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Review

Molecular Insight and Antioxidative Therapeutic Potentials of Plant-Derived Compounds in Breast Cancer Treatment

Sandhya Shukla [1,†], Arvind Kumar Shukla [2,*,†], Adarsha Mahendra Upadhyay [3], Navin Ray [4], Fowzul Islam Fahad [2], Arulkumar Nagappan [4,5], Sayan Deb Dutta [6,7,8] and Raj Kumar Mongre [9,*]

1 Department of Pharmacology, Bharti Vidyapeeth Deemed University Medical College, Pune 411043, India; sandhyashukla020@gmail.com
2 School of Biomedical Convergence Engineering, Pusan National University, Yangsan 50612, Republic of Korea; fowzul.fahad19@gmail.com
3 Department of Gastrointestinal Surgery, School of Overseas Education, Guizhou Medical University, Guiyang 550025, China; adarshupadhyay595@gmail.com
4 Laboratory of Mucosal Exposome and Biomodulation, Department of Integrative Biomedical Sciences, Pusan National University, Yangsan 50612, Republic of Korea; navin.ray@gmail.com (N.R.); arulbiotechtnau@gmail.com (A.N.)
5 Center for Global Health Research, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai 602105, India
6 Department of Biosystems Engineering, Kangwon National University, Chuncheon 24341, Republic of Korea; sayan91dutta@gmail.com
7 Institute of Forest Science, Kangwon National University, Chuncheon 24341, Republic of Korea
8 School of Medicine, University of California Davis, Sacramento, CA 95817, USA
9 Department of Surgery, Boston Children's Hospital, Harvard Medical School, Harvard University, 300 Longwood Ave, Boston, MA 02115, USA
* Correspondence: arvindkumarshuklapnu@gmail.com or arvindkumarshukla@pusan.ac.kr (A.K.S.); raj.mongre@childrens.harvard.edu (R.K.M.)
† These authors contributed equally to this work.

Simple Summary: Breast cancer is one of the most prevalent cancers that affects women globally, and it is still difficult to treat because of problems like relapse, side effects, and drug resistance. This review investigates how plant-based natural compounds may enhance the treatment of breast cancer. These plant-based compounds may help slow or even stop the growth and spread of cancer by targeting particular molecular signals in cancer cells. This review seeks to shed light on how these substances interact with significant biological processes in order to better understand how they might complement existing treatments. Future research may be guided by the findings, which could help create safer and more efficient breast cancer treatment options.

Abstract: Breast cancer is one of the most common and difficult-to-treat cancers affecting women globally. Long-term treatment success is still limited by problems like drug resistance, toxicity, and recurrence, even with advancements in conventional therapies. The application of substances derived from plants for medical purposes, or phytotherapy, has become a viable adjunctive approach to the treatment of breast cancer. An integrative approach to phytotherapy is examined in this review, focusing on how it can alter important molecular pathways implicated in the development, progression, and metastasis of breast cancer. By focusing on important signaling cascades like TGF-β, Wnt, Hedgehog, Notch, IL-6, Integrins, VEGF, HER2, EGFR, PI3K/Akt, and MAPK, and estrogen receptor pathways, a variety of phytochemicals, such as flavonoids, alkaloids, terpenoids, and polyphenols, demonstrate strong anticancer effects. This review also discusses how they affect immune modulation, angiogenesis, cell cycle regulation, and apoptosis. Moreover, it also emphasizes the challenges with these natural compounds' bioavailability, standardization, and clinical translation while highlighting preclinical and clinical research that supports their

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therapeutic potential. This review attempts to give a thorough grasp of how plant-based compounds can support efficient and focused breast cancer treatments by fusing molecular insights with phytotherapeutic approaches.

Keywords: phytotherapy; breast cancer; molecular pathways; phytochemicals; targeted therapy; drug resistance

1. Introduction

Breast cancer continues to be a major cause of cancer-related morbidity and death for women worldwide, presenting significant clinical and public health issues. Because of its high frequency and intricate biological makeup, more efficient and long-lasting treatment approaches are desperately needed [1,2]. Long-term success is still hampered by issues like drug resistance, systemic toxicity, and tumor recurrence, even though traditional modalities like surgery, chemotherapy, radiation, and hormone therapy have greatly increased survival rates [3,4]. To improve therapeutic efficacy and lessen side effects, these limitations have spurred research into complementary and alternative approaches. Among these tactics, phytotherapy—the application of bioactive substances extracted from therapeutic plants—has drawn more attention as a potentially useful supplement in the treatment of breast cancer [5,6]. The naturally occurring substances found in plants, known as phytochemicals, have long been known for their pharmacological qualities and are now being investigated more and more for their potential to treat cancer [7,8]. They are desirable candidates for integration into integrative cancer therapy due to their pleiotropic mechanisms of action and comparatively low toxicity. Numerous phytochemicals have shown promise in modifying important molecular pathways implicated in tumorigenesis, proliferation, and metastasis in breast cancer [9,10]. These comprise signaling pathways that are essential to the pathophysiology of breast cancer, including PI3K/Akt/mTOR, MAPK/ERK, NF-κB, and the estrogen receptor axis. Phytochemicals may inhibit tumor growth, restore normal cellular homeostasis, and make cancer cells more sensitive to traditional treatments by focusing on these pathways [11–14].

The phytochemical classes flavonoids, alkaloids, terpenoids, and polyphenols are among the most researched; each has a variety of bioactivities. It has been been demonstrated that flavonoids like quercetin, genistein, and apigenin cause breast cancer cells to undergo apoptosis and stop their cell cycle progression [15–17]. The antiproliferative effects of alkaloids, such as vinca alkaloids and berberine, are also mediated by DNA damage and mitochondrial dysfunction. The inhibition of angiogenesis and tumor invasion has been linked to terpenoids like limonene and ursolic acid. Polyphenols, particularly resveratrol and curcumin, are well-known for their antioxidant and anti-inflammatory properties, which can alter the tumor microenvironment and slow the spread of cancer [18–20]. By acting on several targets simultaneously, these phytochemicals provide a comprehensive strategy for reducing cancer cell viability while maintaining healthy tissue function. Phytochemicals are essential for modifying the tumor microenvironment in addition to their direct cytotoxic attacks on tumor cells. For example, some compounds derived from plants can suppress vascular endothelial growth factor (VEGF) and associated signaling molecules, which prevents angiogenesis—the development of new blood vessels required for tumor growth and metastasis [21–23]. Some have immunomodulatory qualities that boost the activity of immune cells like cytotoxic T lymphocytes and natural killer (NK) cells, aiding in the immune system's removal of cancer cells. The epithelial-mesenchymal transition (EMT), a crucial step in cancer metastasis, can also be reversed by certain phytochemicals, which

prevent tumor cells from spreading [24,25]. These mechanistic details—such as induction of apoptosis and regulation of the cell cycle—are further elaborated in Section 5 in relation to specific signaling pathways.

Recent studies have placed a strong emphasis on phytochemicals' pro-apoptotic and cell cycle-regulatory functions. Through the modification of death receptors, caspases, and Bcl-2 family proteins, numerous compounds derived from plants trigger intrinsic and extrinsic apoptotic pathways. They also disrupt cyclins and cyclin-dependent kinases (CDKs), which cause cell cycle arrest at different checkpoints [26–28]. A significant drawback of single-target conventional medications is the development of resistance, which is less likely to occur when multitargeted mechanisms are used to suppress tumor growth. The potential of phytochemicals as chemopreventive and chemotherapeutic agents in the treatment of breast cancer is highlighted by these findings. Despite their encouraging therapeutic effects, the bioavailability, pharmacokinetics, and standardization of phytochemicals are the main obstacles to their clinical use [29–31]. Numerous phytochemicals have low systemic absorption, fast metabolism, and poor water solubility, all of which reduce their effectiveness in vivo. To get around these restrictions and improve bioavailability, techniques like liposomal encapsulation, structural modification, and drug delivery systems based on nanoparticles are being investigated. Furthermore, standardization and reproducibility are made more difficult by variations in plant sources, extraction techniques, and compound purity, which create obstacles to clinical adoption and regulatory approval. To determine the ideal dosage, safety profiles, and therapeutic indices, thorough preclinical and clinical research is required [32–34].

Currently, numerous clinical studies have started to assess the effectiveness of phytochemicals as stand-alone treatments or in conjunction with other therapies. For instance, the potential of genistein and curcumin to lessen the toxicity of chemotherapeutic agents while simultaneously enhancing their effects has been studied. Likewise, it has been demonstrated that resveratrol may make hormone-refractory breast cancers more sensitive to tamoxifen. To validate phytotherapy's translational potential and incorporate it into evidence-based oncology practice, these clinical evaluations are essential. Nevertheless, additional extensive randomized controlled trials are required to address the variability of patient responses and validate the therapeutic benefits. This review emphasizes that combining phytotherapeutic methods with molecular insights presents a promising path toward the creation of tailored and focused treatments for breast cancer. Phytotherapy may become more than just an adjuvant; it may become a fundamental part of all-encompassing cancer treatment as studies continue to clarify the intricate interactions between plant-derived compounds and cellular signaling networks. This review explores the antioxidant properties and anticancer mechanisms of phytochemicals derived from a diverse array of plants, with representative examples such as *Arenga porphyrocarpa*, *Vitis vinifera* (grapevine), *Citrus sinensis* (orange), and *Panax ginseng*. Future research should emphasize a systems biology approach and concentrate on finding synergistic interactions between phytochemicals, clarifying their effects on tumor heterogeneity and cancer stem cells, and investigating their potential to overcome drug resistance. By redefining existing paradigms in breast cancer management, such integrative strategies may give rise to more patient-tailored, less toxic, and more effective treatment options.

2. Phytotherapy in Cancer: Historical Background and Modern Perspectives

Modern scientific discoveries and traditional medical knowledge have profoundly intersected in the development of plant-based therapies for cancer treatment. For centuries, medicinal plants have been used to treat a wide range of illnesses in humans, including

cancer. Early therapeutic practices in ancient civilizations like Egypt, India, and China were based on herbal remedies [35–38]. Plant-derived compounds are used to treat chronic illnesses, inflammations, and abnormal growths, many of which are now known to be cancerous conditions, according to texts from Ayurveda, Traditional Chinese Medicine (TCM), and Greco-Arabic medicine [39–42]. Despite the lack of understanding of the biological foundations of cancer in these conventional frameworks, the empirical use of particular plants proved effective in lowering symptoms and improving patient outcomes, setting the stage for further research [43–45]. In the 19th and 20th centuries, the identification and isolation of bioactive plant compounds marked the beginning of the shift from empirical herbalism to evidence-based phytotherapy [46–51]. During this time, alkaloids from *Catharanthus roseus*, such as vincristine and vinblastine, emerged, revolutionizing cancer chemotherapy. It was further demonstrated how naturally occurring compounds could be used to stop the growth of cancer cells and trigger apoptosis with the discovery of paclitaxel from *Taxus brevifolia* and camptothecin from *Camptotheca acuminata* [52,53]. In addition to confirming the therapeutic potential of medicinal plants, these discoveries spurred a systematic search for anticancer properties in botanical sources. In modern cancer pharmacology, substances derived from plants are either used directly as chemotherapeutic medications or as building blocks to create stronger analogs with better pharmacokinetics and lower toxicity [54–57].

The schematic figure highlights the mechanisms of action and immunomodulatory effects of natural compounds and phytochemicals, providing a thorough overview of their potential as therapeutic agents in breast cancer. Both in vitro and in vivo, the diverse functions of phytochemicals in targeting breast cancer cells are depicted in Figure 1A [58,59]. By altering important molecular pathways linked to tumor growth, such as metastasis and multidrug resistance, these bioactive substances reduce the aggressiveness of cancer cells. Phytochemicals provide a more affordable and accessible option to traditional breast cancer treatments, which are frequently linked to limited efficacy, high cost, and toxicity. They have a wide range of biological activities, including pro-apoptotic, anti-inflammatory, antioxidant, anti-proliferative, anti-angiogenic, and anticancer effects [60–62]. Furthermore, these natural substances have shown the ability to specifically target different populations of breast cancer stem cells and molecular subtypes, which makes them attractive options for integrative cancer treatment approaches. The various forms of breast cancer are schematically represented in Figure 1B, which highlights the disease's multifactorial etiology and its prevalence as the primary cause of cancer-related death for women globally [63]. The dysregulation of signaling pathways implicated in angiogenesis, metastasis, and cell survival is facilitated by the overexpression of hormone receptors, specifically those for estrogen and progesterone. Ductal, lobular, mucinous, inflammatory, and mixed tumors are the main subtypes, and they typically start in the milk ducts and lobules of the breast tissue [64–66]. Keeping with the topic of natural compound-induced cancer immunotherapy, Figure 1C shows a conceptualization of the mechanism by which natural products induce immunogenic cell death (ICD), laying the groundwork for the creation of innovative and secure immunotherapeutic strategies. Particular attention is paid to resveratrol in Figure 1D, a polyphenolic compound with immunomodulatory and anticancer effects that is present in red wine and grapes. Resveratrol has been demonstrated to trigger the classical hallmarks of ICD, including calreticulin (CRT) exposure, HMGB1 release, and ATP secretion, in both in vitro and in vivo models. This activation results in the proliferation of cytotoxic T lymphocytes and antigen-presenting dendritic cells (DCs). Additionally, when combined with immune checkpoint inhibitors like PD-1 antibodies, it dramatically increased antitumor responses; however, these effects were reversed when CD8+ T cells were depleted, suggesting a T-cell-mediated mechanism [67,68]. Through

endoplasmic reticulum stress, baicalin and other terpenoids such as wogonin and tripterine contribute to the promotion of ICD, as shown in Figure 1E. These substances not only inhibit the growth of tumors but also alter the immune environment surrounding tumors by stimulating DCs, increasing the infiltration of cytotoxic T and NK cells, and decreasing immunosuppressive populations like myeloid-derived suppressor cells (MDSCs) [69]. We propose a novel integrative framework in which antioxidant phytochemicals are classified according to their capacity to modulate distinct redox-sensitive molecular cascades. This synthesis highlights therapeutic windows where these compounds can synergize with conventional cancer therapies, particularly in contexts like immunogenic cell death (ICD), where redox balance is critical.

The application of phytotherapy has focused on breast cancer, one of the most common cancers in the world. The potential of plant-based therapies to supplement traditional treatments like radiation, chemotherapy, and surgery is being investigated in light of the growing interest in integrative oncology [70–72]. Preclinical breast cancer models have shown anti-proliferative, anti-inflammatory, and anti-angiogenic effects from phytochemicals like genistein from soy, curcumin from turmeric, and epigallocatechin gallate from green tea. The progression of breast cancer and resistance to treatment is largely attributed to the modulation of multiple molecular targets by these compounds, such as PI3K/Akt signaling pathways, NF-κB, and estrogen receptors. Additionally, it has been demonstrated that dietary polyphenols can improve patient outcomes and quality of life by increasing the effectiveness of chemotherapeutic agents while reducing their side effects [73–75]. A translational approach that combines traditional plant knowledge with molecular oncology and personalized medicine is the focus of the contemporary viewpoint on phytotherapy in the treatment of breast cancer. A more thorough understanding of compounds derived from plants and their mechanisms of action has been made possible by developments in systems biology, metabolomics, and high-throughput screening. Although standardization, bioavailability, and regulatory approval issues still exist, clinical trials assessing botanical extracts and purified phytochemicals are becoming more widespread. However, the changing face of cancer treatment encourages the use of phytotherapy as a component of a comprehensive, patient-focused approach. Future studies should concentrate on thorough pharmacological validation, delivery system optimization, and investigating potential synergistic effects between phytochemicals and currently used cancer treatments. Plant-based therapies could become essential parts of evidence-based cancer treatment as a result of these initiatives, particularly when it comes to treating complicated illnesses like breast cancer.

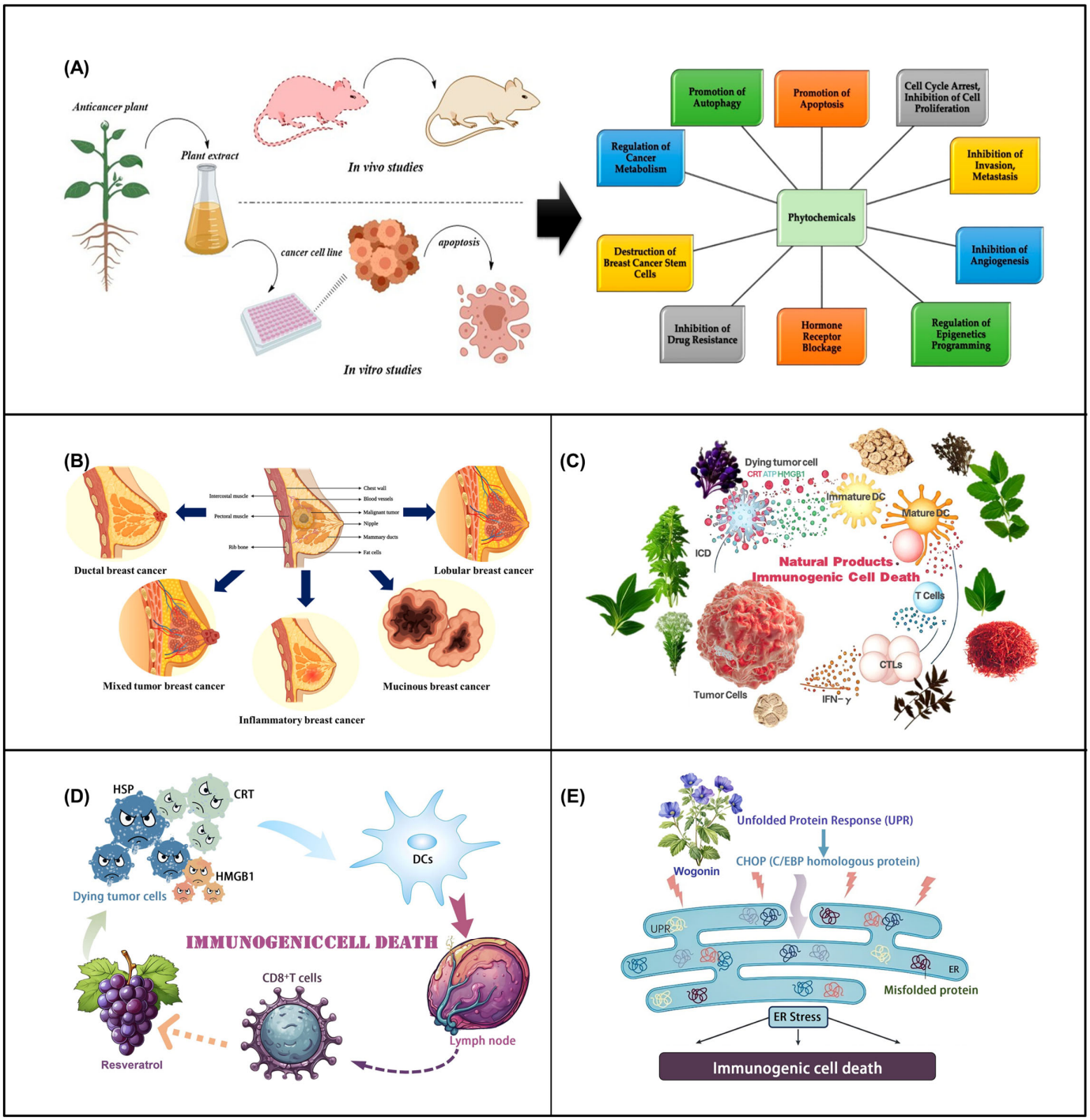


Figure 1. (**A**) Studies of the mechanisms of action of phytochemicals in breast cancer cells, both in vitro and in vivo: Phytochemicals exert their antitumor potential through several mechanisms, as shown here. Phytochemicals frequently affect several pathways that are essential to the aggressiveness and progression of cancer cells, such as metastasis and multidrug resistance [58,59]. (**B**) Breast cancer types [63]. (**C**) Schematic of immunogenic cell death induced by natural products [69]. (**D**) Mechanism of resveratrol-induced immunogenic cell death [69]. (**E**). Baicalin causes endoplasmic reticulum stress, which results in immunogenic cell death. This section is adapted under the Creative Commons Attribution 4.0 (CC BY 4.0) license [69].

3. Methodology: Aim, Review Process, Search Strategy, Data Extraction, and Analysis

This comprehensive narrative review aims to compile and critically examine the molecular targets and mechanisms through which anti-inflammatory and antioxidant phytochemicals may prevent breast cancer. Finding plant-derived substances that have shown promise in preclinical research (both in vitro and in vivo) by altering important molecular pathways implicated in metastasis suppression, proliferation inhibition, and apoptotic induction is the main focus. A wide range of phytochemicals, including flavonoids, alkaloids, terpenoids, and polyphenols, have demonstrated strong anticancer effects by concentrating on important signaling cascades like TGF-β, Wnt, Hedgehog, Notch, IL-6, Integrins, VEGF, HER2, EGFR, and estrogen receptor pathways. Systematic searches were performed to find peer-reviewed articles published between 2000 and 2024 using databases such as PubMed, ScienceDirect, and Google Scholar. Keywords like plant chemicals, breast cancer, preclinical research, molecular pathways, apoptosis, anti-inflammatory, antioxidant, natural compounds, and particular tumor subtypes were all included in the search strategy. To hone search results, Boolean operators (AND, OR) were used. Studies that (1) assessed plant-derived compounds for the treatment of breast cancer, (2) clarified molecular mechanisms of action, and (3) were original research or peer-reviewed articles met the inclusion criteria. Clinical trials and studies with insufficient molecular data were among the exclusion criteria. Targeted molecular pathways, tumor models, phytochemical classification, and botanical nomenclature were the main areas of data extraction. To shed light on the intricate relationships between phytochemicals and the molecular targets of breast cancer, the compiled results are shown in tabular form. This review lays the groundwork for further translational and clinical research while highlighting the therapeutic potential of natural compounds in reducing inflammation and oxidative stress in breast cancer.

4. Therapeutic Potentials of Antioxidants in Breast Cancer Treatment

Oxidative stress has become increasingly significant in the pathophysiology and development of breast cancer, according to recent studies. Building upon the antioxidant mechanisms outlined earlier, the discussion explores how phytochemicals influence apoptosis, cell cycle regulation, and other hallmarks of cancer. An imbalance between the body's ability to neutralize reactive oxygen species (ROS) and the production of ROS leads to oxidative stress. Increased ROS levels can cause lipid peroxidation, protein modification, and DNA damage, which can aid in angiogenesis, tumor growth, carcinogenesis, and metastasis formation. Because of their potential therapeutic role in reducing oxidative damage and regulating the progression of cancer, antioxidants have gained attention in this context. They are endogenous antioxidants (e.g., superoxide dismutase, glutathione), as well as exogenous (e.g., vitamins C and E, flavonoids, and polyphenols), which scavenge free radicals and lessen oxidative stress. Their use in cancer treatment can be divided into two areas: they may directly prevent tumor growth through pro-apoptotic and anti-proliferative mechanisms, and they may shield healthy cells from oxidative damage brought on by radiation and chemotherapy. Numerous studies conducted both in vitro and in vivo have shown that specific antioxidants can alter important signaling pathways, including PI3K/Akt, MAPK, and NF-κB, which are crucial for controlling inflammation, metastasis, and cell survival in breast cancer. Curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) are examples of natural substances that have demonstrated promise in improving the effectiveness of traditional treatments while lowering the toxicities that come with them. For example, it has been observed that curcumin protects non-cancerous tissues while sensitizing breast cancer cells to chemotherapeutic agents. In a similar vein, resveratrol has been shown to have anti-proliferative properties through angiogenesis

inhibition and estrogen receptor modulation. The bioavailability, dosage optimization, and possible interference with the ROS-mediated cytotoxic mechanisms of conventional therapies are some of the obstacles that the clinical translation of antioxidant-based therapies must overcome. Some clinical trials have reported conflicting or inconclusive results, while others have suggested the potential benefits of antioxidant supplementation. An in-depth comprehension of the context-specific function of antioxidants is therefore crucial, taking into account the patient's redox state, cancer type, stage, and treatment approach. Antioxidants, in summary, are a promising adjunct in the treatment of breast cancer, providing a way to improve therapeutic efficacy and lessen side effects. Additionally, carefully planned clinical research is necessary to create standardized procedures and completely clarify their therapeutic potential in the treatment of breast cancer.

The antioxidative and anticancer properties of natural products, especially flavonoids and polyphenols, have attracted a lot of interest in the treatment of breast cancer. Table 1 demonstrates that several flavonoids, including kaempferol, luteolin, apigenin, and quercetin, have strong antioxidant properties that can reduce oxidative stress and stop the growth of breast cancer cells. By scavenging reactive oxygen species (ROS), triggering apoptosis, stopping the cell cycle, and inhibiting pro-oncogenic signaling pathways like PI3K/Akt and MAPK, these substances produce their therapeutic effects. The function of polyphenols, such as resveratrol, curcumin, and epigallocatechin gallate (EGCG), as well as other flavonoids, is further demonstrated in Table 2. These substances have been demonstrated to improve the effectiveness of traditional chemotherapeutic agents, inhibit metastasis, and suppress tumor growth. Notably, curcumin and resveratrol have anti-breast cancer properties by inhibiting angiogenesis and modifying estrogen receptor signaling. These natural antioxidants' synergistic effects demonstrate their potential as supplemental treatments for breast cancer. However, issues like low bioavailability and pharmacokinetic restrictions still exist. To fully utilize their therapeutic potential in antioxidative breast cancer therapy, more research into formulation techniques and clinical validation is necessary. Tables 1 and 2 collectively provide a comprehensive overview of the other phytochemical constituents, their structural characteristics, therapeutic potential, and concentration-dependent activities, particularly in the context of cancer biology, with a strong emphasis on breast cancer [75].

Table 1. Flavonoids are natural products for the treatment of breast cancer.

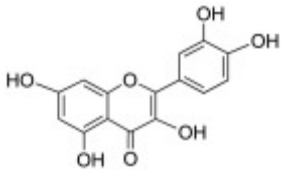
Flavonoids and Chemical Structure	Mechanism	Function	Activity	Ref.
Quercetin 	Decreases in activity of P53, Bcl2/BAX, β-catenin, vimentin, E-cadherin, and VEGFR2 indicates suppressed tumor progression, reduced EMT (epithelial-mesenchymal transition), and decreased angiogenesis.	Induce apoptosis Inhibit tumor metastasis	MCF-7 (IC_{50} = 30.8 μM) MDA-MB-231 (IC_{50} = 100 μM)	[76–79]

Table 1. *Cont.*

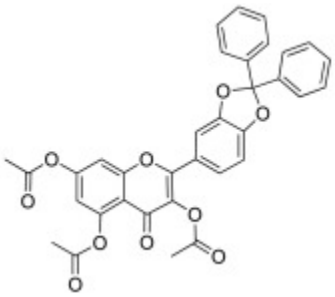
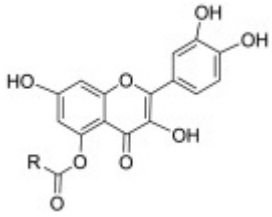
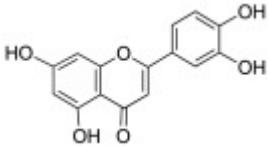
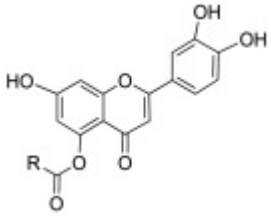
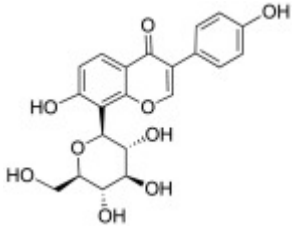
Flavonoids and Chemical Structure	Mechanism	Function	Activity	Ref.
QD3 	Decreases activity of p27, IL-1β, and IL-8.	Induce apoptosis and aging	\	[80]
5-O-acyl quercetin compounds 	Decreases activity of reactive oxygen species (ROS).	Scavenge free radicals	MDA-MB-231 (IC_{50} = 2.82 μM)	[81]
Luteolin 	Decreases activity of inflammation and oxidative stress (TNF-α, IL-6, NF-κB), enhanced antioxidant response and apoptosis (FOXO3a, NQO1, Bax/Bcl-2 ratio).	Induce apoptosis Inhibit tumor metastasis Anti-inflammatory	MCF-7 (IC_{50} = 43 μM)	[82]
5-O-methyl succinyl luteolin 	Decreases activity of reactive oxygen species (ROS).	Scavenge free radicals	MDA-MB-231 (IC_{50} = 4.87 μM)	[83]
Puerarin 	Decreases activity of P65, IκBα, and NF-κB indicate suppression of the NF-κB signaling pathway.	Induce apoptosis Anti-inflammatory Inhibit proliferation and metastasis	MCF-7 (50 μM Inhibition rate = 50%)	[84]

Table 1. *Cont.*

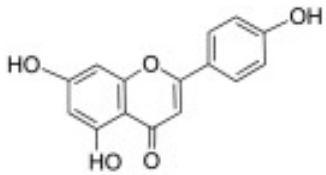
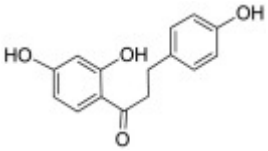
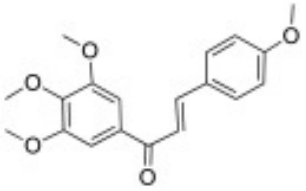
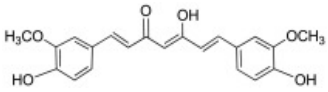
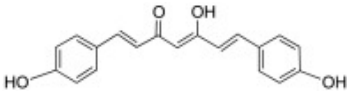
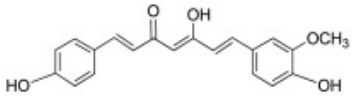
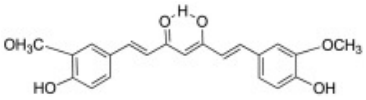
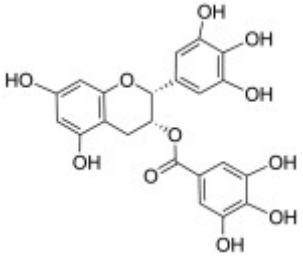
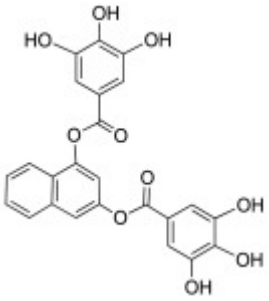
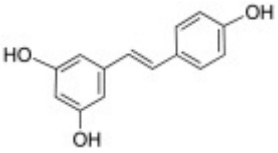
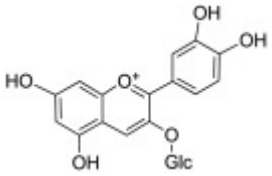
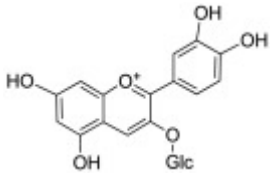
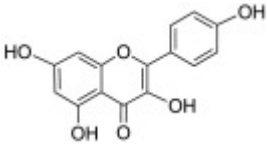
Flavonoids and Chemical Structure	Mechanism	Function	Activity	Ref.
Apigenin 	Decreases activity of cyclin A, cyclin B, CDK1, IL-6, TNFα, CCL2, VEGF, and STAT3; increased levels of p53, cleaved caspase-3, cleaved caspase-8, and cleaved PARP.	Induce apoptosis and cell cycle arrest Inhibit proliferation and oxidative stress	IC_{50} = 216.84 μg/mL	[85–88]
Isoliquiritigenin 	Decreases activity of CDK1, VEGFR2, MMP2, MMP9, and mTOR.	Induce apoptosis and cycle arrest Inhibits proliferation and metastasis	\	[89,90]
3′,4′,5′,4″ -tetramethoxychalcone 	Increased Bax, decreased Bcl-2, and Decreases activity miR-374a.	Induce apoptosis Inhibit tumor metastasis	MDA-MB-231 (IC_{50} = 8.696 μM, 24 h)	[91]
Curcumin 	Decreases activity of NF-κB, PECAM-1, p65, and cyclinD1; increased caspase-3, caspase-9, and Bax; decreasedBcl-2.	Induce apoptosis Inhibit proliferation	MDA-MB-231 (IC_{50} = 75 μM) MCF-7 (IC_{50} = 75 μM)	[92–94]
Bisdemethoxycurcumin 	Decreases activity of NF-κB, PECAM-1, p65, and cyclinD1 levels; increased caspase-3, caspase-9, and Bax; decreasedBcl-2.	Induce apoptosis Inhibit proliferation	MCF-7 (IC_{50} < 10 μM)	[95]
Demethoxycurcumin 	Reduced levels of VEGFR2, NF-κB, MMP2, and MMP9.	Inhibit tumor metastasis	MDA-MB-231 (IC_{50} = 9 μM)	[96]
Pentadineone curcumin 	Decreases activity of NF-κB, AP-1, and COX-2.	Inhibit proliferation	MCF-7 (IC_{50} = 0.4 μM) MDA-MB-231 (IC_{50} = 0.6 μM)	[97]

Table 2. Polyphenols and flavonoids for the treatment of breast cancer.

Polyphenols, Flavonoids, and Chemical Structure	Mechanism	Function	Activity	Ref.
Epigallocatechin gallate 	Decreases VEGF, HIF-1α, NFκB; activates caspase-3 and -9	Promotes apoptosis; suppresses growth and spread	Reduces MCF-7 cell growth by 40–75% in a dose-dependent manner	[98–100]
G28 	Increases vimentin; decreases FASN	Blocks cell growth and spread	Reduces cell viability by 30% after 48 h at 50 µM	[101]
Resveratrol 	Lowers PDE, ERα, VEGF, vimentin; increases cAMP, AMPK, H3K9Ac	Triggers apoptosis and autophagy; stops proliferation	Not specified	[102–107]
3,5,3′,4′,5′ -pentamethoxystilbene 	Suppresses phospho-Akt, CDK4/6; increases P21, P27, P53	Causes cell cycle arrest; limits proliferation	Inhibits MCF-7 cells with IC50 of 37.8 µM	[108]
Cyanidin-3-glucoside 	Decreases CDK, PI3K/Akt, VEGF, Bcl-2, MMP2, MMP9; activates caspase-3	Induces cell cycle arrest; curbs growth and invasion	Over 90% inhibition of MDA-MB-231 cells at 500 µM	[109–114]
Kaempferol 	Activates caspase-3, cleaved-PARP, Bax; reduces ERα and Bcl-2	Promotes apoptosis and cell cycle arrest; prevents metastasis	IC50 of 43 µM on MDA-MB-231 cells	[115–119]

5. Oncogenic Molecular Pathways in Breast Cancer

The development and spread of breast cancer are significantly influenced by cell signal transduction, which is a crucial modulator of cellular communication that affects migration, apoptosis, differentiation, and proliferation. These signaling pathways work in concert and under strict control to preserve tissue homeostasis in healthy cells. However,

in breast cancer, genetic and epigenetic changes commonly cause disruptions in these pathways, which result in abnormal signal propagation [120–122]. These phytochemicals often exert their modulatory effects on signaling pathways in part through their antioxidant action, which reduces oxidative stress and alters redox-sensitive molecular cascades. Signal transduction cascades are crucial targets for therapeutic intervention because dysregulated signaling not only encourages unchecked cell growth and survival but also causes resistance to traditional therapies, as illustrated in Figure 2. The pathophysiology of breast cancer has been widely linked to many canonical signaling pathways. One of these, the transforming growth factor-beta (TGF-β) pathway, has two functions: it promotes tumor invasion and metastasis in advanced stages while suppressing tumors in normal epithelial cells and early-stage tumors.

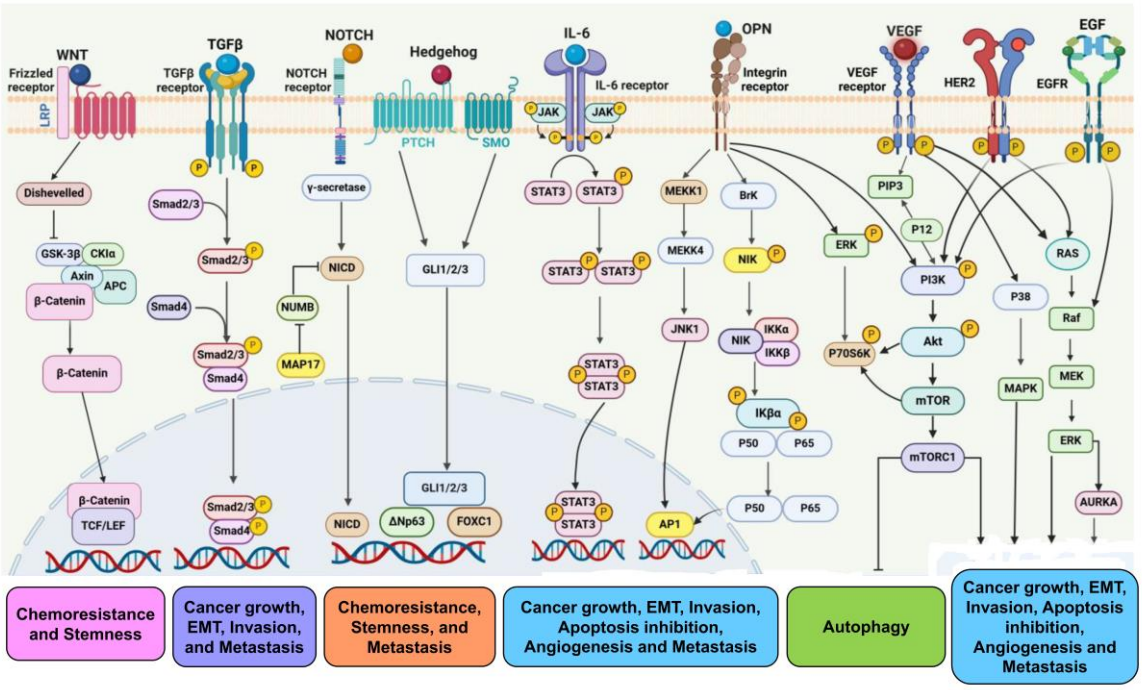


Figure 2. Breast cancer involves several cell signaling cascades. The main signaling events and how they affect tumor growth, survival, and metastasis include Wnt/β-catenin, TGF-β, Notch, MAPK, Hedgehog, JAK/STAT, PI3K/Akt/mTOR, and NF-κB pathways. The Wnt/β-catenin pathway is in charge of boosting chemoresistance and increasing stemness. Breast cancer growth, invasion, and metastasis are linked to TGF-β-mediated signaling. Hedgehog signaling and the Notch pathway both promote metastasis and chemoresistance. Breast cancer growth, invasion, metastasis, and angiogenesis are all influenced by the JAK/STAT and NF-κB signaling cascades. The PI3K/Akt/mTOR, MAPK, and ERK pathways that are mediated by VEGFR, HER2, and EGFR are crucial for controlling the growth, metastasis, angiogenesis, and apoptosis of breast tumors. This section is adapted from under the Creative Commons Attribution 4.0 (CC BY 4.0) license [123].

The Wnt/β-catenin signaling cascade promotes the maintenance of cancer stem cells and the spread of cancer metastases, and it is often triggered in triple-negative breast cancer [124,125]. In a similar vein, aggressive breast cancer subtypes frequently exhibit upregulated Hedgehog and Notch pathways, which support tumor plasticity and resistance to treatment. Additionally, by stimulating downstream STAT3, which improves angiogenesis, immune evasion, and cell survival, interleukin-6 (IL-6) signaling promotes tumor growth [123,126,127]. In breast cancer, oncogenic responses are further amplified by receptor-mediated signaling events. It is common for members of the EGFR family, including HER2, to be overexpressed or mutated, especially in HER2-positive subtypes.

These receptors trigger the activation of downstream pathways essential to oncogenic transformation, including PI3K/Akt and MAPK. Particularly, the PI3K/Akt pathway plays a key role in the pathophysiology of breast cancer by promoting growth, metabolic reprogramming, and apoptosis avoidance. PI3K catalytic subunit mutations and PTEN loss, which inhibit this pathway, are frequent molecular occurrences [128–130]. For example, Curcumin has been shown to suppress the PI3K/Akt pathway by enhancing PTEN activity through oxidative stress reduction, thereby decreasing Akt phosphorylation.

Hormone receptor-positive breast cancers are associated with endocrine resistance due to aberrant activation of the MAPK pathway, which promotes cellular proliferation and differentiation. In breast cancer, tumor-stromal interactions also alter signal transduction via vascular endothelial growth factor (VEGF) pathways and integrin-mediated signaling. Integrins control how tumor cells interact with the extracellular matrix (ECM), which affects invasion, migration, and cell adhesion. VEGF signaling plays a key role in tumor angiogenesis by guaranteeing a sufficient supply of nutrients and promoting the spread of metastases. By focusing on these dysregulated pathways, many therapeutic agents, such as immune modulators, small molecule inhibitors, and monoclonal antibodies, have been developed [131–134]. Therapeutic resistance persists despite progress, frequently as a result of tumor heterogeneity or compensatory pathway activation. Therefore, improving the efficacy and longevity of breast cancer treatment strategies requires a better understanding of the feedback mechanisms and crosstalk between these pathways [123]. In conclusion, the development, spread, and resistance to treatment of breast cancer are all greatly influenced by the dysregulation of several oncogenic signaling pathways. Although there is encouraging therapeutic potential in targeting these pathways, overcoming resistance necessitates a thorough comprehension of their intricate interactions and adaptive mechanisms.

6. Antioxidative Phytochemicals as Molecular Modulators of Breast Cancer Pathways

The composition of flavonoids, alkaloids, terpenoids, and polyphenols, phytochemicals, has significant mechanistic roles in modifying important signaling pathways implicated in the pathophysiology of breast cancer. These organic substances have an impact on many cancer hallmarks, such as angiogenesis, metastasis, apoptosis, and cell proliferation [135–137]. For example, flavonoids alter the PI3K/Akt, MAPK, and NF-κB signaling pathways to prevent cell cycle progression and trigger apoptosis. One of the ways they suppress tumors is by upregulating pro-apoptotic proteins like Bax and downregulating anti-apoptotic proteins like Bcl-2 [138–141]. Alkaloids have strong anti-pluripotential and pro-apoptotic properties by modulating the p53 pathway and inhibiting topoisomerase enzymes. Some alkylates also interfere with the dynamics of microtubules, thereby inhibiting mitosis and promoting cell death. In breast cancer models, alkylating agents such as berberin and vincristine inhibit HER2 and estrogen receptor signaling, which suggests that they may play a role in overcoming hormonal resistance mechanisms. They also have the potential to sensitize tumor cells to chemotherapy and increase therapeutic efficacy [142–146]. Terpenoids, such as monoterpenes and diterpenes, suppress oncogenic signaling cascades such as Ras/Raf/MEK/ERK and modulate oxidative stress responses to produce anticancer effects. Terpenoids prevent DNA damage and stop the growth and spread of tumors by lowering ROS levels and strengthening antioxidant defense systems [147–149]. Furthermore, they hinder tumor vascularization and growth by interfering with angiogenic factors like VEGF. Polyphenols, which are found in many foods, target several molecular pathways, such as Notch signaling, Wnt/β-catenin, and STAT3 [150–152]. Their application in the prevention and treatment of breast cancer is further enhanced by their epigenetic regulatory potential, which is mediated through DNA methylation and

histone modification. When combined, these phytochemicals function as multi-target agents that can interfere with the tumor microenvironment and slow the growth of breast cancer by utilizing complex and overlapping molecular pathways [153,154]. The antioxidative properties of flavonoids and alkaloids contribute to their ability to prevent cell cycle progression and trigger apoptosis by lowering ROS levels that otherwise activate PI3K/Akt, MAPK, and NF-κB signaling. This reduction in oxidative stress modulates the phosphorylation and activity of these pathways, ultimately promoting cancer cell death.

Kim et al. and colleagues investigate the role of Resveratrol (REV), a polyphenol with potent antioxidant capacity, which mitigates oxidative stress-induced activation of the YAP/TAZ pathway, likely through reduction of ROS-mediated upstream mechanical signals and redox-sensitive kinase activity, as illustrated in Figure 3. Resveratrol's antioxidative capacity helps suppress oxidative stress-mediated activation of YAP/TAZ signaling, thereby reducing oncogenic transcriptional activity. The studies shown in these figures demonstrate how REV inhibits important facets of YAP/TAZ-driven cancer progression, such as RhoA activation, cell invasion, and gene expression. A schematic representation of REV targeting YAP/TAZ signaling in breast cancer is shown in Figure 3A [155,156]. The way that REV prevents YAP/TAZ activation, which is usually brought on by growth factors like lysophosphatidic acid (LPA) and epidermal growth factor (EGF), is depicted in this figure. By interfering with this pathway, REV lowers the expression of downstream target genes that contribute to the development of cancer. The effect of REV on YAP target gene expression is depicted in Figure 3B. The chemical structure of REV is shown in Figure 3B(a), which serves as a visual aid for understanding its bioactive characteristics. Figure 3B(b) shows the results of an MTT assay, demonstrating that 25 μM REV does not significantly reduce cell viability, confirming its non-toxic nature at this concentration.

After LPA or EGF stimulation, REV pretreatment dramatically lowers the expression of YAP target genes AREG, CTGF, and CYR61 in MDA-MB-231 and MDA-MB-468 breast cancer cells, according to quantitative RT-PCR data shown in Figure 3B(c). This implies that YAP activation is suppressed at the transcriptional level by REV. The effect of REV on LPA/EGF-induced YAP activation is investigated in Figure 3C. Immunoblotting data in Figure 3C(a) demonstrate that REV pretreatment inhibits YAP phosphorylation, a crucial sign of YAP activation. Figure 3C(b) quantifies this reduction using densitometric analysis, confirming the inhibitory effect of REV on YAP activation. Immunofluorescence images are shown in Figure 3C(c). Untreated cells show nuclear localization of YAP, which is indicative of its active form, whereas REV-treated cells show YAP primarily in the cytoplasm, which is consistent with the immunoblotting data. The functional effects of REV on cell invasion are examined in Figure 3D. When MDA-MB-231 and MDA-MB-468 cells are stimulated with LPA or EGF, REV pretreatment dramatically lowers cell invasion, according to Transwell assays shown in Figure 3D(a,b). This implies that REV prevents invasion mediated by YAP/TAZ. The role of YAP/TAZ in promoting cell invasion is highlighted by additional experiments with siRNA-mediated knockdown of YAP/TAZ, which further inhibits cell invasion when combined with REV treatment, as shown in Figure 3D(c,d). The impact of REV on RhoA, an upstream regulator of YAP/TAZ activation, is the main topic of Figure 3E. RhoA activation in MDA-MB-231 cells is decreased by REV treatment, as shown in Figure 3E(a–e), indicating that REV disrupts RhoA signaling. This effect is also seen following transfection with RhoAV14, suggesting that REV targets RhoA signaling separately from RhoAV14. The combined effects of REV and simvastatin, a RhoA inhibitor, are examined as shown in Figure 3E(f–h), which indicates an enhancer. In conclusion, YAP/TAZ signaling in breast cancer cells is efficiently inhibited by resveratrol (REV), which lowers YAP target gene expression, cell invasion, and RhoA activation. The potential of REV as a therapeutic agent to prevent cancer progression triggered by YAP/TAZ signaling

is suggested by its capacity to block YAP activation at both the transcriptional and protein levels. These results demonstrate the potential of REV to target important pathways in the treatment of breast cancer [156].

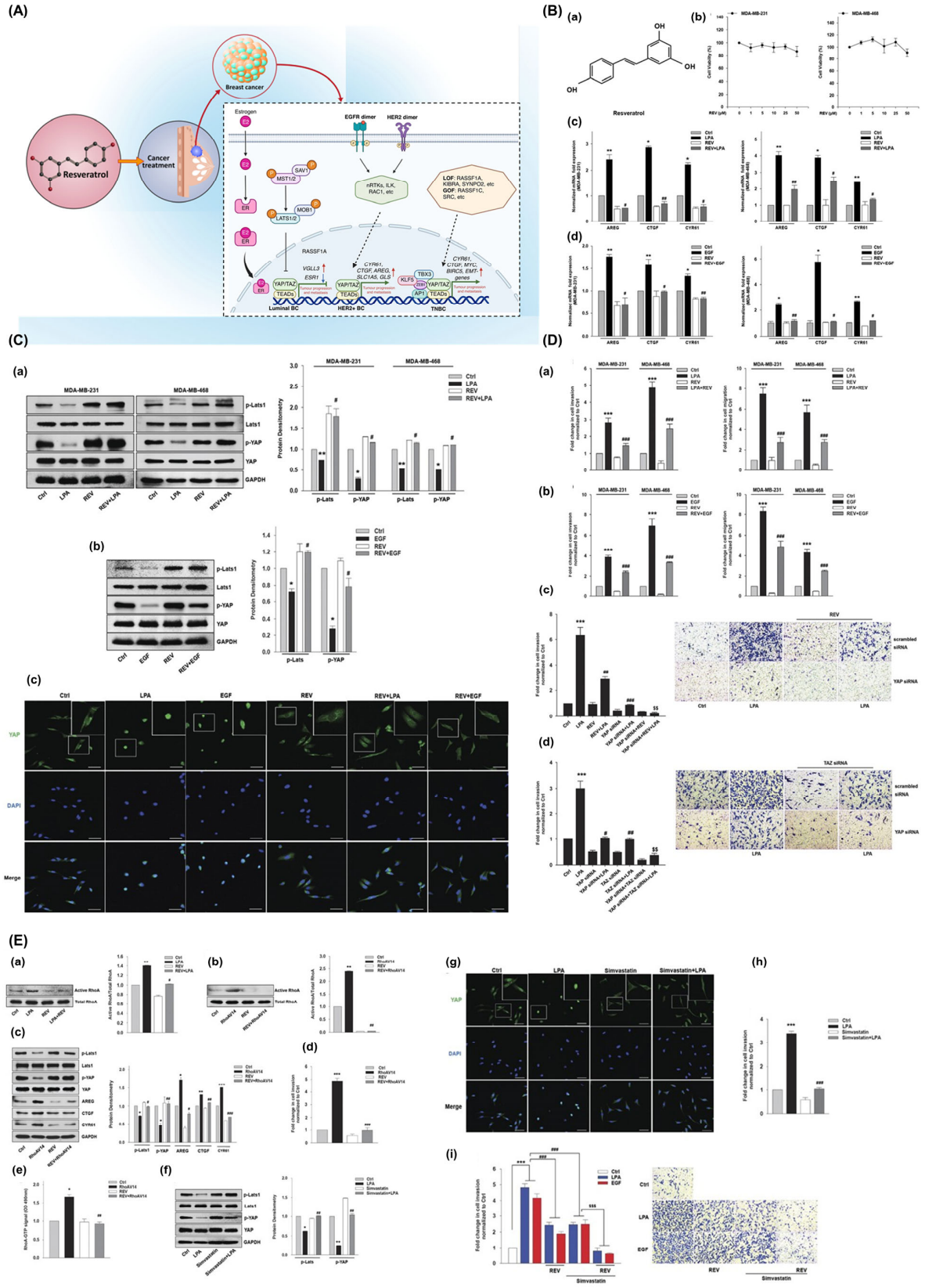


Figure 3. Resveratrol (REV) inhibits YAP/TAZ signaling and suppresses breast cancer cell viability, invasion, and RhoA activation. (**A**) Schematic illustration of REV targeting YAP/TAZ in breast

cancer. (**B**) REV reduces YAP target gene expression. (**a**) Chemical structure of REV. (**b**) MTT assay of REV-treated breast cancer cells. (**c**,**d**) qRT-PCR analysis of REV-pretreated MDA-MB-231 and MDA-MB-468 cells following LPA or EGF stimulation. (**C**) REV inhibits LPA/EGF-induced YAP activation. (**a**,**b**) Immunoblotting and densitometric analysis. (**c**) Immunofluorescence (×200, scale bar: 50 μm). (**D**) REV suppresses LPA/EGF-induced cell invasion. (**a**,**b**) Transwell assays. (**c**,**d**) siRNA-mediated knockdown of YAP/TAZ followed by REV and LPA treatment. (**E**) REV inactivates RhoA. (**a**–**e**) RhoA activation assays following REV treatment and RhoAV14 transfection. (**f**–**h**) Simvastatin or REV pretreatment inhibits LPA-induced YAP signaling and invasion. (**i**) Combined effects of REV and simvastatin on LPA/EGF-induced invasion. All data represent three independent experiments. Statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$; $$ $p < 0.01$, $$$ $p < 0.001$. This section is adapted from under the Creative Commons Attribution 4.0 (CC BY 4.0) license [156].

The study by Shakiba et al. reported that hesperidin's anti-tumor potential in a murine breast cancer model was thoroughly assessed. As illustrated in Figure 4. Hesperidin's chemical structure and the experimental groups' classification are shown in Figure 4A, which shows a well-planned design that includes treatment with doxorubicin, hesperidin, or regular saline. In Figure 4B(a), body weight monitoring showed that, in contrast to the doxorubicin group, hesperidin treatment maintained comparatively stable weights. In mice treated with hesperidin, the tumor volume significantly decreased Figure 4B(b–d), suggesting that hesperidin is an effective tumor growth inhibitor when compared to the saline and doxorubicin groups. Serum cytokine analysis performed on Figure 4C(a,c) revealed that hesperidin treatment increased IFN-γ and decreased IL-4 levels, indicating an immunomodulatory shift toward a Th1-dominant response that is advantageous for anti-tumor immunity. Figure 4 shows the analysis of survival. The higher survival rates seen in the treated groups in Figure 4C(b,d) provide additional evidence of hesperidin's therapeutic effect. The compound's ability to both prevent tumor growth and promote host survival is highlighted by these results. Profiles of cytotoxicity. Hesperidin exhibited selective toxicity toward 4T1 breast cancer cells, as shown by Figure 4D(a–d), with IC_{50} values that were noticeably lower than those found in bone marrow stem cells and normal lymphocytes, whereas breast cancer cell (4T1) survival 24–48 h, show much effective compared with 72 h [157].

This selective cytotoxicity allays worries about the off-target effects that are frequently associated with conventional chemotherapeutics and suggests a promising therapeutic index. Angiogenesis and inflammation gene expression analyses are described in detail in Figure 4E(a–d). Inhibiting vascular support for tumors and altering the tumor microenvironment are two possible functions of hesperidin, as evidenced by the downregulation of genes linked to inflammation and tumor growth, such as VEGF and pro-inflammatory cytokines. In Figure 4F, Histological analysis using H&E and IHC staining showed diminished MMP2, MMP9, and VEGF expression along with elevated E-cadherin levels, all of which suggest decreased invasion, angiogenesis, and improved cell-cell adhesion. Finally, Figure 4G(a–d) emphasizes the use of Allred scoring to evaluate pathologic complete response. Hesperidin-treated groups showed significant reductions in Ki-67 expression, indicating decreased proliferation, and modulated expression of other key markers, further affirming the compound's multi-targeted approach. In conclusion, evaluations of hesperidin's diverse anti-cancer properties in vitro and in vivo. In addition to preventing tumor growth and metastasis, the substance boosts immunity and targets cancer cells specifically while leaving healthy cells unaffected. These findings support the potential of hesperidin as a natural cancer treatment adjunct, indicating the need for additional translational studies to assess its clinical efficacy [157]. Hesperidin reduces ROS accumulation, which plays a key upstream role in PI3K/Akt pathway attenuation and apoptosis induction.

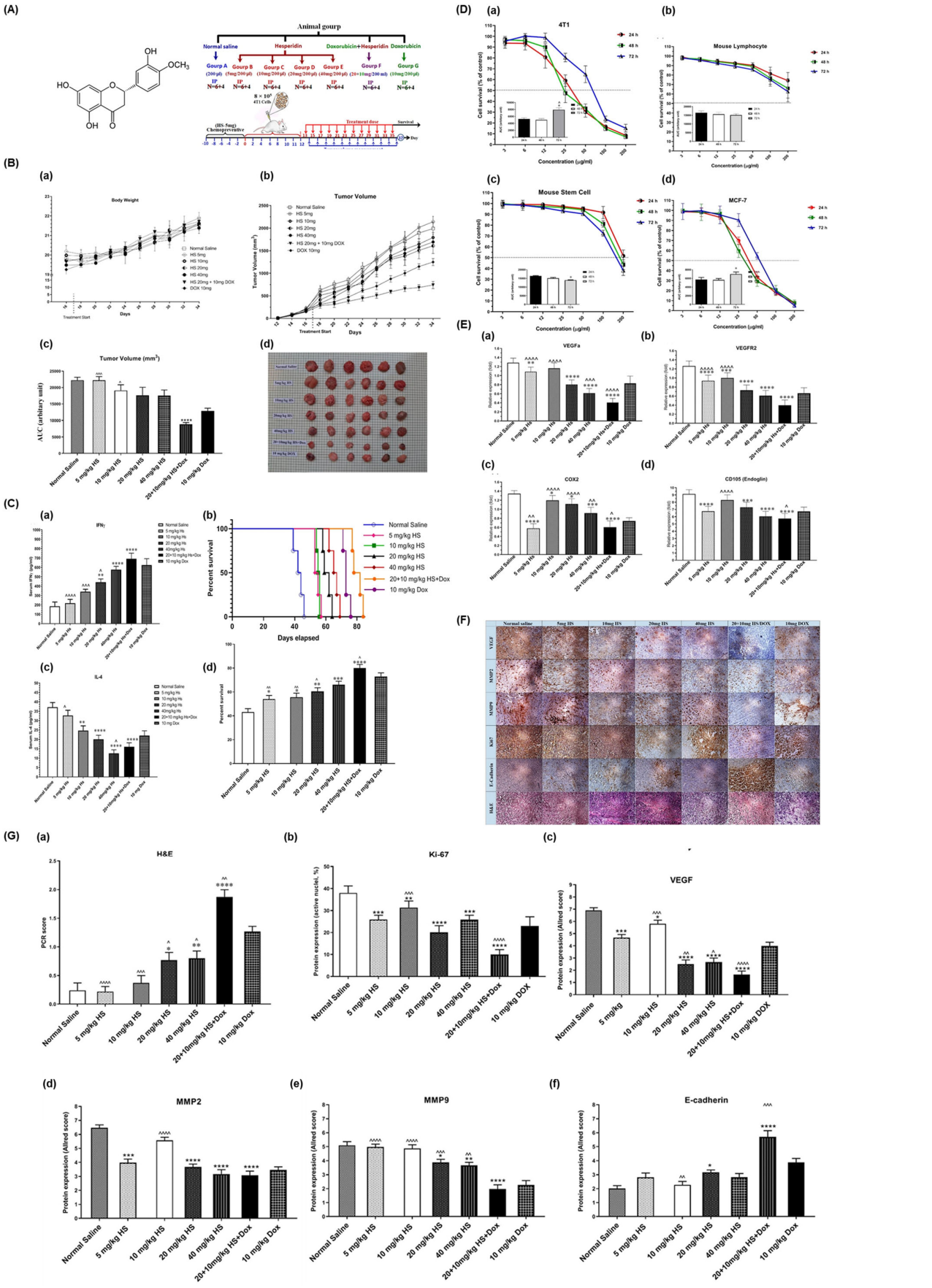


Figure 4. (**A**) Chemical structure of hesperidin and experimental grouping of mice. (**B**) Changes in body weight (**a**) and tumor volume (**b**–**d**) in tumor-bearing mice treated with hesperidin, saline, or

doxorubicin. Data are mean ± SEM ($n = 6$). "n" represents the number of samples. Statistical significance is indicated as follows: * $p < 0.05$ vs. saline; ^ $p < 0.05$ vs. doxorubicin. (**C**) Serum levels of IFN-γ (**a**) and IL-4 (**c**), and survival analysis (**b**,**d**) in treated mice. Data are mean ± SEM ($n = 6$); survival groups, $n = 3$. "n" represents the number of samples. Statistical significance is indicated as follows: * or ^ $p < 0.05$, ** or ^^ $p < 0.01$, *** or ^^^ $p < 0.001$, **** or ^^^^ $p < 0.0001$ vs. respective controls. (**D**) IC_{50} values for hesperidin in 4T1 cells (**a**), lymphocytes (**b**), bone marrow stem cells (**c**), and MCF-7 cells (**d**) at 24–72 h. * or ^ $p < 0.05$ vs. saline or doxorubicin. (**E**) Gene expression analysis of angiogenesis and inflammation markers (**a**–**d**) in 4T1 tumor-bearing mice post-treatment. Data are mean ± SEM ($n = 6$), "n" represents the number of samples. (**F**) H&E and IHC staining of tumor tissues for MMP9, MMP2, E-cadherin, Ki-67, and VEGF post-treatment. (**G**) (**a**) PCR score of H&E. (**b**–**f**) Gene expression was assessed by the percentage of active nuclei and positive cells. Ki67, VEGF, MMP2, MMP9, and E-cadherin intensities were measured using the Allred scoring system. Statistical significance is indicated as follows: * or ^ $p < 0.05$; ** or ^^ $p < 0.01$; *** or ^^^ $p < 0.001$; **** or ^^^^ $p < 0.0001$ vs. controls. This section is adapted from under Creative Commons Attribution 3.0 (CC BY 3.0) [157].

Dong et al. and collagenous reported the novel creation of folic acid (FA)-modified bovine serum albumin (BSA) nanoparticles (FA-Rg5-BSA NPs), which are intended to improve the therapeutic efficacy and tumor-targeting potential of ginsenoside Rg5, a bioactive substance drawn from ginseng that is known to have anticancer effects. Rg5's clinical use is severely limited by its poor water solubility, limited bioavailability, and non-specific biodistribution, despite its therapeutic potential. To get around these restrictions, the study suggested a nanocarrier system that uses BSA nanoparticles functionalized with FA. Its goal is to target tumors passively and actively using receptor-mediated endocytosis and the enhanced permeability and retention (EPR) effect, respectively [158].

The synthesis of FA-Rg5-BSA NPs was carried out using a modified desolvation technique, a cost-effective and scalable approach suitable for albumin-based drug delivery systems. The process was optimized by adjusting key variables such as BSA concentration, pH, ethanol-to-water ratio, and ethanol addition rate. This resulted in nanoparticles with a mean diameter of 201.4 nm and a polydispersity index of 0.081, indicating uniform size distribution and colloidal stability. Figure 5A provides a schematic overview of the nanoparticle fabrication process, followed by the Rg5 release profile from FA-Rg5-BSA NPs and Rg5-BSA NPs. The sustained and controlled release profile of the FA-Rg5-BSA NPs suggests an improved pharmacokinetic profile, which is vital for achieving therapeutic efficacy and reducing systemic toxicity. According to in vitro research, FA-Rg5-BSA NPs significantly reduced the toxicity of L929 normal fibroblast cells while inducing greater cytotoxic effects in MCF-7 breast cancer cells when compared to free Rg5 or non-targeted Rg5-BSA NPs [158].

These results highlight the FA-functionalized nanoparticles' improved internalization potential and selective cytotoxicity. Moreover, FA-Rg5-BSA NP-treated cancer cells showed enhanced intracellular accumulation and apoptotic induction, according to flow cytometry and fluorescence imaging. The overexpression of folate receptors on tumor cell surfaces, which permits FA-mediated receptor binding and internalization, is thought to be the cause of this selective targeting. Together, the apoptotic effectiveness and targeted delivery point to a strong antitumor mechanism made possible by the nanoparticle system. A 21-day treatment period was used to assess the in vivo effectiveness of FA-Rg5-BSA NPs in a nude mouse model bearing an MCF-7 xenograft, as demonstrated in Figure 5B. The antioxidative properties of ginsenoside Rg5 help to remodel the tumor microenvironment by reducing oxidative stress, which in turn affects angiogenic signaling and immune suppression. Compared to both free Rg5 and Rg5-BSA NPs, the FA-Rg5-BSA NPs demonstrated superior tumor growth inhibition, as evidenced by a significant decrease in tumor size, volume, and

weight. Body weight tracking showed little systemic toxicity, and in vivo bioluminescence imaging verified that FA-Rg5-BSA NPs were more abundant at the tumor site. Together with targeted delivery and fewer off-target effects, the strong therapeutic benefits underscore FA-Rg5-BSA NPs' clinical potential in breast cancer treatment. According to these results, such a nano-platform merits more research using a range of tumor models and may be a viable option for the creation of targeted anticancer treatments [158].

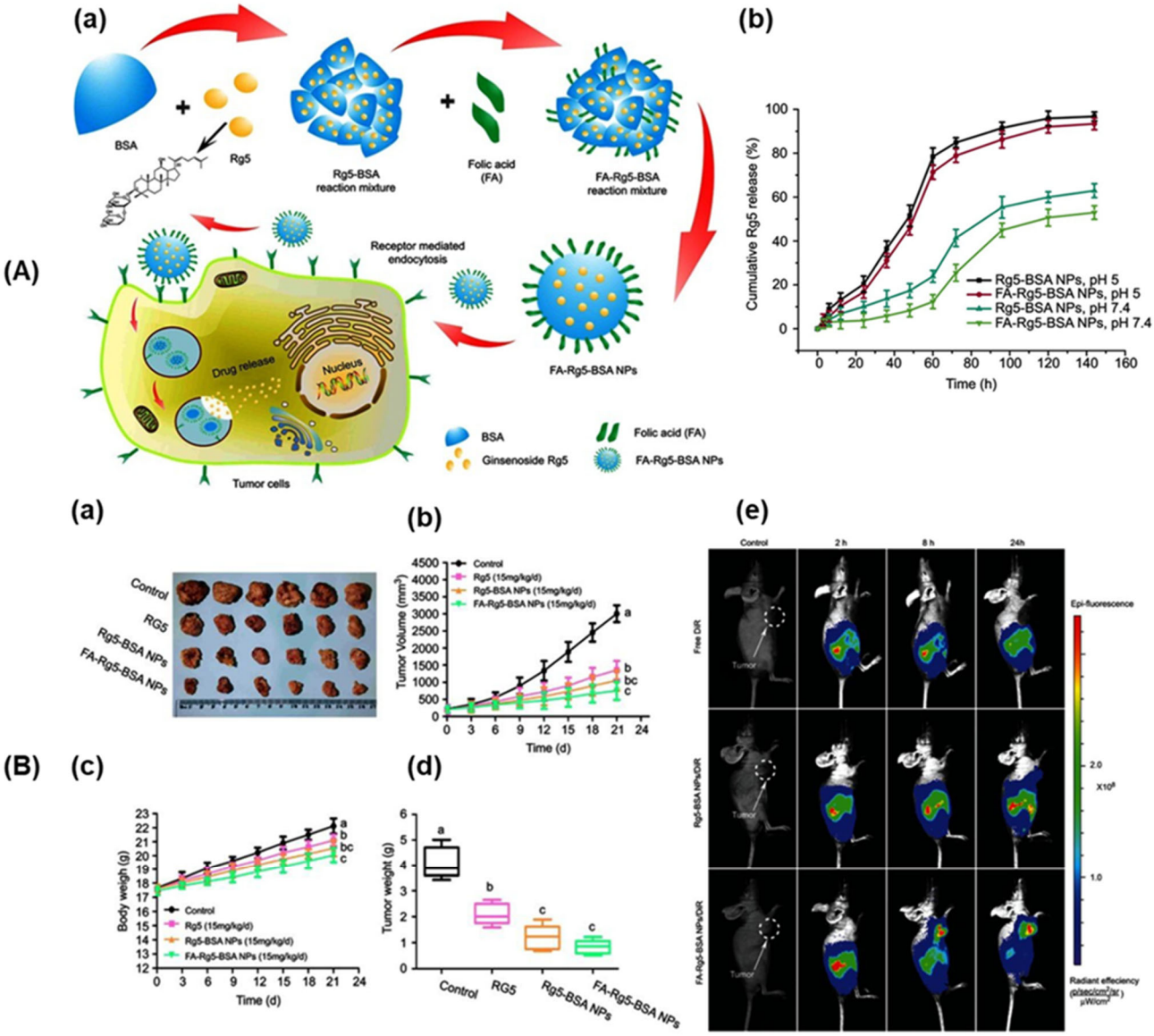


Figure 5. (**A**) Diagrammatic representation of FA-Rg5-BSA NPs' preparation (**a**). This is the Rg5 release curve from FA-Rg5-BSA NPs and Rg5-BSA NPs (**b**). (**B**) Ginsenoside-fabricated BSA NPs demonstrated significant inhibition of breast cancer xenografts in the following in vivo evaluations: (**a**) tumor size, (**b**) tumor volume, (**c**) body weight, (**d**) tumor weight, and (**e**) in vivo bioluminescence following a 21-day treatment period, whereas a, b, and c represent the experimental groups of mice. This section is adapted from under the Creative Commons Attribution 4.0 (CC BY 4.0) license [158]. (Abbreviation: FA: Folic acid, Rg5: Ginsenoside Rg5, a triterpene saponin derived from ginseng, BSA: Bovine Serum Albumin, NPs: Nanoparticles.

7. Antioxidant Functional Effects of Phytochemicals: Apoptosis, Cell Cycle Arrest, Angiogenesis, and Immune Modulation

A broad class of bioactive substances derived from plants, phytochemicals, have important anti-tumor effects by altering important cellular mechanisms linked to the development of cancer. The antioxidative ability of phytochemicals, which reduces oxidative stress and consequently affects redox-sensitive signaling pathways, is frequently the primary driver of their functional effects, which include induction of apoptosis, cell cycle regulation, and modulation of immune responses. The induction of apoptosis is a key mechanism by which phytochemicals suppress tumor growth. Through the regulation of pro- and anti-apoptotic proteins, disruption of mitochondrial membrane potential, and stimulation of caspase cascades, these substances activate both intrinsic and extrinsic apoptotic pathways [26,159–161]. Flavonoids and alkaloids, for instance, have been demonstrated to selectively cytotoxically target cancer cells while sparing healthy cells, indicating their potential for therapeutic use [162–164]. Phytochemicals are important because they not only stimulate apoptosis but also cause cell cycle arrest, which stops the unchecked growth that is a hallmark of cancerous cells. At several checkpoints in the cell cycle, especially the G1/S and G2/M transitions, these substances can stop the cycle by modifying the expression and activity of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors [165,166]. This arrest increases the effectiveness of traditional treatments by making tumor cells more vulnerable to cytotoxic agents, in addition to stopping DNA replication in damaged cells. Additionally, by inhibiting angiogenesis and modifying immune responses, phytochemicals affect the tumor microenvironment. They prevent the development of new blood vessels that are necessary for tumor growth and metastasis by blocking vascular endothelial growth factor (VEGF) signaling. While downregulating immunosuppressive pathways, some phytochemicals simultaneously increase antitumor immunity by promoting the activity of cytotoxic T lymphocytes, dendritic cells, and natural killer cells. These diverse effects highlight the potential of phytochemicals as adjuvants in cancer treatment, providing a viable approach to controlling tumor growth and immune evasion simultaneously [59,167,168].

8. Preclinical and Clinical Evidence Supporting Antioxidant Therapy

Numerous compounds derived from plants have been shown to have important pharmacological characteristics, such as anti-inflammatory, anti-cancer, and antioxidant effects, through extensive in vitro studies. These bioactive components, which include terpenoids, alkaloids, polyphenols, and flavonoids, have demonstrated the capacity to alter important cellular pathways related to immunological regulation, oxidative stress, and apoptosis. Curcumin, resveratrol, and quercetin in particular have been thoroughly investigated for their capacity to suppress tumor cell growth and trigger programmed cell death in a variety of cancer cell lines [169–171]. A fundamental understanding of how phytochemicals have therapeutic effects at the cellular and molecular levels is provided by the mechanistic insights gleaned from these investigations. The therapeutic potential of phytotherapy is further supported by preclinical in vivo research employing animal models. In models of chronic diseases, such as diabetes, neurodegenerative diseases, and different types of cancer, several compounds derived from plants have shown promise [172–176]. For example, by altering metabolic and inflammatory signaling pathways, silymarin and berberine have demonstrated hepatoprotective and antidiabetic effects, respectively. These investigations provide crucial translational insights for clinical development by highlighting the phytochemicals' systemic bioavailability, pharmacokinetics, and organ-specific responses. The safety and effectiveness of several phytotherapeutic agents in human populations have been confirmed by clinical trials more and more. Garlic extract, green tea catechins,

and ginseng have all been the subject of randomized controlled trials that have shown positive effects on cardiovascular health, cancer prevention, and metabolic regulation. The incorporation of plant-derived therapeutics into traditional medical practice is still supported by growing clinical evidence, highlighting their applicability in evidence-based complementary medicine, even though variations in study design and dosage continue to be a limitation [177–180].

9. Challenges, Future Directions, and Integration of Antioxidants into Clinical Practice

The application of plant-derived compounds for medicinal purposes, or phytotherapy, has demonstrated significant promise in the treatment of breast cancer because of its many different mechanisms, which include anti-inflammatory, anti-proliferative, and antioxidant effects. However, there are many obstacles to the clinical translation of phytotherapeutic agents, especially bioavailability [181–183]. Numerous phytochemicals have limited systemic circulation, fast metabolism, and poor solubility, all of which seriously impair their therapeutic effectiveness. Advanced formulation techniques, such as liposomal carriers, nanoencapsulation, and co-administration with bio-enhancers, are required to improve stability, absorption, and targeted delivery in light of these pharmacokinetic constraints. Another significant obstacle is the standardization of phytotherapeutic preparations [184–186]. It is challenging to guarantee consistent therapeutic results because of the inherent variability in phytochemical composition brought on by variations in plant species, cultivation conditions, and extraction techniques. Reproducibility and dependability in clinical settings require the establishment of standardized procedures for the sourcing of raw materials, quality assurance, and dosage optimization. Furthermore, to clarify the safety profile, therapeutic index, and possible interactions of phytotherapeutics with traditional chemotherapeutic agents, thorough preclinical and clinical evaluations are needed. Including phytotherapy in standard breast cancer treatment plans necessitates a multidisciplinary strategy. To create evidence-based recommendations that support the co-administration of phytotherapeutics with proven therapies, oncologists, pharmacologists, and regulatory agencies must work together. Future studies should concentrate on customized phytotherapy approaches that combine metabolomic and genomic information to customize treatments and increase therapeutic efficacy while reducing side effects [187–190].

10. Conclusions

Breast cancer is still a common and difficult cancer, and the efficacy of traditional treatments is limited by enduring problems like toxicity, recurrence, and drug resistance. This review demonstrates how different plant-derived compounds can modulate important molecular pathways involved in the progression and metastasis of breast cancer, underscoring the promising role of phytotherapy as an adjuvant strategy. Flavonoids, alkaloids, terpenoids, and polyphenols are examples of phytochemicals that have a variety of anticancer effects. They affect immune response, angiogenesis, cell cycle, and apoptosis in addition to targeting signaling cascades like TGF-β, Wnt, Hedgehog, Notch, and others. The therapeutic potential of phytotherapy is supported by growing preclinical and clinical evidence, notwithstanding issues with bioavailability and clinical translation. Targeted and efficient management of breast cancer may be improved by combining these natural substances with existing therapeutic approaches.

Author Contributions: Conceptualization, S.S., A.K.S., A.M.U. and R.K.M.; methodology, S.S., A.M.U., A.K.S., N.R., A.N., S.D.D. and R.K.M.; writing—original draft preparation, S.S., A.K.S., A.M.U. and R.K.M.; writing—review and editing, S.S., A.M.U., A.K.S., N.R., A.N., S.D.D., F.I.F. and

R.K.M.; visualization, S.S., A.M.U., A.K.S., N.R., A.N., S.D.D. and R.K.M.; management, S.S., A.K.S., N.R., F.I.F. and R.K.M. All authors have read and agreed to the published version of the manuscript.

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