects. These natural compounds following the pathways such as, NF-κB, PI3K/Akt/mTOR, MAPK/ERK, Notch, and Wnt/β-catenin, leading to apoptosis, cell cycle arrest, reduced angiogenesis, and inhibition of metastasis. Nanoparticulate drug delivery increases their efficacy, and their combination with conventional therapies improves treatment outcomes and reduces resistance.

**Keywords:** Breast Cancer, Curcumin, Docetaxel, Natural medicine, Paclitaxel, Triple Negative Breast Cancer

(Article Chronicle: Article Received on: 23.05.2025; Revised on: 09.01.2026; Accepted on: 22.01.2026)

## 1. Introduction

The disease category of cancer kills numerous people worldwide as research indicates that 19.3 million people received new diagnoses of cancer while 10 million people died of cancer in 2020.

The conventional cancer treatments like chemotherapy radiation and surgery have important drawbacks which include both severe side effects from drug exposure along with negative drug characteristics and treatment resistance. Improved cancer-focused treatment approaches focus on developing novel therapeutic solutions that provide better treatment effects and reduced adverse effects and improved tolerability. Scientists hold promises for using plant-derived compounds as well as compounds found in fungi and marine organisms. The research community shows increased interest in natural compounds, since these compounds exhibit potent bioactive effects which include antioxidants and anti-inflammatory and antitumour properties that indicate their value for cancer treatment development. These compounds

*Author for correspondence

demonstrate a preferential toxic effect on cancer cells without harming regular body tissues. Natural compounds show great therapeutic potential but multiple barriers exist before they can be used clinically. These compounds do not dissolve well in water and this affects their ability to access cancer cells properly. Such compounds leave the bloodstream quickly because the body breaks them down rapidly and removes them quickly which results in reduced availability at therapeutic targets.

Teamwork between scientists and researchers explores the use of nanotechnology-based drug delivery systems for these medical applications. Tumour sites receive therapeutic agents through engineered submicron-sized carriers known as nanoparticles. Nanoparticle-based drug delivery systems deliver better performance than conventional chemotherapy through elevated solubility levels and controlled medication releases and enhanced cellular drug absorption properties. Such advantages enhance therapeutic effects and reduce toxic side effects during treatment. Targeting ligands attached to nanoparticles represent an essential strategy to enhance drug delivery and specificity because they allow precise identification and binding toward cancer cells. Through functionalisation the drug delivery precision improves alongside optimised therapeutic effectiveness. Nanotechnology-based drug delivery systems when combined with natural compounds show immense potential for cancer treatment. Nanoparticle-based encapsulation systems improve the pharmacokinetic profile and stability and bioavailability of natural bioactive molecules which result in better therapeutic outcomes. Nanocarriers help minimise normal cell damage caused by natural compounds while making the compounds more active against tumours. Research teams can create safe cancer treatments by combining these two treatment strategies[1-3].

## 2. Natural Products against Breast Cancer

Among women, breast cancer is the second most common cause of death and because of its increasing numbers; it has become a major concern worldwide. Currently, treatment methods for metastatic BC are limited to surgery, radiotherapy, chemotherapy, hormone therapy, aromatase inhibitors, anti-angiogenic agents and anthracyclines. Therefore, we need better and faster therapies as soon as we can. In the context of cancer treatment, natural products are considered interesting alternatives, thanks to their low cost, low danger to humans and small chance of unwanted effects. They help control breast cancer growth by blocking angiogenesis, tumour expansion, cell movement and division. They also induce apoptosis, promote cell cycle arrest, and modulate key signalling pathways including Notch, NF-κB, PI3K/Akt/mTOR, MAPK/ERK, and NFAT-MDM2. Additionally, natural products can regulate Epithelial-Mesenchymal Transition (EMT) and work synergistically with conventional drugs to overcome resistance, making them promising candidates in breast cancer therapy[4].

The use of traditional medicines and their main ingredients has long been important in treating diseases like cancer. Natural products and their derivatives remain key ingredients in treating cancers. Notable examples include paclitaxel (derived from the bark of *Taxus brevifolia*), camptothecin (*Camptotheca acuminata*), vinblastine and vincristine (*Vinca rosea*), and podophyllotoxin (*Podophyllum*). Such phytochemicals, as well as their synthetic relatives, are well known to influence specific cell processes that allow cancer cells to survive and divide. Paclitaxel blocks the action of microtubules, resulting in mitotic arrest. Camptothecin can prevent topoisomerase I from working and leads to DNA damage and cell death in cancer cells. Vinblastine uses an attachment to certain microtubular proteins to stop mitosis and podophyllotoxin binds to tubulin and stops topoisomerase II from functioning. Their powerful effects on cells and their equivalent properties in medicine mean these compounds are widely employed, either by themselves or in combination with other drugs, for cancer care. Several anticancer agents are derived from microbial sources, notably from *Streptomyces* species, including bleomycin, actinomycin D, mitomycin C, doxorubicin, pentostatin, and daunorubicin, as well as carfilzomib from *Actinomyces* species. These agents exhibit distinct mechanisms of action: Bleomycin binds to DNA, causing strand breaks and subsequent DNA damage; actinomycin D intercalates into DNA, inhibiting RNA synthesis and cell proliferation; mitomycin C alkylates DNA, leading to cross-linking and inhibition of DNA synthesis; doxorubicin intercalates into DNA

and inhibits topoisomerase II, resulting in DNA damage and cell death; pentostatin acts as an antimetabolite by inhibiting adenosine deaminase, disrupting nucleotide metabolism; daunorubicin intercalates into DNA and inhibits topoisomerase II activity, disrupting DNA replication and repair; and carfilzomib is a proteasome inhibitor that disrupts protein degradation pathways, leading to apoptosis. Clinical trials have verified these microbial anticancer agents and derivatives and they remain central in cancer chemotherapy. Their effectiveness depends on their role in damaging cancer cell DNA, avoiding cancer cell repair, disrupting cell division in mitosis and decreasing proteasome activity. In addition to terrestrial microbes, marine-derived natural products have shown significant promise as anticancer agents. For example, salinosporamide A, also known as marizomib, is a potent proteasome inhibitor derived from the marine bacterium *Salinispora tropica*. Marizomib has entered phase III clinical trials for the treatment of various cancers, including non-small-cell lung cancer, pancreatic cancer, melanoma, lymphoma, and multiple myeloma. The mechanism works by binding with the 20S proteasome which causes extra proteins to collect in cancer cells and starts the process of apoptosis. The progress of marizomib highlights the possibility that marine natural products could improve the range of proven anticancer therapies. Scientists are still exploring microorganisms from different habitats and finding new substances that fight cancer in unique manners. It is anticipated that additional natural product-derived anticancer agents will be approved for clinical applications, offering the efficacy of their predecessors with potentially reduced toxic side effects[5-13]. In the Table 1 there are examples of drugs, its source, mechanism of action and clinical relevance shown.

## 3. Pathogenesis of Breast Cancer

Breast Cancer (BC) is the most frequently diagnosed malignant tumour globally. It typically arises from genetic mutations affecting the breast ductal tissues. Clinically, BC is initially classified based on the presence or absence of Estrogen Receptors (ER) into ER-positive and ER-negative types. Further subclassification is done according to specific molecular biomarkers, dividing BC into subtypes such as luminal A, luminal B, and basal-like[4]. During Breast Cancer (BC) development, epithelial cells undergo transformation from neoplastic to cancerous states[14]. Adipose tissue plays a significant role in initiating and promoting BC progression. Key contributing factors include inflammatory mediators and mutagens, particularly estrogens, which stimulate the production of Reactive Oxygen Species (ROS)[15]. These ROS lead to major damage to breast epithelial cells DNA. Damage to DNA caused by estrogen may block the system that repairs DNA which can increase the chance of mutations that may lead to BC. BC is accelerated additionally by too much estrogen, leptin and inflammatory substances, allowing more cells from BC to multiply, settle in areas far from the original tumour and attack healthy ones. Chronic inflammation in BC is controlled or regulated by various cells, including those called tumour-infiltrating lymphocytes, cancer-associated fibroblasts, tumour cells and tumour-associated macrophages. Neither DAMPs nor PAMPs are alive, but they can activate inflammatory responses. These triggers activate innate and adaptive immune cells, leading to the release of chemokines and cytokines that sustain the inflammatory environment[16].

Angiogenesis is promoted through the activation of several regulatory molecules, including IL-6, TNF-α, NF-κB, VEGF, Jun/Fos, and Lipid Peroxidation (LPO). Chronic inflammation in BC is associated with several signalling pathways, such as Notch, NF-κB, PI3K/Akt/mTOR, MAPK/ERK, and NFAT-MDM2, all of which are also involved in regulating Epithelial-Mesenchymal Transition (EMT)[17-20]. Among these, the NF-κB pathway is particularly crucial, as it drives the expression of inflammatory genes such as IER3L, COX2, CXCL12, and CCND3 in BC patients. Also, transcription factors such as Signal Transducer and Activator of Transcription (STAT) and Activator Protein-1 (AP-1) are turned on during the inflammatory response in BC18. Chronic inflammation, classified as a seventh hallmark of cancer, is particularly important in BC since it affects how cancer cells grow, spread and live. It occurs from the first stages of infection to the development and ongoing progression of the illness. Understanding and identifying the specific inflammatory events in BC could offer valuable strategies for early intervention, risk reduction, and prevention, especially among high-risk populations[19-25]. In the Table 2 list of drugs, brand names, dosage form and its pharmacokinetic effects in breast cancer were mentioned.

**Table 1.** List of drugs, source, its mechanism of action used in breast cancer

| Natural Drug | Source | Mechanism of Action | Clinical Relevance | Clinical Status and References |
|---|---|---|---|---|
| Paclitaxel | Pacific yew tree (*Taxus brevifolia*) | Inhibits microtubule depolymerisation, causing cell cycle arrest at G2/M phase | Widely used in chemotherapy regimens for breast cancer | FDA approved[5–7, 78–80] |
| Docetaxel | European yew tree (*Taxus baccata*) | Like paclitaxel, stabilises microtubules, inducing apoptosis | Effective against metastatic and advanced breast cancer | FDA approved[8, 9, 92, 93] |
| Epigallocatechin-3-gallate (EGCG) | Green tea (*Camellia sinensis*) | Induces apoptosis, inhibits angiogenesis and metastasis | Potential for chemoprevention; adjunct therapy | Under investigation[10, 52–55, 107–110] |
| Genistein | Soybeans (*Glycine max*) | Inhibits tyrosine kinase and topoisomerase II, modulates estrogen receptors | Potential chemopreventive role; mixed clinical outcomes | Experimental[11, 29–32] |
| Curcumin | Turmeric (*Curcuma longa*) | Suppresses NF-κB, inhibits proliferation, induces apoptosis | Potential as an adjuvant in breast cancer therapy | Clinical trials ongoing[12, 40–45, 56–60] |
| Resveratrol | Red grapes (*Vitis vinifera*) | Modulates estrogen receptors, inhibits tumour proliferation, and angiogenesis | Role in chemoprevention and therapy | Investigational[13, 100–106] |
| Berberine | *Berberis* species (e.g., *Berberis vulgaris*) | Induces apoptosis *via* AMPK activation and mitochondrial pathways | Potential adjuvant therapy with chemotherapy | Preclinical and clinical trials[111–117] |
| Quercetin | Fruits, vegetables (*e.g.*, onions, apples) | Antioxidant, induces apoptosis, inhibits cell proliferation | Promising but limited human trials | Experimental[65–77] |
| Sulforaphane | Broccoli (*Brassica oleracea*) | Epigenetic modulation, induces apoptosis, inhibits cancer stem cells | Potential chemopreventive agent | Investigational[118–128] |
| Indole-3-carbinol | Cruciferous vegetables (*Brassica* species) | Modulates estrogen metabolism, induces apoptosis | Potential for prevention and therapy | Clinical trials ongoing[129–132] |
| Withaferin A | *Withania somnifera* (*Ashwagandha*) | Inhibits NF-κB and proteasomal pathways, induces apoptosis | Potential for combination therapy | Preclinical research[88–90] |
| Camptothecin | *Camptotheca acuminata* | Inhibits topoisomerase I, leading to DNA damage and apoptosis | Basis for analogs like irinotecan and topotecan | FDA approved (for other cancers)[5–7] |
| Betulinic Acid | Betula species (Birch trees) | Induces apoptosis *via* mitochondrial pathways, inhibits angiogenesis | Investigational | Preclinical research[13] |
| Guggulsterone | Commiphora wightii (Guggul) | Modulates nuclear receptors, induces apoptosis | Under study for anticancer effects | Experimental[132–134] |

## 4. The Role of Bioactive Natural Products in Reprogramming Tumour-immune Interactions

### 4.1 Flavonoids

Flavonoids naturally occur in plants and vegetables and have many benefits for your health[25-28]. They are important in health care because they act as antimalarial, antibacterial, antioxidant, anti-inflammatory and antiallergic agents. These compounds can act in the body as phytoestrogens, mimicking estrogen signals, so they help in the management of heart disease, osteoporosis and hormone-sensitive cancers such as those found in breast and prostate tissue. Regarding cancer of the breast, isoflavones from the flavonoid family have been proven to reduce both the amount and effect of estrogen (Figure 1). They manage this task by slowing down aromatases that support the

**Table 2.** List of drugs, brand names, dosage form, its pharmacokinetic effects and its clinical studies used in breast cancer

| Drug Name | Brand Name | Dosage Form | Route of Administration | FDA-Approved Dosage | Pharmacokinetics | Clinical Studies and other Information |
|---|---|---|---|---|---|---|
| Paclitaxel | Taxol® | Injectable solution (Conventional) | Intravenous (IV) | 175 mg/m$^2$ IV over 3 hours every 3 weeks or 80-90 mg/m$^2$ IV weekly | Absorption: IV only, 100% bioavailability Distribution: High tissue penetration, Vd: 198-688 L/m$^2$ Metabolism: Hepatic (CYP2C8, CYP3A4) Elimination: Biliary (90%), Halflife: 5.3-17.6 hrs Protein Binding: ~89-98% | Approved for metastatic and HER2+ breast cancer (with trastuzumab). Studies show efficacy in Triple-Negative Breast Cancer (TNBC). |
| | Abraxane® (Nab-Paclitaxel) | Nanoparticle albumin-bound injectable suspension | Intravenous (IV) | 260 mg/m$^2$ IV over 30 min every 3 weeks | Absorption: IV only, 100% bioavailability Distribution: Enhanced tumour penetration, Vd: 632 L Metabolism: Hepatic (CYP2C8, CYP3A4) Elimination: Biliary excretion, $t_1/_2$: ~27 hrs Protein Binding: ~94% | Higher tumour uptake, reduced hypersensitivity, no need for premedication. Studies show improved response *vs.* conventional paclitaxel. |
| Docetaxel | Taxotere® | Injectable solution | Intravenous (IV) | 60-100 mg/m$^2$ IV over 1 hour every 3 weeks | Absorption: IV only, 100% bioavailability Distribution: High tissue penetration, Vd: 113 L/m$^2$ Metabolism: Hepatic (CYP3A4) Elimination: Biliary (75%), renal (6%), Half life: 11 hrs Protein Binding: ~94% | Approved for locally advanced and metastatic breast cancer. Combination with trastuzumab improves survival. Side effects: Neutropenia, neuropathy, fluid retention. |
| | Docefrez® | Injectable lyophilised powder | Intravenous (IV) | 75 mg/m$^2$ IV every 3 weeks | Absorption: IV only, 100% bioavailability Distribution: Extensive, Vd: ~88 L/m$^2$ Metabolism: Hepatic (CYP3A4) Elimination: Biliary (main), renal (6%), $t_1/_2$: ~20 hrs Protein Binding: ~95% | Used in combination therapy (trastuzumab, cyclophosphamide, doxorubicin). Studies show improved survival in HER2+ breast cancer. |
| Curcumin | Theracurmin® | Liposomal curcumin IV formulation | Intravenous (IV) | Under clinical trials (not FDA-approved for breast cancer) | Absorption: IV only, avoids first-pass metabolism Distribution: Low plasma concentration, accumulates in tumours Metabolism: Rapid hepatic glucuronidation Elimination: Biliary excretion, $t_1/_2$: ~6-7 hrs Protein Binding: ~80% | Used in experimental studies for chemoprevention and adjunct therapy. Research suggests anti-inflammatory, apoptotic effects in breast cancer cells. |
| | Curcumin C3 Complex® | Oral capsule (standardised curcuminoids) | Oral | 500-2000 mg/day in clinical trials | Absorption: Poor oral bioavailability Distribution: Rapid metabolism, low systemic levels Metabolism: Hepatic glucuronidation and sulfation Elimination: Fecal excretion, $t_1/_2$: ~2 hrs Protein Binding: ~95% | Being studied for adjunct therapy in breast cancer patients undergoing chemotherapy. Enhances apoptosis and reduces oxidative stress. |

**Table 2.** Continued...

| Drug Name | Brand Name | Dosage Form | Route of Administration | FDA-Approved Dosage | Pharmacokinetics | Clinical Studies and other Information |
|---|---|---|---|---|---|---|
| | Meriva® | Phytosome formulation (enhanced absorption) | Oral | 500-1000 mg/day | Absorption: Enhanced vs. standard curcumin (~29x higher) Distribution: Low systemic levels, accumulates in liver/ tumours Metabolism: Hepatic conjugation Elimination: Fecal excretion, $t_1/_2$: ~6 hrs Protein Binding: ~90% | Studied for chemoprevention and anti-inflammatory properties. Improves bioavailability compared to standard curcumin. |

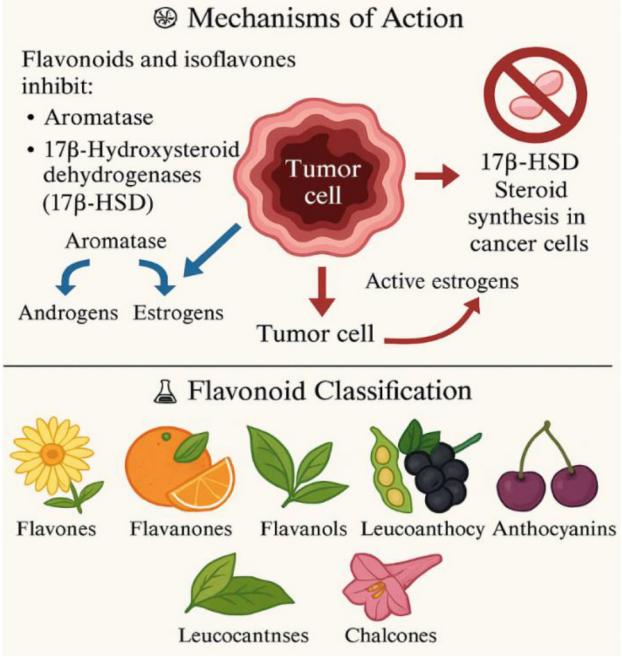



**Figure 1.** Classification and mechanism of flavonoids.

conversion of androgens to estrogens and 17β-HSD that help regulate different estrogen forms[29-32]. When enzymes are targeted, flavonoids help stop the production of powerful estrogens in cells. As a result, estrogen receptor-positive breast cancer cells have less chance to grow. Flavonoids are divided into various subgroups relying on their main chemical framework and additional changes[33,34]. The group is composed of flavones, flavanones, flavanols, isoflavones, leucoanthocyanidins, anthocyanins and chalcones. The various classes of vitamins are distinctive in their effects on medicine and show differences in defending against oxygen damage, regulating hormones and warding off cancer. Due to their wide-ranging characteristics, many studies focus on their role in cancer treatment[35-39].

## 4.2 Polyphenols

This group of phytochemicals, called polyphenols, consists of more than 8,000 compounds grouped as flavonoids and non-flavonoids. Most fruits, vegetables, grains and drinks made from plants are excellent sources because their polyphenols appear as glycosides or aglycones. There is increasing research to support the use of polyphenols in breast cancer as they display anti-inflammatory, strengthen the immune response and fight cancer[40-45]. In breast cancer, polyphenols are known to interact with many different molecular signalling pathways. One example of this is curcumin, derived from *C. longa*, which stops tumour cells from growing and causes apoptosis, doing so by controlling the NF-κB, PI3K/Akt and Wnt/β-catenin pathways. It controls the production of harmful inflammatory molecules TNF-α and IL-6 which is useful for reducing diseases related to inflammation. When breast cancer appears, resveratrol, a stilbene in grapes and red wine, stops progression by controlling Estrogen Receptor (ER) action, putting cell division to a halt, and increasing cell death through mitochondrial disturbances. Citrus peel extract acts against angiogenesis by lowering VEGF and makes breast cancer cells more sensitive to chemotherapy. The flavone called apigenin found in parsley and chamomile works against breast cancer by blocking cell division at the G2/M checkpoint, reducing the activity of cyclin-dependent kinases, and cutting down Bcl-2 to induce cell death. When isolated from *Scutellaria baicalensis*, wogonin leads to death of breast

cancer cells through the release of ROS, interference with the function of mitochondria and modulation of the MAPK/ERK signalling mechanism[46-51]. EGCG, a major compound in green tea, has been proven to stop the spread and growth of breast cancer by decreasing VEGF-guided blood supply to cancer cells, lowering EGFR signaling and cutting back MMP-9 activity. It also stimulates NK cells and guides T cell responses, so it helps maintain a favorable immunity against tumours. In models of hormone-sensitive and triple-negative breast cancer, icariin, a substance found in *Epimedium* species, showed good antitumour activity. It controls both the ERK1/2 and p38 MAPK pathways and promotes apoptosis by increasing caspase-3 and Bax and lowering Bcl-2. The presence of several polyphenols acts to improve treatment by influencing both tumour growth and the immune response. The power to affect proliferation, apoptosis, angiogenesis, immune evasion and immunotherapeutics makes such glycoproteins valuable for use in combined treatment for breast cancer[52-55].

### 4.3 *Curcumin*

In cases where cancer cells no longer respond to hormones, including MCF-7/TAM tamoxifen-resistant cells, tetrandrine has assisted in making those cells receptive to hormones again by stimulating autophagy and increasing cancer cell death[56,57]. Thanks to these models, it covers for the reduced presence of apoptotic proteins such as caspase-3, caspase-7, and Bax, so that the remaining cancer cells cannot escape treatment. Tetrandrine stops cells from continuing with the cell cycle at important checkpoints. It slows the transition from the G1 to S phase by turning down major controllers such as CDK2, CDK4 and cyclin E. It attaches to CDKs at their Adenosine Triphosphate (ATP) sites and prevents them from working, just as certain isoflavones also do. Because of this inhibition, Retinoblastoma (RB) is not phosphorylated, so the cells do not move forward in the cell cycle[58-60]. The presence of the compound increases tumour suppressor p53 and lifts up CIP/KIP family proteins, adding more strength to the G1 arrest process. Tetrandrine is thought to speed up the breakdown of cyclin D1 by triggering Glycogen Synthase Kinase 3 (GSK-3). Flavoclinol works in the same way as other anticancer agents such as resveratrol and aspirin. In addition, tetrandrine turns off the PI3K/AKT/mTOR pathway, an important regulator of growth, migration, survival, and the spread of blood vessels in cancer cells. If this pathway is blocked, cell division is stopped and cancer cells become less aggressive, in endothelial and hepatocellular carcinoma cases. Tetrandrine, by activating autophagy, blocking CDK proteins and suppressing the PI3K/AKT/mTOR signalling pathway, looks to be amazingly effective in treating breast cancer and similar cancers that fail to respond to traditional therapies[61-64].

### 4.4 Quercetin

Quercetin is a naturally occurring flavonol found in a variety of plants, including *Opuntia ficus-indica*, *Lychnophora staavioides*, *Allagopappus viscosissimus*, and species of *Rhamnus*[65-67]. It is appropriate to the broader class of polyphenolic flavonoids. Flavonoids can be found in fruits, vegetables, tea, coffee, and red wine and are accepted for their antioxidant, anti-inflammatory and anticancer effects. Scientific studies have discovered that quercetin can trigger apoptosis in cells from the prostate, lung, colon, cervix, and breast. Quercetin in breast cancer has been demonstrated to reduce tumour cell growth and trigger apoptosis using multiple strategies. It accomplishes this by decreasing the levels of Bcl-xL, Bcl-2 and survivin, while enhancing the levels of Bax and Bad. There have been studies showing that formulations with quercetin included nanoparticles boost these results. In cancer cells from the breast, quercetin acts to induce programmed cell death by increasing DR5 and lessening c-FLIPL which normally contributes to keeping cells alive. It also stops the cell cycle, making it unable for more cancer cells to develop. In breast cancer stem-like cells from the MDA-MB-231-line, quercetin halts their growth and reduces their ability to spread by turning off gene markers such as aldehyde dehydrogenase 1A1 and several adhesion molecules related to cancer advancement and metastasis[68-73]. Quercetin has an effect on key systems that help regulate the way cells divide and remain alive. In MCF-7 cells, this agent causes the cell cycle to stop at the G1 phase, decreasing cyclin D1, P21 and Twist levels. By stimulating the P38MAPK pathway, it also lowers the amount of Twist present, a protein involved in cell migration and invasion. Also, in BT-474 breast cancer cells, quercetin controls HER2 overproduction and STAT3 activity through caspase-assisted apoptosis.

Various substances formed from quercetin such as Q3S and Q3G have been tested for their ability to fight cancer. In particular, quercetin is the most active, followed by Q3S and then Q3G. They cause cancer cells to die by way of apoptosis or necrosis. Parts of Quercetin's anticancer role can be traced to its blocking of main cell signalling pathways such as PI3K, EGFR and HER2/neu. Healthy breast cells have shown strong resistance to division when exposed to even insignificant amounts of rapamycin, so rapamycin appears helpful for future breast cancer treatment[74-77].

## 4.5 Paclitaxel

Paclitaxel helps to treat breast cancer and has become a common treatment for the disease. Its identification started with the isolated bark of the Pacific yew (*Taxus brevifolia*) which put it in the group of compounds named taxanes. Since paclitaxel is a natural diterpenoid, it mostly stops cancer by disturbing the work of microtubules needed for the division of cells. It binds to the β-tubulin part of the microtubule, preventing removal during the process of cell cycle control. Therefore, cells get stuck at the G2/M phase and this sometimes triggers apoptosis, meaning the cell will die intentionally. It is also well known that paclitaxel stimulates Bax and suppresses Bcl-2 or Bcl-xL. By using caspase pathways and reducing mitochondrial membrane potential, the drug helps cancer cells die entirely. Paclitaxel affects important cell signalling mechanisms that support cancer survival. It suppresses the PI3K/Akt/mTOR and NF-κB pathways which are frequently too active in breast cancer and make treatments less effective. When survival signs are forced to be low, paclitaxel increases the chance that tumour cells will undergo apoptosis. Furthermore, paclitaxel reduces VEGF levels which decrease angiogenesis and helps stop the growth and spread of cancer. It supports immune response at the weak doses it is usually given, allowing dendritic and natural killer cells to attack tumours. Despite being helpful, the ability of paclitaxel to treat cancer is often reduced by problems of low water solubility, side effects and more cases of resistance found in triple-negative breast cancer. To bypass these challenges, researchers have been testing how paclitaxel works combined with natural compounds that fight cancer. Curcumin from turmeric improves paclitaxel's effects by reducing NF-κB and boosting the process of cell death. Resveratrol living in grapes plays a role in therapeutic outcomes by controlling the protein p53 and causing endoplasmic reticulum stress. Because it is found in many fruits and vegetables, quercetin decreases expression of P-glycoprotein and regulates the PI3K/Akt route, allowing drugs to work again. Similarly, EGCG, a natural component in green tea and DIM, found in cruciferous vegetables, have shown that together with paclitaxel they encourage cancer cells to stop multiplying and die. When carnosol from rosemary is paired with paclitaxel, it improves the drug's action on aggressive cancer cells by starting oxidative stress and initiating autophagy. Merits to improvements in medicine, clinical use now features albumin-bound paclitaxel (nab-paclitaxel or Abraxane), a new type that delivers the drug with greater effectiveness and causes fewer side effects for patients. Combinations of traditional and natural drugs, along with new ways to deliver them, show enormous potential in improving breast cancer therapy. Overall, paclitaxel is still important in breast cancer treatment, even when used together with active natural products, mainly when ways are found to handle resistance and lower the side effects[78-87].

## 4.6 Tetrandrine

This natural substance, tetrandrine, can stop or slow down the growth of tumour cells and may treat certain types of cancer. The plant *Stephania tetrandra*, a known medicinal plant in traditional Chinese herbal medicine, is the source of this dibenzyl tetrahydroisoquinoline alkaloid. Extensive research shows that chemotherapy works by inducing apoptosis in several different cancers such as leukemia, melanoma, prostate, and breast cancers[88-90]. Tetrandrine influences several aspects of physiology which makes it useful for treatment. One key task of the drug is to stop resistance to drugs by blocking proteins used in multidrug resistance processes. It additionally targets positive ion channels which help it cause tumour cells to grow less. Specifically, tetrandrine is able to reverse drug resistance in breast cancer. The drug encourages autophagy which leads to cell death even in cancer cells that normally resist apoptosis. As a result, tetrandrine can target cancer cells that have learned to survive the usual forms of cell death. The substance reduces the number of mammospheres which contain breast cancer stem-like

cells and lowers aldehyde dehydrogenase levels which have been connected to cancer growth and resistance to treatment. Tetrandrine stops cell growth in SUM-149 and SUM-159 cells which suggests it may work against aggressive breast cancer types. In cases where cancer cells no longer respond to hormones, including MCF-7/TAM tamoxifen-resistant cells, tetrandrine has assisted in making those cells receptive to hormones again by stimulating autophagy and increasing cancer cell death. Thanks to these models, it covers for the reduced presence of apoptotic proteins such as caspase-3, caspase-7, and Bax, so that the remaining cancer cells cannot escape treatment. Tetrandrine stops cells from continuing with the cell cycle at important checkpoints. It slows the transition from the G1 to S phase by turning down major controllers such as CDK2, CDK4 and cyclin E. It attaches to CDKs at their Adenosine Triphosphate (ATP) sites and prevents them from working, just as certain isoflavones also do. Because of this inhibition, Retinoblastoma (RB) is not phosphorylated, so the cells do not move forward in the cell cycle. The presence of the compound increases tumour suppressor p53 and lifts up CIP/KIP family proteins, adding more strength to the G1 arrest process. Furthermore, tetrandrine might elevate the breakdown of cyclin D1 which controls whether cells begin the cell cycle, by triggering GSK-3. The effects are the same as what other anticancer agents like resveratrol and aspirin achieve. In addition, tetrandrine turns off the PI3K/AKT/mTOR pathway, an important regulator of growth, migration, survival, and the spread of blood vessels in cancer cells. If this pathway is blocked, cell division is stopped and cancer cells become less aggressive, in endothelial and hepatocellular carcinoma cases. Tetrandrine, by activating autophagy, blocking CDK proteins and suppressing the PI3K/AKT/mTOR signaling pathway, looks to be amazingly effective in treating breast cancer and similar cancers that fail to respond to traditional therapies[56,61,91].

## 4.7 Docetaxel

Docetaxel is made from 10-deacetylbaccatin III, a natural precursor in the needles of the European yew tree (*Taxus baccata*). It is a taxane drug, like paclitaxel and is widely applied in the treatment of different cancers such as breast cancer. Because docetaxel can destroy cancerous cells very effectively, it is now commonly used for treatment, especially in advanced forms and triple-negative or hormone-resistant breast cancers[92]. Docetaxel helps fight cancer by helping to stabilise microtubules. Microtubules usually consist of two types of tubulin molecules, α- and β- and are dynamic, cycles of assembly and disassembly help form the mitotic spindle and make sure chromosomes are divided during cell division. Docetaxel has high affinity for tubulin and supports microtubule production, all while blocking their breakdown. As a result, the microtubules form large and useless groups which interrupt the mitotic spindle assembly and make cells stop at the G2/M phase of the cell cycle. Staying stuck in mitosis at a long phase causes cells to activate apoptosis, as seen by the outer membrane of mitochondria opening up, cytochrome c escaping and caspase enzymes become active. In addition to acting on microtubules, docetaxel counteracts several key pathways involved in triggering cell death. It decreases the activity of proteins like Bcl-2 and Bcl-xL and at the same time raises the activity of proteins like Bax and p53, making the body more likely to use apoptosis. Docetaxel targets key molecules such as PI3K/AKT and MAPK, which are usually over activated in breast cancer cells. Inhibiting these pathways increases the chance that cancer cells will die and stimulates the drug's efficacy. Because it lowers the levels of Vascular Endothelial Growth Factor (VEGF), docetaxel stops the tumour from creating and sustaining new blood vessels. It works in clinical medicine, but there are concerns about its toxic effects, resistance, and low solubility. It has been researched to determine if adding natural substances can strengthen docetaxel's therapeutic abilities and help tackle resistance. Research shows that adding curcumin from *C. longa*, resveratrol from grapes and berries, quercetin from many fruits and vegetables or EGCG from green tea to docetaxel is promising. They can make docetaxel successfully induce cancer cell death, lower damage from free radicals and inhibit the main drug efflux protein, P-glycoprotein (P-gp) which helps cancer cells resist drugs. For instance, curcumin stops NF-κB and STAT3 signaling, making breast cancer cells more likely to die from docetaxel. Thanks to resveratrol, cell cycle regulators are controlled and non-cancerous genes are reduced, helping docetaxel succeed. Docetaxel is recognised as a potent chemotherapy medication whose main mechanism involves stabilising microtubules and

arresting cell division. Combining Taxol with certain natural substances can increase its effectiveness, reduce unwanted effects, and make the cancer less likely to resist the treatment, putting it in the spotlight for integrated breast cancer therapy[92,93].

## 4.8 Thymoquinone

Thymoquinone (TQ), a bioactive compound derived from the seeds of *Nigella sativa*, a plant commonly cultivated in Mediterranean and Western Asian regions, has demonstrated strong anticancer potential across a variety of malignancies. Among these types are myeloblastic leukemia, pancreatic adenocarcinoma, osteosarcoma, liver, ovarian, breast and colorectal cancers[94,95]. TQ has its anticancer effects by influencing different proteins and signals in cells, including p53, p73, STAT3, NF-κB, PPARs and by increasing Reactive Oxygen Species (ROS). In these models, TQ can both restrict cell growth and encourage apoptosis in breast cancer cells. It achieves this by boosting the activity of pro-apoptotic proteins and reducing survivin as well as the Bcl-2 and Bcl-xL proteins. As a result of both actions, the viability of breast cancer cells decreases a lot. Results from MCF-7 cell work show that TQ increases reactive oxygen species and phosphorylates p38 MAPK, leading to slower cell migration and a rise in apoptosis. Due to these molecular transformations, the substance could become a useful medicine for treating breast cancer. TQ stopping the cell cycle through sub-G1 arrest and preventing S-phase progression which means cancer cells cannot replicate their DNA while dividing. It is important to note that TQ can set off both pathways dependent on p53 and those independent of it which allows it to benefit breast cancer patients with either functional or inactivated p53. A keyway in which it affects molecules is by cutting poly (ADP-ribose) polymerase (PARP), a signal indicating apoptosis and by raising the amount of γ-H2AX, a sign of DNA damage. This also leads to a decrease in Akt phosphorylation, cruelty to cell survival signalling and increases XIAP which enhances apoptosis. At test levels in MCF-7/DOX cells, TQ demonstrates good potential. It binds to PPARs, lessens the growth of cells, and allows drugs like doxorubicin to work again. The mechanism at work is PTEN raising to block Akt which disturbs survival signals. TQ also shuts down cyclin D1 and cyclin E, two proteins that help drive the cell cycle and slows down the phosphorylation of protein synthesis factors 4E-BP1, eIF4E, S6 ribosomal protein and p70S6 kinase. Another way TQ contributes is by blocking the G2/M phase which prevents cancer cell division[96-99].

## 4.9 Resveratrol

Resveratrol, which is abbreviated as RES, is a natural polyphenol that comes from grapes, berries, peanuts, soybeans, and pomegranates. An important source of resveratrol is the plant known as *Polygonum cuspidatum* or Japanese knotweed which is commonly used in Asian medicine for preventing and managing many ailments, including cancer. Resveratrol is recognised for its anti-inflammatory, antioxidant, and anticancer effects. Several processes in the body help make its anticancer property effective. Resveratrol can block the multiplication of cancer cells by making the cells halt their growth and encouraging them to die. It prevents tumours from growing by turning off enzymes such as tumour-derived nitric oxide synthase and by avoiding oxidative damage to DNA in the cells. Resveratrol is believed to work by influencing the transcription factor NF-κB which helps regulate genes essential for cell survival and growth. Reducing NF-κB's DNA-binding activity means resveratrol can reduce the transcription of genes that support cancer cell development. Resveratrol blocks the formation of ROS inside cancer cells, brings down the potential of their mitochondrial membranes and prevents the mTOR signalling pathway from activating by reducing the phosphorylation of the ribosomal protein S6 and 4EBP1. Vitamin E is known to help treat viruses, control inflammation, and lower the growth of leukemic cells. Activation of pro-apoptotic paths by p53, Rb and cyclin-dependent kinases leads to the death of cancer cells due to the compound. Several studies have found that resveratrol has high effectiveness against cancer types such as breast, prostate, pancreatic, liver, and colorectal cancers. Because it is active across many pathways, inexpensive and interacts with several cellular systems, it represents a promising drug for cancer. In TNBC cell lines such as MDA-MB-231 and MDA-MB-231/PacR which are resistant to paclitaxel, resveratrol decreases cell numbers, encourages the phenomenon of senescence, lower survivin, causes cells to die and can do so mainly through increased caspase-7 action. In cells from estrogen receptor-positive breast cancer (MCF-7), resveratrol obstructs the metabolism

of glucose by suppressing Phosphofructokinase (PFK) which reduces ATP levels, blocks cell viability, and diminishes cell survival. Research on animals has also confirmed that they can fight cancer. Resveratrol has been demonstrated in female rats to suppress breast cancer growth by controlling COX-2, inhibiting NF-κB DNA binding and changing the level of 5-LOX, TGF-β1 and DNA damage indicators like ssDNA. They confirm that it works both to avoid forming tumours forming and to control their ability to spread. Resveratrol is known to change the activity of microRNA which is essential for controlling gene expression and cell death. As an example, it adjusts tumour-suppressing microRNAs called miR-122-5p, miR-200c-3p, miR-409-3p, miR-125b-5p and miR-542-3p in breast cancer cells. It is interesting that miR-122-5p encourages apoptosis in the MDA-MB-231 cells, but miR-542-3p delays apoptotic processes in the MCF-7 cells. In MCF-7 cells, resveratrol triggers apoptosis by raising the levels of ASPP1, a p53 activator, along with two pro-apoptotic proteins, BAX, and the cell cycle regulator p21. At the same time, it decreases Bcl-2, increases caspases 7 and 9 and lessens the level of procaspase-8. Furthermore, resveratrol causes cells to stop at the S-phase and boosts the phosphorylation level of Chk2, indicating activation of DNA damage response. It hinders CDK7 activity and the active version of CDK2 which helps slow the growth of tumour cells. In HER2-positive breast cancer cells, resveratrol stops Fatty Acid Synthase (FASN), an enzyme involved in building the cell membrane which hampers the cell cycle and increases apoptosis. p53's apoptotic role in breast cancer cells is strengthened by binding to integrinαvβ3 on the cell surface. Resveratrol's main function in breast cancer and many other cancers is to block how cancer cells grow, thrive and search for fuel which suggests it may be used as a therapeutic drug[100-106].

## 4.10 Green Tea

Camellia sinensis, otherwise known as green tea, has bioactive compounds, polyphenols which have proven to have anticancer potential. The common and active ingredient EGCG is a catechin which is known for being a strong antioxidant. Green tea's health benefits are partly due to the moderate level of EGCG it contains. It has been recognised that green tea contains active substances that help prevent cancer and stop harmful changes in genes. Because of EGCG, cellular DNA can be defended against damage by reactive oxygen species, leading to its chemopreventive activity. It has been found that animal experiments with green tea polyphenols lead to a decrease in cancer cell numbers, damage to cancerous cells and the occurrence of apoptosis. In addition, these chemicals support the immune system and hinder cancer cell growth by blocking angiogenesis, the production of blood vessels needed by tumours to grow. There is evidence that green tea catechins can help protect several organs, showing how widely they may be used as cancer preventatives. Green tea is also known for decreasing the negative effects of radiation. This is mainly because green tea polyphenols are strong antioxidants and help reduce the effects of radicals in the body[107-110].

## 4.11 Berberine

Berberine is a bioactive isoquinoline alkaloid extracted from various medicinal plants such as *Berberis vulgaris*, *Coptis chinensis*, *Hydrastis canadensis*, and *Berberis aristata*[111,112]. It has been traditionally used in Chinese and *Ayurvedic* medicine for treating infections and inflammatory conditions, but modern research has revealed its potent anticancer properties, particularly in breast cancer. Berberine exhibits a wide range of pharmacological effects, including antimicrobial, anti-inflammatory, antioxidant, and antitumour activities. Its anticancer efficacy has been supported by both *in-vitro* and *in-vivo* studies, demonstrating the compound's ability to inhibit cancer cell proliferation, induce apoptosis, and suppress metastasis. There are many ways in which berberine works in breast cancer. One main part of its actions against cancer is blocking the cell cycle. Berberine is linked to stopping cells at the G1 and G2/M checkpoints by revising the function of cyclin D1, cyclin B1, CDK1 and CDK4 regulatory proteins. This disruption stops cancer cells from dividing and finishing their cell cycle. This substance aids in triggering apoptosis by using the mitochondrial pathway and the one that is not linked with them. Because of this, pro-apoptotic proteins, like Bax, are increased and anti-apoptotic proteins such as Bcl-2 and Bcl-xL, are lowered, resulting in the depolarisation of the mitochondrial membrane, cytochrome c being released and the activation of caspases, especially caspase-3 and caspase-9[113,114].

In addition, berberine plays a role in managing important pathways related to the start and progress of tumours. It reduces the activity of the PI3K/Akt/mTOR signalling axis which is often turned on too much in women with breast cancer and supports cell growth, survival, and their ability to resist drugs. Berberine, by turning off this pathway, can both decrease cancer cell growth and increase the cells vulnerability to chemotherapy. It also stops the MAPK/ERK and NF-κB pathways, each of which contributes to inflammation, survival, and metastasis. Reducing NF-κB by berberine brings down the expression of genes responsible for invasion and new blood vessel creation, for example, Matrix Metalloproteinases (MMPs) and Vascular Endothelial Growth Factor (VEGF), so the tumour is prevented from invading or forming fresh blood vessels. Berberine stops Estrogen Receptor alpha (ERα) from interacting with estrogen and so reduces hormone-caused tumour development in this type of breast cancer. For Triple-Negative Breast Cancer (TNBC) which often behaves aggressively and does not respond to certain treatments, berberine has demonstrated success by affecting cell metabolism, preventing EMT and lessening the number of stemness markers, thus making the tumour less able to grow and less resistant to therapy. Berberine is known for stopping metastasis by blocking cell movement and invasion, as shown by the pathways and integrin expression it regulates. Further, Berberine helps control epigenetic regulation by modifying non-coding RNAs called microRNAs (*e.g.*, miR-21, miR-34a) which both prevent tumours and influence tumour growth. Hence, Berberine can act in several ways-such as regulating cell cycle, calling for cell death, blocking oncogenic pathways, stopping metastasis, and stabilising hormone and metabolism-making it useful in breast cancer treatment. Its ability to work well with traditional chemotherapy drugs increases the importance of using it in integrative cancer treatments[115-117].

### 4.12 Sulforaphane

The natural isothiocyanate sulforaphane is found in broccoli, broccoli sprouts, cabbage, kale, and water lily. The compound has attracted much attention because of its effectiveness in fighting breast cancer. Studies have proved that sulforaphane works well in preventing cancer cell growth, blood vessel growth for tumours and movement of cancer cells to distinct parts of the body[118]. The main mechanism by which it helps fight breast cancer is by inducing cell cycle arrest and making the cells undergo apoptosis. SFN acts partly by adjusting the levels of epigenetic modifications. In breast cancer cell lines MCF-7 and MDA-MB-231, the compound has been shown to quiet down expression of human Telomerase Reverse Transcriptase (hTERT) by changing DNA methylation and histone modifications[119]. The inhibition depends on the amount of neurotoxin and how long it has been present, which means epigenetic regulation is involved. Moreover, sulforaphane increases the formation of cyclin B1 and stimulates PARP and caspases, two proteins needed for carrying out apoptosis. Cells become stuck at the G2/M stage and, as a result, die in a regulated manner. SFN disrupts the cycle of microtubules by stopping tubulin from compacting which only adds to the disruption of the cell cycle. It decreases activity in the NF-κB signalling pathway which is important for both inflammation and tumour growth. Besides, SFN changes the level of anti-apoptotic proteins in cells such as Bcl-2 and stimulates the phosphorylation of Akt which changes the survival signals in cancer cells. These changes stop tumours from growing and improve how sensitive breast cancer cells become to paclitaxel and other therapies[120-123]. Researchers have seen that sulforaphane shows significance in hormone-resistant or ER- breast cancers. As a result of its epigenetic effects, it may help estrogen receptors show up again which enhances a cell's sensitivity to therapies like tamoxifen. The protein SFN reduces inflammatory factors such as NF-κB and COX-2 through the ERK1/2-IKK and NAK-IKK signalling pathways[124-128]. In Table 3, all the natural products and their immunomodulatory effects were given.

## 5. Future Aspects of Herbal Medicine in Breast Cancer

There are still many obstacles to treating breast cancer, especially the rise of drug resistance and the severe issues related to treatments with chemotherapy and radiotherapy. Despite being useful in many situations, these treatments may not work because cancer cells acquire resistance. In this regard, compounds found in food have become important because they

**Table 3.** Natural products and their immunomodulatory effects (*in vitro* and *in vivo* evidence)

| Natural Compound | Target Immune Cells | *In Vitro* Effects | *In Vivo* Effects | Key Mechanisms |
|---|---|---|---|---|
| Curcumin | Macrophages, T cells, B cells, dendritic cells | Reduces cytokine (TNF-α, IL-1β) production; inhibits cell activation | Reduces tissue inflammation in models of arthritis and colitis | Suppresses NF-κB signaling and blocks pro-inflammatory gene expression |
| Resveratrol | T cells, NK cells, macrophages | Limits T cell activation; enhances NK cytotoxicity | Reduces autoimmune symptoms in animal models (*e.g.*, EAE, asthma) | Modulates SIRT1 pathway and reduces oxidative stress |
| Quercetin | Mast cells, neutrophils, macrophages | Inhibits histamine release and ROS generation | Reduces allergic responses and lung inflammation | Acts as antioxidant; blocks MAPK and NF-κB pathways |
| EGCG (Green tea extract) | T cells, macrophages, B cells | Reduces cytokines like IL-2, IFN-γ | Lowers inflammation in autoimmune and cancer models | Inhibits inflammatory mediators; regulates gene expression |
| Berberine | Macrophages, T cells | Decreases expression of IL-6, IL-1β, TNF-α | Improves immune balance in colitis and diabetes models | Activates AMPK; suppresses inflammatory enzymes |
| Ginsenosides | Dendritic cells, NK cells | Enhances antigen presentation; boosts NK cell activity | Enhances immune defense in infection and cancer models | Balances cytokine production and cell signalling pathways |
| Andrographolide | Macrophages, dendritic cells | Suppresses TNF-α and IL-6 production | Reduces inflammation in asthma and arthritis studies | Inhibits JAK/STAT and NF-κB pathways |
| Luteolin | T cells, mast cells | Reduces IL-4, IL-5 from Th2 cells | Relieves symptoms in allergic disease models | Blocks mast cell degranulation and cytokine release |

may boost the results of present cancer therapies. Using these substances with standard chemotherapy medicines seems to improve treatment in many cases. Several combinations of substances from nature with anticancer medicines have resulted in better treatment outcomes. Natural compounds in soy such as genistein improve doxorubicin's efficacy and equol improves tamoxifen. Likewise, when combined with tamoxifen, pomegranate extract has been reported to both increase cell death and lower the chances of breast cancer cells surviving. Research shows that 3,3′-Diindolylmethane (DIM) orally can work together with paclitaxel to trigger cancer cell apoptosis[129-132]. Additionally, extract of rosemary may boost how tamoxifen, trastuzumab and paclitaxel (breast cancer drugs) function. This research shows that using natural products along with regular treatment could enhance results and lower side effects. Chemotherapy is still used to treat cancer and works well, but the growing number of chemo resistant cancers creates a big issue. Because of this resistance, ATP-binding Cassette (ABC) transporters move drugs out of cancer cells and reduce their effectiveness. The search for natural ingredients that can break through multidrug resistance (MDR) is now underway. Ordinary MCF-7 and drug-resistant MCF-7 cells both responded to Elemene's powerful ability to limit MDR. DIM has demonstrated that it may sensitise cancer cells to radiation, making it an attractive option for study in tumours that do not respond well to radiation. A major need for alternative treatments is especially visible in Triple-Negative Breast Cancer (TNBC), as it has very few treatment options and a poor outcome. Scientists have found that natural substances called curcumin and resveratrol affect TNBC cells with very few side effects. One more substance in green tea, Epigallocatechin Gallate (EGCG), has been seen to stop the movement of TNBC cells. It has been found that carnosol, from herbs like rosemary, can cause G2 cell arrest and set in motion both ROS-induced apoptosis and autophagy inside TNBC cells. There is evidence that it may contribute to future ways we treat chronic diseases. Overall, natural substances could be useful in making standard breast cancer therapies work even better and in overcoming drug resistance. They might

help additional medicines work better or focus on the reasons things might not work with other treatments. Further investigation of how these treatments work and the conditions they treat could produce safer, better therapies for breast cancer, especially the more aggressive types like TNBC[132-134].

## 6. Conclusion

Therapies for preventing and treating breast cancer have been developed using natural materials found in living organisms. Previously, herbal medicine and raw ingredients in diverse cultures relied on these compounds and now science is recognising how they can influence cancer causes. These drugs may be used alone or along with chemotherapy to improve results because they can influence several different cellular functions. Due to their low-risk profile, ability to tell cancer cells to self-destruct, block cell cycles and slow their growth, they are much better suited compared to traditional therapies that commonly result in severe side effects. Earlier research has established that these natural materials can combat drug resistance, block tumour-promoting processes and damage only cancer cells and not healthy ones. They support murder of cancerous cells through both forms of apoptosis and influence autophagy which plays a role in their cancer-fighting abilities. Even though they show enormous potential, concerns about their limited absorption, uncertain pharmacokinetics and unknown mechanisms of action remain serious problems. By studying these gaps in science, we can make these devices better suited for use in medical settings. Still, various natural substances have successfully passed preclinical tests and early tests on patients, indicating they may play a significant role in breast cancer therapies. These could prove important when conventional solutions either fail or raise health risks for patients. Natural products could bring down the mortality rate from breast cancer and lead to better outcomes for patients and it is important to keep studying their effects in order to develop more effective cancer treatments that are accessible to all.

## 7. References


1. Sivaganesh V, Promi N, Maher S, Peethambaran B. Emerging immunotherapies against novel molecular targets in breast cancer. Int J Mol Sci. 2021; 22(5):2433. PMid: 33670942. PMCid: PMC7957700. https://doi.org/10.3390/ijms22052433
2. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. Cancer Epidemiol. 2009; 33(5):315-318. PMid: 19896917. https://doi.org/10.1016/j.canep.2009.10.003
3. Dave P, Jani R, Chakraborthy GS, Jani KJ, Upadhye V, Kahrizi D, Mir MA, Siddiqui S, Saeed M, Upadhyay TK. Phytosomes: A promising delivery system for anticancer agents by using phytochemicals in cancer therapy. Cellular and Molecular Biology. 2023; 69(14):1-8. PMid: 38279505. https://doi.org/10.14715/cmb/2023.69.14.1
4. Hudis CA, Gianni L. Triple-negative breast cancer: An unmet medical need. Oncologist 2011; 16(S1):1-11. PMid: 21278435. https://doi.org/10.1634/theoncologist.2011-S1-01
5. Bhardwaj P, Brown KA. Obese adipose tissue as a driver of breast cancer growth and development: Update and emerging evidence. Front Oncol. 202; 11:638918. PMid: 33859943. PMCid: PMC8042134. https://doi.org/10.3389/fonc.2021.638918
6. Hui Z, Wen H, Zhu J, Deng H, Jiang X, Ye XY, Wang L, Xie T, Bai R. Discovery of plant-derived anti-tumor natural products: Potential leads for anti-tumor drug discovery. Bioorg Chem. 2024; 142:106957. PMid: 37939507. https://doi.org/10.1016/j.bioorg.2023.106957
7. Al-Antary ET, Gupte A, Carter J, Kaafarani M, Howard M, Edwards H, Ge Y, Taub JW. Curing childhood cancer the "Natural" way: Nature as the source of chemotherapy agents. Biochem Pharmacol. 2023; 213:115630. PMid: 37263301. https://doi.org/10.1016/j.bcp.2023.115630
8. Giurini EF, Godla A, Gupta KH. Redefining bioactive small molecules from microbial metabolites as revolutionary anticancer agents. Cancer Gene Ther. 2024; 31(2):187-206. PMid: 38200347. PMCid: PMC10874892. https://doi.org/10.1038/s41417-023-00715-x
9. Cech NB, Oberlies NH. From plant to cancer drug: Lessons learned from the discovery of taxol. Nat Prod Rep. 2023; 40(7):1153-1157. PMid: 37449327. PMCid: PMC10354831. https://doi.org/10.1039/D3NP00017F
10. Shaik BB, Katari NK, Jonnalagadda SB. Role of natural products in developing novel anticancer agents: A perspective. Chem Biodivers. 2022; 19(11):e202200535. PMid: 36347633. https://doi.org/10.1002/cbdv.202200535
11. Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, Zheng Q. Natural products as anticancer agents: Current status and future perspectives. Molecules. 2022; 27(23):8367. PMid: 36500466. PMCid: PMC9737905. https://doi.org/10.3390/molecules27238367
12. Chunarkar-Patil P, Kaleem M, Mishra R, Ray S, Ahmad A, Verma D, Bhayye S, Dubey R, Singh HN, Kumar S. Anticancer drug discovery based on natural products: From computational approaches to clinical studies. Biomedicines.

2024; 12(1):201. PMid: 38255306. PMCid: PMC10813144. https://doi.org/10.3390/biomedicines12010201

13. Guo M, Jin J, Zhao D, Rong Z, Cao LQ, Li AH, Sun XY, Jia LY, Wang YD, Huang L, Li YH. Research advances on anti-cancer natural products. Front Oncol. 2022;12:866154. PMid: 35646647. PMCid: PMC9135452. https://doi.org/10.3389/fonc.2022.866154
14. Marino N, German R, Rao X, Simpson E, Liu S, Wan J, Liu Y, Sandusky G, Jacobsen M, Stovall M, Cao S. Upregulation of lipid metabolism genes in the breast prior to cancer diagnosis. NPJ Breast Cancer. 2020; 6(50). PMid: 33083529. PMCid: PMC7538898. https://doi.org/10.1038/s41523-020-00191-8
15. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. Carcinog. 2009; 30(7):1073-1081. PMid: 19468060. https://doi.org/10.1093/carcin/bgp127
16. Suman S, Sharma PK, Rai G, Mishra S, Arora D, Gupta P, Shukla Y. Current perspectives of molecular pathways involved in chronic inflammation-mediated breast cancer. Biochem Biophys Res Commun. 2016; 472(3):401-409. PMid: 26522220. https://doi.org/10.1016/j.bbrc.2015.10.133
17. Puar YR, Shanmugam MK, Fan L, Arfuso F, Sethi G, Tergaonkar V. Evidence for the involvement of the master transcription factor NF-κB in cancer initiation and progression. Biomedicines. 2018; 6(3):82. PMid: 30060453. PMCid: PMC6163404. https://doi.org/10.3390/biomedicines6030082
18. Oshi M, Newman S, Tokumaru Y, Yan L, Matsuyama R, Endo I, Nagahashi M, Takabe K. Intra-tumoral angiogenesis is associated with inflammation, immune reaction and metastatic recurrence in breast cancer. Int J Mol Sci. 2020; 21(18):6708. PMid: 32933189. PMCid: PMC7555442. https://doi.org/10.3390/ijms21186708
19. Michels N, van Aart C, Morisse J, Mullee A, Huybrechts I. Chronic inflammation towards cancer incidence: A systematic review and meta-analysis of epidemiological studies. Crit Rev Oncol Hematol. 2021; 157:103177. PMid: 33264718. https://doi.org/10.1016/j.critrevonc.2020.103177
20. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: Food sources and bioavailability. Am J Clin Nutr. 2004; 79(5):727-747. PMid: 15113710. https://doi.org/10.1093/ajcn/79.5.727
21. Dou QP. Molecular mechanisms of green tea polyphenols. Nutr Cancer. 2009; 61(6):827-835. PMid: 20155623. PMCid: PMC3769684. https://doi.org/10.1080/01635580903285049
22. Ferguson JJ, Oldmeadow C, Bentley D, Garg ML. Antioxidant effects of a polyphenol-rich dietary supplement incorporating *Pinus massoniana* bark extract in healthy older adults: A two-arm, parallel group, randomized placebo-controlled trial. Antioxidants. 2022; 11(8):1560. PMid: 36009279. PMCid: PMC9405161. https://doi.org/10.3390/antiox11081560
23. Kim JH, Gupta SC, Park B, Yadav VR, Aggarwal BB. Turmeric (*Curcuma longa*) inhibits inflammatory nuclear factor (NF)-κB and NF-κB-regulated gene products and induces death receptors leading to suppressed proliferation, induced chemosensitization, and suppressed osteoclastogenesis. Mol Nutr Food Res. 2012; 56(3):454-465. PMid: 22147524. PMCid: PMC3392043. https://doi.org/10.1002/mnfr.201100270
24. Bharti AC, Takada Y, Aggarwal BB. Curcumin (Diferuloylmethane) inhibits receptor activator of NF-κB ligand-induced NF-κB activation in osteoclast precursors and suppresses osteoclastogenesis. J Immunol. 2004; 172(10):5940-5947. PMid: 15128775. https://doi.org/10.4049/jimmunol.172.10.5940
25. Bhat KP, Pezzuto JM. Cancer chemopreventive activity of resveratrol. Ann N Y Acad Sci. 2002; 957(1):210-229. PMid: 12074974. https://doi.org/10.1111/j.1749-6632.2002.tb02918.x
26. Fulda S, Galluzzi L, Kroemer G. Targeting mitochondria for cancer therapy. Nat Rev Drug Discov. 2010; 9(6):447-464. PMid: 20467424. https://doi.org/10.1038/nrd3137
27. Shukla S, Gupta S. Apigenin: A promising molecule for cancer prevention. Pharmaceutical Research. Springer. 2010; 27:962-978. PMid: 20306120. PMCid: PMC2874462. https://doi.org/10.1007/s11095-010-0089-7
28. Tsai CF, Yeh WL, Huang SM, Tan TW, Lu DY. Wogonin induces reactive oxygen species production and cell apoptosis in human glioma cancer cells. Int J Mol Sci. 2012; 13(8):9877-9892. PMid: 22949836. PMCid: PMC3431834. https://doi.org/10.3390/ijms13089877
29. Lv P, Shi F, Chen X, Xu L, Wang C, Tian S, Yang H, Hou L. Tea polyphenols inhibit the growth and angiogenesis of breast cancer xenografts in a mouse model. J Tradit Chin Med Sci. 2020; 7(2):141-147. https://doi.org/10.1016/j.jtcms.2020.05.001
30. Mokra D, Joskova M, Mokry J. Therapeutic effects of green tea polyphenol (-)-Epigallocatechin-3-Gallate (EGCG) in relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. Int J Mol Sci. 2023; 24(1):340. PMid: 36613784. PMCid: PMC9820274. https://doi.org/10.3390/ijms24010340
31. Wang X, Zheng N, Dong J, Wang X, Liu L, Huang J. Estrogen receptor-α36 is involved in icaritin induced growth inhibition of triple-negative breast cancer cells. J Steroid Biochem Mol Biol. 2017; 171:318-327. PMid: 28529129. https://doi.org/10.1016/j.jsbmb.2017.05.009
32. Liu K, Sun Q, Liu Q, Li H, Zhang W, Sun C. Focus on immune checkpoint PD-1/PD-L1 pathway: New advances of polyphenol phytochemicals in tumor immunotherapy. Biomed Pharmacother. 2022; 154:113618. PMid: 36055113. https://doi.org/10.1016/j.biopha.2022.113618

33. Onu EO, Ugwoke JI, Edeh HO, Onu MC, Onyimonyi AE. A review: Flavonoid; a phyto-nutrient and its impact in livestock animal nutrition. WJARR. 2024; 21(1):311-320. https://doi.org/10.30574/wjarr.2024.21.1.2701
34. Das S, Jha AN. Role of flavonoids as ethnomedicine for the treatment of complex neurodegenerative diseases. Traditional Resources and Tools for Modern Drug Discovery: Ethnomedicine and Pharmacology. Springer. 2024: pp. 295-313. https://doi.org/10.1007/978-981-97-4600-2_11
35. Chirumbolo S. The role of quercetin, flavonols and flavones in modulating inflammatory cell function. Inflamm Allergy Drug Targets. 2010; 9(4):263-285. PMid: 20887269. https://doi.org/10.2174/187152810793358741
36. Chesnokova NY, Levochkina LV, Prikhod'Ko YV, Kuznetsova AA, Chebukin PA. Influence of ultrasound and extraction conditions on the intensity of extraction of anthocyanin pigment from berry raw materials. IOP Conf Ser Earth Environ Sci. 2021; 848(1):012211. https://doi.org/10.1088/1755-1315/848/1/012211
37. Samota MK, Yadav DK, Koli P, Kaur M, Kaur M, Rani H, Selvan SS, Mahala P, Tripathi K, Kumar S. Exploring natural chalcones: Innovative extraction techniques, bioactivities, and health potential. Sustain Food Technol. 2024; 2:1456-1468. https://doi.org/10.1039/D4FB00126E
38. Patil VM, Masand N. Anticancer potential of flavonoids: Chemistry, biological activities, and future perspectives. Stud Nat Prod Chem. 2018; 59:401-430. https://doi.org/10.1016/B978-0-444-64179-3.00012-8
39. Biesiada A, Tomczak A. Biotic and abiotic factors affecting the content of the chosen antioxidant compounds in vegetables. J Fruit Ornam Plant Res. 2012; 76(1):55. https://doi.org/10.2478/v10032-012-0004-3
40. Russo GL, Tedesco I, Spagnuolo C, Russo M. Antioxidant polyphenols in cancer treatment: Friend, foe or foil?. Semin Cancer Biol. 2017; 46:1-13. PMid: 28511887. https://doi.org/10.1016/j.semcancer.2017.05.005
41. Keating E, Martel F. Antimetabolic effects of polyphenols in breast cancer cells: Focus on glucose uptake and metabolism. Frontiers in nutrition. 2018; 5:25. PMid: 29713632. PMCid: PMC5911477. https://doi.org/10.3389/fnut.2018.00025
42. Farghadani R, Naidu R. The anticancer mechanism of action of selected polyphenols in Triple-negative Breast Cancer (TNBC). Biomed Pharmacother. 2023; 165:115170. PMid: 37481930. https://doi.org/10.1016/j.biopha.2023.115170
43. Losada-Echeberria M, Herranz-Lopez M, Micol V, Barrajon-Catalan E. Polyphenols as promising drugs against main breast cancer signatures. Antioxidants. 2017; 6(4):88. PMid: 29112149. PMCid: PMC5745498. https://doi.org/10.3390/antiox6040088
44. Zhou Y, Zheng J, Li Y, Xu DP, Li S, Chen YM, Li HB. Natural polyphenols for prevention and treatment of cancer. Nutrients. 2016; 8(8):515. PMid: 27556486. PMCid: PMC4997428. https://doi.org/10.3390/nu8080515
45. Chen D, Li D, Xu XB, Qiu S, Luo S, Qiu E, Rong Z, Zhang J, Zheng D. Galangin inhibits epithelial-mesenchymal transition and angiogenesis by downregulating CD44 in glioma. J Cancer. 2019; 10(19):4499-4508. PMid: 31528214. PMCid: PMC6746128. https://doi.org/10.7150/jca.31487
46. Sukjoi W, Ngamkham J, Attwood PV, Jitrapakdee S. Targeting cancer metabolism and current anti-cancer drugs. Reviews on New Drug Targets in Age-Related Disorders: Part II. Springer. 2021: pp. 15-48. PMid: 33725343. https://doi.org/10.1007/978-3-030-55035-6_2
47. Sun W, Zhang ND, Zhang T, Li YN, Xue H, Cao JL, Hou WS, Liu J, Wang Y, Jin CH. Cyanidin-3-O-glucoside induces the apoptosis of human gastric cancer MKN-45 cells through ROS-mediated signaling pathways. Molecules. 2023; 28(2):652. PMid: 36677726. PMCid: PMC9860697. https://doi.org/10.3390/molecules28020652
48. Situmorang PC, Ilyas S, Nugraha SE, Syahputra RA, Rahman NMAN. Prospects of compounds of herbal plants as anticancer agents: A comprehensive review from molecular pathways. Front Pharmacol. 2024; 15:1387866. PMid: 39104398. PMCid: PMC11298448. https://doi.org/10.3389/fphar.2024.1387866
49. Akash S, Aovi FI, Azad MA, Kumer A, Chakma U, Islam MR, Mukerjee N, Rahman MM, Bayıl I, Rashid S, Sharma R. Computational investigation of Scutellarein derivatives as an inhibitor against triple-negative breast cancer by quantum calculation, and drug-designed approaches. BioRxiv. 2023:2023-03. https://doi.org/10.1101/2023.03.06.531447
50. Yin Z, Zhang J, Chen L, Guo Q, Yang B, Zhang W, Kang W. Anticancer effects and mechanisms of action of plumbagin: Review of research advances. BioMed Res Int. 2020. PMid: 33344645. PMCid: PMC7725562. https://doi.org/10.1155/2020/6940953
51. Li Y, Tu M, Cheng C, Tian J, Zhang F, Deng Z, *et al*. Wogonoside induces apoptosis in Bel-7402, a hepatocellular carcinoma cell line, by regulating Bax/Bcl-2. Oncol Lett. 2015; 10(3):1831-1835. PMid: 26622760. PMCid: PMC4533296. https://doi.org/10.3892/ol.2015.3408
52. Pang H, Badehnoosh B. Synergistic strength: Unleashing exercise and polyphenols against breast cancer. Cancer Cell International. Springer. 2025; 25(144). PMid: 40234950. PMCid: PMC11998149. https://doi.org/10.1186/s12935-025-03767-1
53. Mocanu MM, Nagy P, Szollosi J. Chemoprevention of breast cancer by dietary polyphenols. Molecules. 2015; 20(12):22578-22620. PMid: 26694341. PMCid: PMC6332464.https://doi.org/10.3390/molecules201219864
54. Carvalho JT, Baldivia DDS, Castro DTH, Santos HF, Santos CM, Oliveira AS, Alfredo TM, Vilharva KN, Picoli Souza K, Santos EL. The immunoregulatory function of polyphenols: Implications in cancer immunity. J Nutr Biochem. 2020; 85:108428. PMid: 32679443. https://doi.org/10.1016/j.jnutbio.2020.108428

55. Izuegbuna OO. Polyphenols: Chemoprevention and therapeutic potentials in hematological malignancies. Front Nutr. 2022; 9:1008893. PMid: 36386899. PMCid: PMC9643866. https://doi.org/10.3389/fnut.2022.1008893
56. Yin J, Lin Y, Fang W, Zhang X, Wei J, Hu G, Liu P, Niu J, Guo J, Zhen Y, Li J. Tetrandrine citrate suppresses breast cancer via depletion of glutathione peroxidase 4 and activation of nuclear receptor coactivator 4-mediated ferritinophagy. Front Pharmacol. 2022; 13:820593. PMid: 35614944. PMCid: PMC9124810. https://doi.org/10.3389/fphar.2022.820593
57. Wang Y, Yue W, Lang H, Ding X, Chen X, Chen H. Resuming sensitivity of tamoxifen-resistant breast cancer cells to tamoxifen by tetrandrine. Integr Cancer Ther. 2021. PMid: 33660534. PMCid: PMC8164553. https://doi.org/10.1177/1534735421996822
58. Knudsen ES, Witkiewicz AK. The strange case of CDK4/6 inhibitors: Mechanisms, resistance, and combination strategies. Trends cancer. 2017; 3(1):39-55. PMid: 28303264. PMCid: PMC5347397. https://doi.org/10.1016/j.trecan.2016.11.006
59. Linn P, Kohno S, Sheng J, Kulathunga N, Yu H, Zhang Z, Voon D, Watanabe Y, Takahashi C. Targeting RB1 loss in cancers. Cancers. 2021; 13(15):3737. PMid: 34359636. PMCid: PMC8345210. https://doi.org/10.3390/cancers13153737
60. El-abadelah MM, Taha MO, Sabri SS, *et al*. The anticancer activity of the substituted pyridone-annelated isoindigo (5'-Cl) involves G0/G1 cell cycle arrest and inactivation of CDKs in the promyelocytic leukemia cell line HL-60. Cell Physiol Biochem. 2015; 35(5):1943-1957. PMid: 25870953. https://doi.org/10.1159/000374003
61. Lin J, Ruan J, Zhu H, Chen Z, Chen J, Yu H. Tenacissoside H induces autophagy and radiosensitivity of hepatocellular carcinoma cells by PI3K/Akt/mTOR signaling pathway. Dose-Response. 2021. PMid: 34035782. PMCid: PMC8127767. https://doi.org/10.1177/15593258211011023
62. Zhang B, Meng M, Xiang S, Cao Z, Xu X, Zhao Z, Zhang T, Chen B, Yang P, Li Y, Zhou Q. Selective activation of tumor-suppressive MAPKP signaling pathway by triptonide effectively inhibits pancreatic cancer cell tumorigenicity and tumor growth. Biochem Pharmacol. 2019; 166:70-81. PMid: 31075266. https://doi.org/10.1016/j.bcp.2019.05.010
63. Wang CH, Yang JM, Guo YB, Shen J, Pei XH. Anticancer activity of tetrandrine by inducing apoptosis in human breast cancer cell line MDA-MB-231 *in vivo*. Evidence-Based Complementary and Alternative Medicine. Willey. 2020. PMid: 32714412. PMCid: PMC7345956. https://doi.org/10.1155/2020/6823520
64. Dai Y, Jin F, Wu W, Kumar SK. Cell cycle regulation and hematologic malignancies. Blood Sci. 2019; 1(1):34-43. PMid: 35402801. PMCid: PMC8975093. https://doi.org/10.1097/BS9.0000000000000009
65. Shabir I, Pandey VK, Shams R, Dar AH, Dash KK, Khan SA, Bashir I, Jeevarathinam G, Rusu AV, Esatbeyoglu T, Pandiselvam R. Promising bioactive properties of quercetin for potential food applications and health benefits: A review. Front Nutr. 2022; 9. PMid: 36532555. PMCid: PMC9748429. https://doi.org/10.3389/fnut.2022.999752
66. Aghababaei F, Hadidi M. Recent advances in potential health benefits of quercetin. Pharmaceuticals. 2023; 16(7):1020. PMid: 37513932. PMCid: PMC10384403. https://doi.org/10.3390/ph16071020
67. Smith AJ, Oertle J, Warren D, Prato D. Quercetin: A promising flavonoid with a dynamic ability to treat various diseases, infections, and cancers. J Cancer Ther. 2016; 7(2):83. https://doi.org/10.4236/jct.2016.72010
68. Gowda NGS, Shiragannavar VD, Puttahanumantharayappa LD, Shivakumar AT, Dallavalasa S, Basavaraju CG, Bhat SS, Prasad SK, Vamadevaiah RM, Madhunapantula SV, Santhekadur PK. Quercetin activates vitamin D receptor and ameliorates breast cancer induced hepatic inflammation and fibrosis. Front Nutr. 2023; 10:1158633. PMid: 37153919. PMCid: PMC10157213. https://doi.org/10.3389/fnut.2023.1158633
69. Suman I, Jezidžić A, Dobrić D, Domitrović R. Differential effects of rutin and its aglycone quercetin on cytotoxicity and chemosensitization of HCT 116 colon cancer cells to anticancer drugs 5-fluorouracil and doxorubicin. Biology. 2025; 14(5):527. PMid: 40427716. PMCid: PMC12109564. https://doi.org/10.3390/biology14050527
70. Vila MP, Shimomura I, Kogure A, Usuba W, Takahashi RU, Ochiya T, Yamamoto Y. Quercetin inhibits Lef1 and resensitizes docetaxel-resistant breast cancer cells. Molecules. 2020; 25(11):2576. PMid: 32492961. PMCid: PMC7321307. https://doi.org/10.3390/molecules25112576
71. Biswas P, Dey D, Biswas PK, Rahaman TI, Saha S, Parvez A, Khan DA, Lily NJ, Saha K, Sohel M, Hasan MM. A comprehensive analysis and anti-cancer activities of quercetin in ROS-mediated cancer and cancer stem cells. Int J Mol Sci. 2022; 23(19):11746. PMid: 36233051. PMCid: PMC9569933. https://doi.org/10.3390/ijms231911746
72. Kim JK, Park SU. Quercetin and its role in biological functions: An updated review. EXCLI J. 2018; 17:856-863. PMCID: PMC6141818. PMID: 30233284. https://doi.org/10.17179/excli2018-1538
73. Ekalu A, Habila JD. Flavonoids: Isolation, characterization, and health benefits. Beni-Suef Univ J Basic Appl Sci. 2020; 9(45). https://doi.org/10.1186/s43088-020-00065-9
74. Ozates NP, Sogutlu F, Erciyas FL, Demir B, Gunduz C, Shademan B, Avci CB. Effects of rapamycin and AZD3463 combination on apoptosis, autophagy, and cell cycle for resistance control in breast cancer. Life Sci. 2021; 264:118643. PMid: 33141044. https://doi.org/10.1016/j.lfs.2020.118643
75. Sharma VR, Sharma AK, Punj V, Priya P. Recent nanotechnological interventions targeting PI3K/Akt/

mTOR pathway: A focus on breast cancer. Semin Cancer Biol. 2019; 59:133-146. PMid: 31408722. https://doi.org/10.1016/j.semcancer.2019.08.005

76. Huang S. Inhibition of PI3K/Akt/mTOR signaling by natural products. Anti-cancer Agents in Medicinal Chemistry. Bentham Science. 2013; 7:967-970. PMid: 23272914. PMCid: PMC3775843. https://doi.org/10.2174/1871520611313070001
77. Mitra S, Dash R. Natural products for the management and prevention of breast cancer. Evidence-Based Complementary and Alternative Medicine. Wiley. 2018. PMid: 29681985. PMCid:PMC5846366.https://doi.org/10.1155/2018/8324696
78. Sharma V, Sharma AK, Punj V, Priya P. Recent nanotechnological interventions targeting PI3K/Akt/mTOR pathway: A focus on breast cancer. Semin Cancer Biol. 2019; 59:133-146. PMid: 31408722. https://doi.org/10.1016/j.semcancer.2019.08.005
79. Zheng Y, Jiang Y. mTOR inhibitors at a glance. Mol Cell Pharmacol. 2015; 7(2):15-20. PMID: 27134695. PMCID: PMC4849280. https://doi.org/10.1016/j.bcp.2006.02.009
80. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol. 2006;71(10):1397–1421. PMID: 16563357
81. Sharifi-Rad J, Quispe C, Patra JK, Singh YD, Panda MK, Das G, *et al*. Paclitaxel: Application in modern oncology and nanomedicine-based cancer therapy. Oxid Med Cell Longev. 2021; 2021(1):3687700. PMid: 34707776. PMCid: PMC8545549. https://doi.org/10.1155/2021/3687700
82. Varghese S, Jisha MS, Rajeshkumar KC, Gajbhiye V, Alrefaei AF, Jeewon R. Endophytic fungi: A future prospect for breast cancer therapeutics and drug development. Heliyon. 2024. https://doi.org/10.2139/ssrn.4728989
83. Guan D, Xuan B, Wang C, Long R, Jiang Y, Mao L, Kang J, Wang Z, Chow SF, Zhou Q. Improving the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients derived from traditional Chinese medicine through cocrystal engineering. Pharmaceutics. 2021; 13(12):2160. PMid: 34959440. PMCid: PMC8704577. https://doi.org/10.3390/pharmaceutics13122160
84. Stengel C, Newman SP, Day JM, Chander SK, Jourdan FL, Leese MP, Ferrandis E, Regis-Lydi S, Potter BV, Reed MJ, Purohit A. *In vivo* and *in vitro* properties of STX2484: A novel non-steroidal anti-cancer compound active in taxane-resistant breast cancer. Br J Cancer. 2014; 111:300-308. PMid: 24960406. PMCid: PMC4102933. https://doi.org/10.1038/bjc.2014.188
85. Fridlender M, Kapulnik Y, Koltai H. Plant derived substances with anti-cancer activity: from folklore to practice. Front Plant Sci. 2015; 6:799. PMid: 26483815. PMCid: PMC4589652. https://doi.org/10.3389/fpls.2015.00799
86. Tang B, Qian Y, Gou Y, Cheng G, Fang G. VE-albumin core-shell nanoparticles for paclitaxel delivery to treat MDR breast cancer. Molecules. 2018; 23(11):2760. PMid: 30366367. PMCid: PMC6278303. https://doi.org/10.3390/molecules23112760
87. Li J, Wang Q, Wang Z, Cui N, Yang B, Niu W, Kuang H. Tetrandrine inhibits colon carcinoma HT-29 cells growth via the Bcl-2/Caspase 3/PARP pathway and G1/S phase. Biosci Rep. 2019; 39(5):BSR20182109. PMid: 31040202. PMCid: PMC6522708. https://doi.org/10.1042/BSR20182109
88. Lin HF, Huang HL, Liao JF, Shen CC, Huang RL. Dicentrine analogue-induced G2/M arrest and apoptosis through inhibition of topoisomerase II activity in human cancer cells. Planta Med. 2015; 81(10):830-837. PMid: 26158522. https://doi.org/10.1055/s-0035-1546128
89. Luan F, He X, Zeng N. Tetrandrine: A review of its anticancer potentials, clinical settings, pharmacokinetics and drug delivery systems. J Pharm Pharmacol. 2020; 72(11):1491-1512. PMid: 32696989. https://doi.org/10.1111/jphp.13339
90. Guo Y, Pei X. Tetrandrine-induced autophagy in MDA-MB-231 triple-negative breast cancer cell through the inhibition of PI3K/AKT/mTOR signaling. Evidence-Based Complementary and Alternative Medicine. 2019; (1):7517431. PMid: 30713576. PMCid: PMC6332987. https://doi.org/10.1155/2019/7517431
91. Samaan TMA, Samec M, Liskova A, Kubatka P, Busselberg D. Paclitaxel's mechanistic and clinical effects on breast cancer. Biomolecules. 2019; 9(12):789. PMid: 31783552. PMCid: PMC6995578. https://doi.org/10.3390/biom9120789
92. Das T, Anand U, Pandey SK, Ashby Jr CR, Assaraf YG, Chen ZS, Dey A. Therapeutic strategies to overcome taxane resistance in cancer. Drug Resist Updat. 2021; 55:100754. PMid: 33691261. https://doi.org/10.1016/j.drup.2021.100754
93. Manjunatha V, Nixon JE, Mathis GF, Lumpkins BS, Guzel-Seydim ZB, Seydim AC, Greene AK, Jiang X. *Nigella sativa* as an antibiotic alternative to promote growth and enhance health of broilers challenged with *Eimeria maxima* and *Clostridium perfringens*. Poult Sci. 2023; 102(8):102831. PMid: 37356299. PMCid: PMC10404756. https://doi.org/10.1016/j.psj.2023.102831
94. Zheng X, Xu Y, Liu B, Qi Y, Zhang Y, Li X, Zhang X, Pu X, Li S, Chen Z, Wan C. Ethyl acetate extract of *Asclepias curassavica* induced apoptosis in human cancer cells *via* activating p38 and JNK MAPK signaling pathways. Evidence-Based Complementary and Alternative Medicine. Willey. 2019. PMid: 31281406. PMCid: PMC6590487. https://doi.org/10.1155/2019/9076269
95. Gali-Muhtasib HU, Abou Kheir WG, Kheir LA, Darwiche N, Crooks PA. Molecular pathway for thymoquinone-induced cell-cycle arrest and apoptosis in neoplastic keratinocytes. Anti-Cancer Drugs. 2004; 15(4):389-99. PMid: 15057144. https://doi.org/10.1097/00001813-200404000-00012
96. Adinew GM, Messeha SS, Taka E, Badisa RB, Antonie LM, Soliman KF. Thymoquinone alterations of the apoptotic

gene expressions and cell cycle arrest in genetically distinct triple-negative breast cancer cells. Nutrients. 2022; 14(10):2120. PMid: 35631261. PMCid: PMC9144154. https://doi.org/10.3390/nu14102120

97. Abdullah O, Omran Z, Hosawi S, Hamiche A, Bronner C, Alhosin M. Thymoquinone is a multitarget single epidrug that inhibits the UHRF1 protein complex. Genes. 2021; 12(5):622. PMid: 33922029. PMCid: PMC8143546. https://doi.org/10.3390/genes12050622
98. Almajali B, Al-Jamal HA, Taib WR, Ismail I, Johan MF, Doolaanea AA, Ibrahim WN. Thymoquinone, as a novel therapeutic candidate of cancers. Pharmaceuticals. 2021; 14(4):369. PMid: 33923474. PMCid: PMC8074212. https://doi.org/10.3390/ph14040369
99. Janani SK, Dhanabal SP, Sureshkumar R, Surya NU, Chenmala K. Guardian of genome on the tract: Wild type p53-mdm2 complex inhibition in healing the breast cancer. Gene. 2021; 786:145616. PMid: 33811963. https://doi.org/10.1016/j.gene.2021.145616
100. Brockmueller A, Buhrmann C, Shayan P, Shakibaei M. Resveratrol induces apoptosis by modulating the reciprocal crosstalk between p53 and Sirt-1 in the CRC tumor microenvironment. Front Immunol. 2023; 14:1225530. PMid: 37575245. PMCid: PMC10413256. https://doi.org/10.3389/fimmu.2023.1225530
101. Brockmueller A, Shayan P, Shakibaei M. Evidence that β1-integrin is required for the anti-viability and anti-proliferative effect of resveratrol in CRC cells. Int J Mol Sci. 2022; 23(9):4714. PMid: 35563105. PMCid: PMC9099493. https://doi.org/10.3390/ijms23094714
102. Raviv T, Shteinfer-Kuzmine A, Moyal MM, Shoshan-Barmatz V. Resveratrol's pro-apoptotic effects in cancer are mediated through the interaction and oligomerization of the mitochondrial VDAC1. Int J Mol Sci. 2025; 26(9):3963. PMid: 40362204. PMCid: PMC12071565. https://doi.org/10.3390/ijms26093963
103. Ozdemir F, Sever A, Kececi YO, Incesu Z. Resveratrol increases the sensitivity of breast cancer MDA-MB-231 cell line to cisplatin by regulating intrinsic apoptosis. Iran J Basic Med Sci. 2021; 24(1):66-72. PMCID: PMC7894626. PMID: 33643572. 10.22038/ijbms.2020.50485.11501
104. Mirzapur P, Khazaei MR, Moradi MT, Khazaei M. Apoptosis induction in human breast cancer cell lines by synergic effect of raloxifene and resveratrol through increasing proapoptotic genes. Life Sci. 2018; 205:45-53. PMid: 29705353. https://doi.org/10.1016/j.lfs.2018.04.035
105. Ho Y, Li ZL, Shih YJ, Chen YR, Wang K, Whang-Peng J, Lin HY, Davis PJ. Integrin αvβ3 in the mediating effects of dihydrotestosterone and resveratrol on breast cancer cell proliferation. Int J Mol Sci. 2020; 21(8):2906. PMid: 32326308. PMCid: PMC7216104. https://doi.org/10.3390/ijms21082906
106. Hotkar K, Jain V, Deshpande N, Sarje M, Chature DS. Radiotherapy radio protective effect of 2-deoxy D-glucose with combination of selective antioxidant medicinal plant *Vitis vinifera, Camellia sinensis,* and *Zingiber officinale* extracts in mice. Int J Clin Biochem Res. 2020; 7(1):102-110. https://doi.org/10.18231/j.ijcbr.2020.021
107. Amararathna M, Hoskin DW, Rupasinghe HV. Cyanidin-3-O-glucoside-rich haskap berry administration suppresses carcinogen-induced lung tumorigenesis in A/JCr mice. Molecules. 2020; 25(17):3823. PMid: 32842605. PMCid: PMC7503524. https://doi.org/10.3390/molecules25173823
108. Kim TJ, Kim YJ, Seo WD, Park SU, Kim JK. Improved quantification of catechin and epicatechin in red rice (*Oryza sativa* L.) using stable isotope dilution liquid chromatography-mass spectrometry. Appl Biol Chem. 2022; 65(1):85. https://doi.org/10.1186/s13765-022-00754-2
109. Farhan M. Green tea catechins: Nature's way of preventing and treating cancer. Int J Mol Sci. 2022; 23(18):10713. PMid: 36142616. PMCid: PMC9501439. https://doi.org/10.3390/ijms231810713
110. Tillhon M, Ortiz LMG, Lombardi P, Scovassi AI. Berberine: New perspectives for old remedies. Biochem Pharmacol. 2012; 84(10):1260-1267. PMid: 22842630. https://doi.org/10.1016/j.bcp.2012.07.018
111. Olewnik-Kruszkowska E, Ferri M, Cardeira MC, Gierszewska M, Rudawska A. Comparison of polylactide-based active films containing berberine and quercetin as systems for maintaining the quality and safety of blueberries. Polymers. 2024; 16(11):1577. PMid: 38891523. PMCid: PMC11174692. https://doi.org/10.3390/polym16111577
112. Green DR, Kroemer G. The pathophysiology of mitochondrial cell death. Science. 2004; 305(5684):626-629. PMid: 15286356. https://doi.org/10.1126/science.1099320
113. Strasser A, Jost PJ, Nagata S. The many roles of FAS receptor signaling in the immune system. Immunity. 2009; 30(2):180-192. PMid: 19239902. PMCid: PMC2956119. https://doi.org/10.1016/j.immuni.2009.01.001
114. Reddy P, Pradeep S, SM G, Dharmashekar C, MR SC, Srinivasa C, Shati AA, Alfaifi MY, Elbehairi SE, Achar RR, Silina E. Cell cycle arrest and apoptotic studies of *Terminalia chebula* against MCF-7 breast cancer cell line: An *in vitro* and *in silico* approach. Frontiers in Oncology. 2023; 13:1221275. PMid: 37706181. PMCid: PMC10497218. https://doi.org/10.3389/fonc.2023.1221275
115. Karami Fath M, Babakhaniyan K, Zokaei M, Yaghoubian A, Akbari S, Khorsandi M, Soofi A, Nabi-Afjadi M, Zalpoor H, Jalalifar F, Azargoonjahromi A. Anti-cancer peptide-based therapeutic strategies in solid tumors. Cell Mol Biol Lett. 2022; 27(1):33. PMid: 35397496. PMCid: PMC8994312. https://doi.org/10.1186/s11658-022-00332-w
116. Schettini F, Santo I, Rea CG, Placido P, Formisano L, Giuliano M, Arpino G, Laurentiis M, Puglisi F, Placido S, Mastro

L. CDK 4/6 inhibitors as single agent in advanced solid tumors. Front Oncol. 2018; 8:608. PMid: 30631751. PMCid: PMC6315195. https://doi.org/10.3389/fonc.2018.00608
117. Bishayee A. Cancer prevention and treatment with resveratrol: From rodent studies to clinical trials. Cancer Prev Res. 2009; 2(5):409-418. PMid: 19401532. https://doi.org/10.1158/1940-6207.CAPR-08-0160
118. Jackson SJ, Singletary KW. Sulforaphane: A naturally occurring mammary carcinoma mitotic inhibitor, which disrupts tubulin polymerization. Carcinogenesis. 2004; 25(2):219-227. PMid: 14578157. https://doi.org/10.1093/carcin/bgg192
119. Lewinska A, Bednarz D, Adamczyk-Grochala J, Wnuk M. Phytochemical-induced nucleolar stress results in the inhibition of breast cancer cell proliferation. Redox Biol. 2017; 12:469-482. PMid: 28334682. PMCid: PMC5362140. https://doi.org/10.1016/j.redox.2017.03.014
120. Kim SH, Park HJ, Moon DO. Sulforaphane sensitizes human breast cancer cells to paclitaxel-induced apoptosis by downregulating the NF-κB signaling pathway. Oncol Lett. 2017; 13(6):4427-4432. PMid: 28599444. PMCid: PMC5453055. https://doi.org/10.3892/ol.2017.5950
121. Li Y, Yuan YY, Meeran SM, Tollefsbol TO. Synergistic epigenetic reactivation of estrogen receptor-α (ERα) by combined green tea polyphenol and histone deacetylase inhibitor in ERα-negative breast cancer cells. Mol Cancer. 2010; 9(274):1-2. PMid: 20946668. PMCid: PMC2967543. https://doi.org/10.1186/1476-4598-9-274
122. Li Y, Meeran SM, Tollefsbol TO. Combinatorial bioactive botanicals re-sensitize tamoxifen treatment in ER-negative breast cancer via epigenetic reactivation of ERα expression. Sci Rep. 2017; 7(9345). PMid: 28839265. PMCid: PMC5570897. https://doi.org/10.1038/s41598-017-09764-3
123. Zhang X, Zhang Q, Liu G. Genome-wide analysis of the FOXA1 transcriptional regulatory network identifies super enhancer associated LncRNAs in tamoxifen resistance. Front Genet. 2022; 13:992444. PMid: 36204307. PMCid: PMC9530462. https://doi.org/10.3389/fgene.2022.992444
124. Zhang R, Neuhoff C, Yang Q, Cinar MU, Uddin MJ, Tholen E, Schellander K, Tesfaye D. Sulforaphane enhanced proliferation of porcine satellite cells via epigenetic augmentation of SMAD7. Animals. 2022; 12(11):1365. PMid: 35681828. PMCid: PMC9179638. https://doi.org/10.3390/ani12111365
125. Yu J, Guo Z, Zhang J. Research progress of the SLFN family in malignant tumors. Front Oncol. 2024; 14:1468484. PMid: 39558948. PMCid: PMC11570580. https://doi.org/10.3389/fonc.2024.1468484
126. Yasunaga A, Ono M, Takeshima M, Nakano S. Sulforaphane suppresses the growth of EGFR-overexpressing MDA-MB-468 triple-negative breast cancer cells *in vivo* and *in vitro*. Int J Funct Nutr. 2022; 3(2). https://doi.org/10.3892/ijfn.2022.26
127. Sun C, Li S, Li D. Sulforaphane mitigates muscle fibrosis in mdx mice via Nrf2-mediated inhibition of TGF-β/Smad signaling. J Appl Physiol. 2016; 120(4):377-390. PMid: 26494449. https://doi.org/10.1152/japplphysiol.00721.2015
128. Xue JP, Wang G, Zhao ZB, Wang Q, Shi Y. Synergistic cytotoxic effect of genistein and doxorubicin on drug-resistant human breast cancer MCF-7/Adr cells. Oncol Rep. 2014; 32(4):1647-1653. PMid: 25109508. https://doi.org/10.3892/or.2014.3365
129. Charalambous C, Pitta CA, Constantinou AI. Equol enhances tamoxifen's anti-tumor activity by induction of caspase-mediated apoptosis in MCF-7 breast cancer cells. BMC Cancer. 2013; 13(238). PMid: 23675643. PMCid: PMC3661348. https://doi.org/10.1186/1471-2407-13-238
130. Nainu F, Masyita A, Bahar MA, Raihan M, Prova SR, Mitra S, Emran TB, Simal-Gandara J. Pharmaceutical prospects of bee products: Special focus on anticancer, antibacterial, antiviral, and antiparasitic properties. Antibiotics. 2021; 10(7):822. PMid: 34356743. PMCid: PMC8300842. https://doi.org/10.3390/antibiotics10070822
131. Gonzalez-Vallinas M, Molina S, Vicente G, Sanchez-Martinez R, Vargas T, Garcia-Risco MR, Fornari T, Reglero G, Molina AR. Modulation of estrogen and epidermal growth factor receptors by rosemary extract in breast cancer cells. Electrophoresis. 2014; 35(11):1719-1727. PMid: 24615943. https://doi.org/10.1002/elps.201400011
132. Islam MN, Rauf A, Fahad FI, Emran TB, Mitra S, Olatunde A, Shariati MA, Rebezov M, Rengasamy KR, Mubarak MS. Superoxide dismutase: An updated review on its health benefits and industrial applications. Crit Rev Food Sci Nutr. 2022; 62(26):7282-7300. PMid: 33905274. https://doi.org/10.1080/10408398.2021.1913400
133. Mitra S, Prova SR, Sultana SA, Das R, Nainu F, Emran TB, Tareq AM, Uddin MS, Alqahtani AM, Dhama K, Simal-Gandara J. Therapeutic potential of indole alkaloids in respiratory diseases: A comprehensive review. Phytomedicine. 2021; 90:153649. PMid: 34325978. https://doi.org/10.1016/j.phymed.2021.153649
134. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: An evolving paradigm. Nat Rev Cancer. 2013; 13(10):714-726. PMid: 24060863. https://doi.org/10.1038/nrc3599

## Authors Contribution

PD supervision wrote and edited final draft, AM and AP collected the data and wrote, BR prepared the manuscript, figures, and tables MK edited final draft. All authors have read and agreed to the published version of the manuscript.