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Medicinal Plant-derived Nutraceuticals in Breast Cancer Therapy: Molecular Mechanisms and Clinical Prospects

Anandharaj Govindaraj[1*], Saravanakumar Arthanari[2], Gowtham Rajendran[1], Hemapriya Anbalagan[1], Jegadheeshwaran Murugan[1], Komaleshwaran Ramesh[1], Sangeetha Saravanan[3], Parthiban Periyasamy[3], Sivakumar Ponnu[1], Pradeep Nagarajan[2] and Manivasakam Prakash[4]

[1]Department of Pharmacy Practice, Vellalar College of Pharmacy (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University), Thindal, Erode - 638012, Tamil Nadu, India; anandpharmacist3@gmail.com

[2]Department of Pharmaceutical Biotechnology, Vellalar College of Pharmacy (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University), Thindal, Erode - 638012, Tamil Nadu, India

[3]Department of Pharmaceutical Chemistry, Vellalar College of Pharmacy (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University), Thindal, Erode - 638012, Tamil Nadu, India

[4]Department of Pharmaceutics, Vellalar College of Pharmacy (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University), Thindal, Erode - 638012, Tamil Nadu, India

Abstract

Breast cancer today is still a leading cause of cancer-related mortality and morbidity around the world, which calls for supplementary and more convenient therapies. Nutraceuticals derived from medical plants have now emerged as promising candidates because they work through multiple mechanisms of action at the cellular level and can be combined with conventional treatments without the high level of accompanying toxicity. Research examines the molecular mechanisms by which leading phytochemicals such as curcumin, withaferin A, Epigallocatechin Gallate (EGCG) and glycosylates exert anti-cancer effects - including induction of apoptosis induction, cell cycle arrest, metastasis from one cell to another; hormone modulation and activation or precursor treatment in immune system cells. Possible adverse effects of these nutraceuticals along with some clinical findings to support their use as adjuvant agents aimed at reducing side effects of treatment and improving patient quality of life is discussed, together with current problems such as poor absorption rates in the human body, lack of internationally standardised chemical composition and regulatory barriers. The outlook is for advanced delivery systems; thorough clinical trials; personalised solutions tailored to individual patients' needs; and training programmes that give doctors and patients better knowledge of the topic. Well-established, scientifically validated nutraceuticals, used to treat breast cancer, have great potential for bringing a new generation of therapies and improving patients' overall health.

Major Findings: Medicinal plant-derived nutraceuticals like curcumin, EGCG, and withaferin A show strong anti-breast cancer effects via multiple mechanisms. Despite promising preclinical results, clinical translation is limited by poor bioavailability and lack of large-scale trials, though these compounds may enhance current therapies if delivery and research gaps are addressed.

Keywords: Adjuvant Therapy, Breast Cancer, Nutraceuticals, Medicinal Plants, Personalised Medicine

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*Author for correspondence

1. Introduction

Breast Cancer (BC) is the most common cancer diagnosed in women worldwide and a disaster of global health care, having been estimated as representing the highest incidence among all cancers[1]. According to the WHO, there were approximately 2.3 million new cases and 670,000 new deaths from the disease worldwide in 2022. Overall disease burden of the pathogen is likely to increase, with predictions suggesting an upward trajectory in both incidence and mortality by 40% at the estimated incidence terms by 2050, especially in areas where healthcare infrastructure remains under-resourced[2]. Crucially, the outcome presents a deep geographic inequity: survival rates at 5 years reach more than 90% in high-income countries and deteriorate considerably in low-resource settings, highlighting the pressing demand for affordable therapeutic approaches for treatment of all[3]. The therapeutic strategy for BC is entirely personalised; it is primarily influenced by the tumour's molecular phenotype, which guides systemic therapy. Breast cancer is classified into four major Immunohistochemical (IHC) subtypes, of which the Luminal A and Luminal B are hormone receptor positive for Estrogen Receptor (ER) or Progesterone Receptor (PR), the HER2+-enriched and Triple Negative Breast cancer group have no expression of ER, PR, or human epidermal growth factor receptor 2 (HER2)[4]. Treatment is traditionally multi-modal, with local therapies (surgery and radiation therapy) and systemic agents[5]. Systemic modalities have relied on endocrine therapy for hormone receptor-positive (HR+) tumours, targeted therapies such as trastuzumab for HER2+ tumours, and chemotherapy, which continues to serve as the backbone in aggressive subtypes such as TNBC[6]. Although targeted agents have been developed, there remain significant clinical challenges, such as primary or secondary resistance to these molecules, high recurrence rates, and treatment-related toxicities that reduce overall survival and quality of life for patients[5,6]. The word "nutraceutical," a short form of the two words "nutrition" and "pharmaceutical," was first introduced in 1989 to describe food or a part of it that improves medical conditions or shows health benefits (Disease prevention and/or treatment)[7,8]. Nutraceuticals. Although there is no uniform regulatory definition, the term nutraceutical encompasses purified nutrients, herbal products, dietary supplements, and processed foods that offer bioactive ingredients other than essential nutrients[9]. Their importance in today's medicine is due to their multitargeted nature and their relatively low toxicity compared to classical chemotherapeutics[10]. Nutraceuticals such as polyphenols, carotenoids, and fatty acids mediate their potential health benefits by altering basic physiological processes implicated in the regulation of oxidative stress, chronic inflammation, and cell-signalling pathways that are pivotal in the pathogenesis of chronic diseases such as cancer[11]. This preventive and additive therapeutic potential has turned nutraceuticals into a fast-growing area of integrative oncology and public health[12]. Phytochemicals or secondary metabolites, etc., being one of the most potent group of nutraceuticals, are leading to extensive research on natural sources, *i.e.*, medicinal plants. More than 50% of anticancer drugs approved from 1940 to 2014 were natural-product-based or designed, indicating the important role of botany in cancer natural-product discovery[13]. The therapeutic potential of natural plant compounds lies in their multicentric interaction with various molecular targets during carcinogenesis -an important edge over some synthetic drugs, which act on a single target[14]. The particular ways of MF action are by promoting cancer cell apoptosis, inhibiting tumour angiogenesis, suppressing metastasis via regulation of Epithelial-to-Mesenchymal Transition (EMT) and reversing Multi-Drug Resistance (MDR)[15]. Thus, the integration of plant-based nutraceuticals provides a promising approach to improve therapeutic effectiveness of traditional breast cancer treatments and meanwhile reduce systemic toxicity.

2. Medicinal Plants with Anticancer Properties

2.1 Overview of Selected Medicinal Plants

2.1.1 Curcuma longa (Turmeric)

The rhizome of *Curcuma longa* (Turmeric) is a source of the polyphenolic compound curcumin (diferuloylmethane), which has been shown to possess diverse therapeutic attributes against breast cancer by virtue of its powerful anti-inflammatory and antioxidant actions[16]. At the molecular level, curcumin exerts its anti-cancer effects by suppressing

the proliferation of breast cancer cells and inducing apoptosis (programmed cell death) by up-regulating pro-apoptotic proteins, including p53 and caspase-5[17]. Notably, curcumin disrupts many of the major signalling pathways which promote cancer survival and resistance to treatment, including by inhibition of the master inflammatory transcription factor NF-κB (nuclear factor-kappa B) and associated proinflammatory cytokines, as well as metastasis-promoting factors such as VEGF [vascular endothelial growth factor] and MMPs [matrix metalloproteinases][18,19]. Although preclinical studies have shown potent anti-tumour activity and chemosensitisation of standard agents, such as Paclitaxel (PTX), the clinical utility of native curcumin is limited by its poor aqueous solubility and low systemic bioavailability[20]. Till now in the clinical trials, curcumin has been mainly assessed as an adjunct to standard care, primarily aiming to improve QoL and ameliorate treatment-related side effects such as chemotherapy toxicity or radiation dermatitis; however, more advanced studies aim at improving its bioavailability, leading to the development of highly bioavailable nanoformulations that are capable for realising the full effect of this potent natural product[20,21].

2.1.2 *Withania somnifera* (Ashwagandha)

Withaferin A (WFA) is a critical natural phytochemical, widely examined for its tumour-suppressive effects across different types of cancer. Withaferin derivatives extracts have been used extensively for the treatment of cancers, although the first anti-cancer effect of a purified withanolide was discovered in 2004. Withaferin A is the most significant withanolide with unique anti-cancer and anti-tumour pharmacological properties; hence, it has high potential in drug development[22]. Extracts of the Ayurvedic medicine *Withania somnifera* can suppress breast cancer cell growth by activating apoptosis via both intrinsic and extrinsic pathways. WA and WS Root Protein Extract (WSPF) causes death in cultured MDA-MB-231 and MCF-7 cancer cells, as well as suppression of mammary tumours from culture-adapted MDA-MB-231 xenograft models by promoting the generation of Reactive Oxygen Species (ROS) through the intrinsic apoptosis pathway[23-25].

2.1.3 *Camellia sinensis* (Green tea)

The second-most-consumed beverage in the world (next to water) is tea. Among the polyphenols contained in green tea (approximately 30% of the total weight of the leaves), one main active constituent, epigallocatechin-3-gallate (EGCG), can inhibit various stages of tumourigenesis both *in vitro* and in animal models for cancer chemoprevention[26]. *Camellia sinensis* (green tea), a medicinal plant, is rich in the polyphenolic catechins, and Epigallocatechin Gallate (EGCG) from green tea has been identified as the main bioactive and potent anticancer compound in breast cancer. Mechanically, EGCG is a multi-target molecule that down-regulates critical signalling pathways such as PI3K/Akt, MAPK, and Wnt signalling[27] and induces apoptosis via caspase activation[28]. Cell proliferation inhibition by cell cycle arrest, downregulation of cell growth receptors such as HER-2 neu, and EGFR[27,29], and inhibition of angiogenesis by targeting factors such as VEGF[27,30]. At the same time, the anti-tumour activity of these extracts is consistent across cases, both *in vitro* and in ethnoclinical studies, across a variety of breast cancer phenotypes, including TNBC[29].

2.1.4 *Cichorium intybus* (Chicory)

Cichorium intybus (commonly called chicory) is a multifaceted herb that has long been used in traditional medicine and is gaining prominence as a nutraceutical for breast cancer treatment[31]. Its anticancer potential has been attributed to an ample phytocomplex, including polyphenolic compounds (cichoric acid), sesquiterpenic lactones (lactucin and lactucopicrin), inulin, flavonoids (rutin), and sterols (taraxerone/stigmasterol)[32,33]. These phytochemicals exhibit multitarget effects in breast cancer, including antioxidant, anti-inflammatory, and direct cytotoxic effects on cancer cells[34]. Significantly, several chicory-derived compounds, including taraxerone and stigmasterol, have been reported to be potent inhibitors of the mammalian target of rapamycin (mTOR) pathway, an important modulator of cell growth and proliferation that is frequently altered in breast cancer[35]. In addition, *in vitro* studies indicate that chicory extracts and their biofabricated AgNPs can mediate apoptosis and exhibit selective cytotoxicity in human aggressive breast cancer cells like MDA-MB-231 and have less impact on normal cell[34]. These findings highlight *Cichorium intybus* as an essential source of lead molecules or as nutraceutical adjuvants for the design of specific and effective strategies in breast cancer[36].

Table 1. Key medicinal plants and their bioactive compounds in breast cancer therapy

Medicinal plant	Active compound(s)	Key mechanisms of action in breast cancer	Clinical evidence and challenges	References
Curcuma longa (Turmeric)	Curcumin	Induces apoptosis via p53, inhibits NF-κB, suppresses VEGF and MMPs, and is anti-inflammatory.	Poor bioavailability; clinical trials focus on adjuvant use to reduce chemotherapy toxicity; nanoformulations under development	16-18,20
Withania somnifera (Ashwagandha)	Withaferin A	Induces ROS-mediated apoptosis, intrinsic/extrinsic pathways, and inhibits proliferation	Preclinical evidence strong; clinical translation limited; potential for combination therapy	22-24
Camellia sinensis (Green Tea)	Epigallocatechin-3-gallate (EGCG)	Inhibits PI3K/Akt, MAPK, Wnt pathways; induces caspase-dependent apoptosis; anti-angiogenic	Chemo preventive effects shown *in vitro/vivo*; human trials limited by bioavailability; studied in TNBC	26-29
Cichorium intybus (Chicory)	Taraxerone, stigmasterol, cichoric acid	mTOR pathway inhibition, antioxidant, anti-inflammatory, selective cytotoxicity against MDA-MB-231 cells	*In vitro* and computational studies are promising; clinical trials are lacking; potential as a nutraceutical adjuvant	31,32,35,36
Cruciferous vegetables	Sulforaphane, Indole-3-carbinol	Activates Nrf2 detox pathways, inhibits NF-κB, induces apoptosis, and is anti-proliferative	Epidemiological support for cancer risk reduction; clinical trials in prevention; bioavailability and dosing challenges	37-40

2.1.5 Cruciferous vegetables (e.g., Broccoli, Cabbage)

Cruciferous vegetables (*e.g.*, broccoli, cabbage, Brussels sprouts) have also consistently been linked to a decreased risk of various types of cancer, such as lung, colon, prostate, and breast cancers, largely because of their high levels of glucosinolates[37,38]. Chopping or chewing the vegetables leads to hydrolysis of glucosinolates by the plant enzyme myrosinase, producing highly bioactive compounds, mainly isothiocyanates (ITCs) such as sulforaphane (SFN) and indoles, including indole-3-carbinol (I3C)[39,40]. These metabolites have chemopreventive effects through various molecular mechanisms. They can act as strong detoxifying factors by modulating xenobiotic metabolism, notably by increasing the activity of Phase II detoxification enzymes through the Nrf-2 (Nuclear Factor Erythroid 2-related Factor 2) pathway, thereby facilitating the elimination of carcinogens and reducing oxidative stress[40,41]. In addition, ITCs and their metabolites exhibit direct anticancer effects by inhibiting cell proliferation, inducing apoptosis (programmed cell death) in cancer cells, arresting the cell cycle, and down-regulating significant inflammatory and survival signalling networks, such as NF-kB[39]. Epidemiological meta-analysis confirms these biological results; the intake of high levels of cruciferous vegetables is inversely associated with several cancers, supporting their inclusion as a key component of an array associated with an anti-cancer diet[37,38] Table 1.

2.2 Active Compounds and their Bioactivity

2.2.1 Polyphenols

Polyphenols, a large class of phytochemicals present in tea, grapes, turmeric, and soy, exhibit potent anticancer activity against breast cancer through their major active compounds, including the flavanol Epigallocatechin Gallate (EGCG), the stilbene Resveratrol, the isoflavone Genistein, and the curcuminoid Curcumin[42,43]. These components operate pleiotropically and affect several hallmarks of breast carcinogenesis, *i.e.*, they promote apoptosis (programmed cell death) and cell cycle

arrest; modulate ERs with Genistein being an anti-estrogenic agent and Resveratrol dampening down the ERalpha signalling pathway necessary for ER-positive tumours; suppress the aggressive phenotype in both ER-positive and TNC cell lines by inhibiting major survival pathways including NF-kB and STAT3, and by blocking angiogenesis and metastasis[44,45]. In addition, their potent antioxidant and anti-inflammatory activity can inhibit tumour initiation, and they are promising as adjuvant therapy in combination with chemotherapy due to their ability to sensitise cancer stem cells, although issues surrounding poor bioavailability remain[42,46].

2.2.2 Alkaloids

Alkaloids, the nitrogen-containing plant-derived nutraceuticals, represent an essential class of compounds with established as well as potential anticancer bioactivities in breast cancer, with traditional and some recent sources, often with low toxicity and the ability to enhance therapeutic efficacy. These secondary metabolites, which include clinically used drugs such as the vinca alkaloids (vinblastine and vincristine from *Catharanthus roseus*) and many others, for example, berberine, matrine, and noscapine, act through multifactorial molecular mechanisms to convey their therapeutic effects. These mechanisms, such as (i) apoptosis induction leading to caspase-dependent pathways to programmed cell death, (ii) anti-proliferation and migration, and (iii) cell cycle arrest (in particular G2/M phase, which is seen in vinca alkaloids resulting from microtubule-disrupting effect). In addition, alkaloids regulate critical signalling pathways (such as PI3K/AKT/mTOR, NF-κB, and VEGF) that block angiogenesis (neovascularisation) and might reverse multidrug resistance in cancer cells, thereby indicating excellent clinical potential for integration into breast cancer management strategies[47-50].

2.2.3 Terpenoids

Terpenoids, the largest and most diverse group of isoprene-derived nutraceuticals from medicinal plants, are well-known for potent anticancer bioactivities against breast cancer, with some, including the taxanes (*e.g.*, Paclitaxel or Taxol; a diterpenoid), already serving as essential agents in clinical chemotherapy. These compounds, such as monoterpenoids (D-limonene), sesquiterpenoids (Artemisinin and its derivative DHA), and triterpenoids (Celastrol, Ursolic Acid), exert pleiotropic effects by acting on various critical molecular targets. These effects include apoptosis induction (frequently associated with mitochondrial-related pathways and caspase activation), abrogation of cell cycle progression, suppression of migration and proliferation, etc. (*e.g.*, paclitaxel stabilises microtubules, leading to a mitotic block). In addition to that, terpenoids inhibit multiple signal transduction pathways, including NF-kappaB and PI3K/AKT/mTOR signalling, downregulate angiogenesis (VEGF), and can reverse multidrug resistance, calling for excellent clinical prospects as either single or adjuvant therapy, especially when formulated with advanced nanoformulations that increase their otherwise poor solubility and bioavailability[51-54].

3. Molecular Mechanisms of Action

Nutraceuticals from medicinal plants for the treatment of breast cancer have been beneficial due to multifunctional actions at the molecular and cellular levels. They frequently act by targeting multiple, interacting pathways essential for carcinogenesis, tumour progression, and the host response[56,57].

3.1 Antioxidant Properties

ROS, the end-products of cellular metabolism, are key molecules that mediate oxidative stress as well and have been observed at higher levels in cancer cells than in normal cells, causing oxidative stress that can induce DNA damage, genetic instability, and abnormal cell signalling, all of which facilitate tumour initiation and progression[58]. Medicinal plants and their derived nutraceuticals, containing bioactive ingredients such as polyphenols (flavonoids, phenolic acids), carotenoids, and stilbenes (resveratrol, curcumin), represent potent antioxidants[56,59,60]. They scavenge ROS, such as superoxide anions and hydroxyl radicals, directly, thereby reducing oxidative damage to cellular components[58]. In addition, they can boost the activity of endogenous antioxidant enzymes, including Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx), by upregulating transcription factors such as Nuclear Factor Erythroid 2-Related Factor 2 (NRF2)[61]. This dual action

of direct scavenging and enzyme modulation would have powerful protective effects against chronic oxidative stress, preserving cellular integrity[61,62].

3.2 Modulation of Cell Signalling Pathways

Regulation of intracellular signalling cascades that mediate cancer cell survival, proliferation, and invasion is disrupted by nutraceuticals[56,63].

3.2.1 Apoptosis and Cancer Cell Proliferation

Most nutraceuticals restrain the uncontrolled growth observed in breast cancer while inducing programmed cell death (apoptosis)[55,57]. Compounds such as curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG) have also been shown to induce both the extrinsic (death receptor) and intrinsic (mitochondrial) apoptotic pathways[61,62]. In many cases, this involves a disruption of the balance of Bcl-2 family proteins, which results in cytochrome c release from mitochondria and activation of caspases (*e.g.*, caspase-9 and 3/7). They also block cells at specific phases of the cell cycle (usually at G0/G1 or G2/M) by affecting the expression of cyclins and cyclin-dependent kinases (CDKs)[62]. Most importantly, they all inhibit pro-survival signalling, including the PI3K-Ser/Thr Kinase (PI3K)/Akt/mTOR and Mitogen-Activated Protein Kinase [MAP K/extracellular signal-regulated kinase (ERK)] pathways that are frequently hyperactivated in breast cancer cells to stimulate cell proliferation[64-67].

3.2.2 Inhibition of Metastasis

Nutraceuticals interfere with the metastatic cascade, or the spread of cancer, at multiple points. They inhibit the expression/activation of Matrix Metalloproteinases (MMPs), proteolytic enzymes that degrade the Extracellular Matrix (ECM) and are crucial for tumour cell invasion of the surrounding stroma[64,68]. They also have anti-angiogenic activity, and can prevent angiogenesis – the generation of new blood vessels necessary for tumour growth and metastasis, frequently via downregulation of factors such as VEGF (Vascular Endothelial Growth Factor) and/or HIF-1alpha (Hypoxia-Inducible Factor 1-alpha)[59,69]. They also inhibit the signalling pathways of major transcription factors, including nuclear factor-kappa B (NF-κB) and STAT3, which mediate the induction of genes responsible for inflammation, survival, proliferation, and metastasis[56,61,63,70].

3.2.3 Regulation of Hormone Response (Estrogen and Progesterone Receptors)

In hormone receptor-positive (ER+/PR+) tumours of the breast, nutraceuticals impede estrogen and progesterone signalling. Phytoestrogens such as isoflavones (found in soy) and lignans (found in flaxseed) have a structure similar to estrogen and can bind to the Estrogen Receptor (ER). They can serve as weak agonists or antagonists for ER-beta, specifically by binding to suppress the growth of cancer cells, or as direct surrogates of endogenous estrogen [61]. Some of these compounds, such as 3,3′-Diindolylmethane (DIM), are known to inhibit the aromatase enzyme that is responsible for the ultimate production of estrogen in postmenopausal women and therefore decrease hormonal stimulation of cancer cells. Some mechanisms even involve the promotion of ER-alpha, the receptor subtype that is frequently associated with breast cancer proliferation, degradation leading to a decrease in hormone sensitivity in the tumour[71].

3.3 Anti-inflammatory Effects

Chronic inflammation is an integral component of the tumour microenvironment that drives cancer progression, metastasis, and drug resistance[57]. There are nutraceuticals based on medicinal plants that have a strong anti-inflammatory effect, and therefore negate this effect. One of the main mechanisms involves blocking NF-κB transcription factor activation and nuclear relocation, which are major regulators of pro-inflammatory genes[63,70]. Through the inhibition of NF-κB, they reduce pro-inflammatory cytokines and chemokines, including Tumour Necrosis Factor-alpha (TNF-alpha) and Interleukins (IL-1beta, IL-6, IL-8), resulting in a less pro-tumorigenic inflammation[61]. In addition to the above, molecules such as curcumin also modulate critical inflammatory enzymes, such as Cyclooxygenase-2 (COX-2) and Lipoxygenase (LOX), which generate pro-inflammatory mediators such as prostaglandins and leukotrienes[58,65].

3.4 Immunomodulation

Nutraceuticals can modulate the immune system to enhance anti-tumour immunity and counteract cancer-induced immunosuppression[72,73]. They promote the activity and maturation of key immune cells, including Natural Killer (NK) cells and cytotoxic

CD- T lymphocytes, which are essential for recognising and killing cancer cells[69,73]. Compounds such as vanillic acid can shift the polarisation of tumour-associated macrophages (TAMs) from the pro-tumorigenic M2 phenotype to the anti-tumorigenic M1 phenotype, thereby repurposing immune cells to fight the tumour. Additionally, certain nutraceuticals, such as resveratrol, have been shown to inhibit immune checkpoints (*e.g.*, the PD-1/PD-L1 Axis)[73]. By blocking this interaction, they restore T-cell function against the tumour while also reducing the presence of immunosuppressive cells, such as Regulatory T cells (T_{reg}) and Myeloid-Derived Suppressor Cells (MDSCs), within the tumour microenvironment[69,73].

4. Clinical Evidence and Trials

4.1 Overview of Clinical Studies

Clinical trials exploring nutraceuticals obtained from medicinal plants for their application in BC therapy have gone beyond the traditional plant-derived chemotherapeutic agents, such as paclitaxel (obtained from *Taxus baccata*) and vinblastine (from *Vinca rosea*), to test whole extracts and distinct starving compounds for adjuvant, adjunctive, or primary anticancer effects[64,65]. These include investigative compounds such as curcumin (from *Curcuma longa*), resveratrol (from grapes/Japanese knotweed), and epigallocatechin gallate (EGCG) (from green tea) that have been confirmed in pre-clinical testing to possess potent anti-proliferative, pro-apoptotic, and anti-angiogenic attributes, affording the basis for their evaluation in human trials[66,67]. Yet, in contrast to the abundance of preclinical potential, there has been only a modest number of well-conducted large RCTs, which have often suffered from trial heterogeneity in design, formulation variation, and patient subsets[74]. Existing clinical evidence so far is mainly centred on the potential use of such nutraceuticals as adjuvant therapeutic agents to prevent side effects induced by standard therapies and to improve quality of life, with some emerging data on their direct anti-tumour actions and on overcoming multi-drug resistance[75].

4.2 Safety and Efficacy

The safety and efficacy of herbal-based nutraceuticals in breast cancer patients seems to be a complicated issue, depending on dose, formulations, and interplay with concomitant conventional treatment.

4.2.1 Dose-response Relationships

Determining the dose-response relationships of most nutraceuticals remains a significant obstacle, in part because of their relatively low systemic bioavailability and biphasic effects[72,74,76]. It has been reported that p53 reactivation, via p53 activators, could regulate cancer cell proliferation or apoptosis, and that low-dose curcumin or resveratrol can have a paradoxical growth-promoting effect on cancer cells. In contrast, high doses are highly cytotoxic *in vitro*. This *in vitro* finding has significant implications, given its contrast with the standard milligram-level dosing used for these products, which is often insufficient and perhaps even unsafe in the clinic[76]. As a result, the optimal therapeutic dosage for clinical efficacy without pro-growth effects is frequently unknown and requires advanced delivery systems to enhance bioavailability[74].

4.2.2 Side Effects and Contraindications

As "natural" products, nutraceuticals are tempting to consider safe, but they are not without potential harm, particularly in the field of oncology[77]. Drug –nutraceutical interaction is a primary concern, in which nutraceuticals may enhance the efficacy or exacerbate toxicity of chemotherapy and endocrine therapy. For example, some antioxidants such as Vitamin C or E and some phytopharmacological agents (*e.g.*, garlic extracts, ginkgo extracts) can affect the metabolism of chemotherapy drugs (taxanes, vinca alkaloids, anthracyclines) by affecting cytochrome P450 enzymes and thereby result in sub-therapeutic blood levels of chemicals for anticancer therapy or augmenting myelosuppression[78]. In addition, phytoestrogenic molecules such as those contained in "super-concentrated" forms of soy or flaxseed extracts (*e.g.*, daidzein and genistein) may be contraindicated or require caution in hormone receptor-positive BC patients, as they may stimulate the regrowth of tumour tissue. However, consumption of whole foods is assumed to be safe. Timely self-reporting by patients to their healthcare team is essential for managing these possible side effects and contraindications[77].

4.3 Integration into Conventional Therapy

4.3.1 Synergistic Effects with Chemotherapy/ Radiotherapy

The most attractive clinical application of these plant-derived nutraceuticals is their potential as chemosensitisers/radiosensitisers, thereby exerting synergistic antineoplastic effects and/or reducing the toxicity associated with cancer treatment[75]. A plethora of preclinical data supports this, demonstrating that agents such as curcumin and resveratrol can potentiate the cytotoxicity of conventional drugs (*e.g.*, docetaxel or tamoxifen) by targeting multiple cancer pathways, inducing apoptosis, or reversing resistance mechanisms[72,73]. Also, in a clinical trial, co-treatment with paclitaxel and curcumin (compared to paclitaxel alone) among metastatic breast cancer patients resulted in a higher overall response rate and a higher physical performance score, indicating superior efficacy and fewer side effects, such as fatigue[73]. Nutraceuticals could potentially shield normal tissues against the oxidative stress caused by radiotherapy and chemotherapy, thus limiting side effects such as myelosuppression, nausea, and neuropathy, which, in turn, may increase patients' compliance and quality of life[75,78]. Most importantly, this cautious combination requires robust clinical data demonstrating synergy and definitively excluding antagonistic effects[74].

5. Challenges and Limitations

5.1 Standardisation and Quality Control of Nutraceuticals

Standardisation and quality control of herbal nutraceuticals remain a significant challenge. Compared to mainstream drugs, which are composed of known active chemical entities, nutraceuticals typically consist of complex mixtures of bioactive classes[79]. Besides, the nutrient composition may vary widely depending on plant species/variety, geographical source, collection period, extraction protocols, and storage conditions[80]. That natural variation poses a challenge to the assurance of consistent potency, efficacy, and safety across different batches and products[81]. Key tasks include the correct characterisation and quantification of the actual active substances, the definition of suitable bioactive markers, and the development of sound analytical methods for contaminants (*e.g.*, heavy metals, pesticides, microbial toxins) or adulterants[82]. The absence of rigorous, universally accepted guidelines hinders the overall reliability of preclinical and clinical data, and patient safety is compromised[83].

5.2 Regulatory Hurdles

The present state of global regulation of nutraceuticals is riddled with ambiguities and discrepancies, resulting in substantial regulatory barriers to their entry into cancer therapy[84]. In most countries, nutraceuticals are defined as foods or dietary supplements and are not regarded as drugs; therefore, they undergo less pre-market regulation for approval[85]. This categorisation difference means that most supplements are exempt from proving efficacy through the rigorous multi-phase clinical trials required of pharmaceutical drugs[86]. These regulatory uncertainties make it very challenging to translate promising preclinical research into clinical practice and for healthcare professionals to recommend which specific products can be safely and effectively used to treat breast cancer[87].

5.3 Need for More Robust Clinical Trials

Although there is considerable optimism in *in vitro* and preclinical data, stronger clinical trials, including large-scale RCTs, are necessary to demonstrate conclusively that certain natural health products or specific medicinal plant-derived nutraceuticals are practical and safe for the treatment of patients with breast cancer[88]. Most studies are small, methodologically weak, lack adequate control groups, or use non-standardised formulations, making them difficult to generalise and to strengthen the evidence base[89]. In addition, these trials need to emphasise clinically meaningful end points (progression-free survival, overall survival, and quality of life) rather than surrogate markers[90]. Finally, it will be crucial to establish baseline clinical data on optimal dosing and potential drug-nutraceutical interactions beyond those presented in our report, and on how they can safely interface with standard-of-care treatments such as chemotherapy or hormone therapy[91].

5.4 Public Perception and Misconceptions

In addition, public attitudes and misperceptions undermine the rational use of these drugs. A

Table 2. Challenges and future directions in nutraceutical development for breast cancer

Challenge area	Key issues	Proposed solutions/future directions
Standardisation and quality control	Variability in composition, contamination risks, and lack of global standards	Develop standardised extracts, use biomarkers, implement GMP, and advanced extraction techniques (*e.g.* SFE)
Regulatory hurdles	Classified as supplements, not drugs; limited pre-market efficacy testing	Advocate for clearer regulatory pathways, require RCTs for therapeutic claims, and harmonise international guidelines
Clinical evidence gap	Limited large-scale RCTs, heterogeneous designs, surrogate endpoints	Conduct robust RCTs with survival outcomes, focus on combination therapy, include diverse populations and subtypes (*e.g.* TNBC)
Public perception and safety	Misconceptions about safety, self-medication, and interaction with conventional therapy	Patient and clinician education, clear labeling, pharmacovigilance systems, and open doctor-patient communication
Bioavailability and delivery	Low solubility, poor absorption, rapid metabolism	Develop nanoformulations (liposomes, nanoparticles), prodrugs, and combinations with absorption enhancers
Personalised therapy	Variable patient response due to genetics, tumor subtype, metabolism	Use pharmacogenomics, biomarker-driven selection, tailored dosing, and integrate with precision oncology

marketing strategy for nutraceuticals is to describe them as "natural" and therefore "safe" or as not producing side effects, which may not always be the case, mainly when used at therapeutic doses alongside other medications[92]. False information may prompt patients to self-administer high doses, postpone or abandon conventional life-saving cancer therapies, and spend money on ineffective, expensive products[93]. Moreover, the broad sentiment characterising these molecules as a panacea easily wanes in the face of increasingly sophisticated knowledge of their possible adjuvant applications to diminish (or enhance) side effects, to sensitise Chemotherapy, or even to ameliorate quality of life[94]. This needs to be improved through better patient education and open discussion with the oncologist[95].

6. Future Directions

6.1 Research Gaps and Potential Areas for Future Study

A significant gap in research exists regarding the poor bioavailability of numerous plant-based nutraceuticals, and future investigations should consider novel delivery systems (nanoparticles, liposomes, or micelles) to maximise systemic absorption and direct tumour targeting. Additional studies are needed to fully understand the synergistic molecular mechanisms of action when nutraceuticals are used conjointly with traditional chemotherapeutics or targeted agents beyond those observed *in vitro* and *in vivo* models and RCTs designed on solid scientific evidence available across different patient populations and breast cancer phenotypes (*e.g.*, TNBC) toward an optimal dosing, timing, and safety profile[96]. This also suggests that nutraceuticals may serve as modifiers of the tumour microenvironment to overcome drug resistance[97].

6.2 Development of New Nutraceutical Formulations

Future investment could be made to develop uniform, high-concentration nutraceutical forms rather than the crude form[98]. This includes the application of more sophisticated methodologies, such as Supercritical Fluid Extraction (SFE) or bio-guided fractionation, to isolate the most active compounds (*e.g.*, certain polyphenols and terpenoids)[99]. In addition, synergistic multi-component formulations that contain purified compounds derived from various plants may exploit complementary modes of action by targeting multiple signalling pathways (*e.g.*, PI3K/AKT/mTOR/NF-kappa B) or by concurrently stimulating immune surveillance and suppressing inflammation[100].

6.3 Personalisation of Breast Cancer Therapy

The development of personalised or individualised nutraceutical applications for breast cancer will depend on pharmacogenomics/molecular

subtyping[101]. Future research should focus on investigating genetic polymorphisms (*e.g.*, in drug-metabolising enzymes such as Cytochrome P450) and epigenetic status in an individual's response to certain compounds from plant sources[102]. The challenge for current clinical trials is to incorporate predictive biomarkers of patient tumour status (*i.e.*, receptor status, mutational load) and systemic inflammation that enable the selection of the most effective nutraceuticals to improve treatment at the adjuvant or supportive level: A therapeutic gain that also minimises interactions[103].

6.4 Promoting Awareness and Education Among Patients and Healthcare Providers

Comprehensive, evidence-based education for patients and healthcare providers is urgently needed to narrow the gulf between science and practice[104]. Clinicians (oncologists, oncology nurses) need to be educated on the mechanisms and potential drug-nutraceutical interactions of these bioactive food components, as well as on quality sourcing for integration into supportive care confidently plans[101]. At the same time, trustworthy supplements and information should be offered to patients, aiming to support informed decision-making and reduce the risks associated with self-medication and mislabelled substances[104] Table 2.

7. Conclusion

In summary, plant-based nutraceuticals for breast cancer therapy are a novel, promising area that provides a multitargeted contribution to BC treatment with generally low toxicity and can enhance the conventional therapies. Their active constituents, *i.e.*, curcumin, EGCG, and withaferin A, have exhibited robust anticancer activity in preclinical models by inducing apoptosis, preventing metastasis, and altering the functions of key signalling pathways. However, their use remains limited mainly by several critical hurdles, including poor bioavailability, the absence of standardised, high-quality formulations, and the need for sufficient clinical data from large-scale trials. Further success will depend on the development of delivery technologies, including nanoformulations, the completion of rigorous clinical trials, and personalised integration based on tumour biology and patient genetics. Once these barriers have been cleared, herbal Nadu can be successfully and safely incorporated into holistic breast cancer treatment such that therapeutic efficacy is maximised. At the same time, toxicity is minimised, thereby increasing overall patient quality of life.

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9. References

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Author Contributions

Anandharaj Govindaraj wrote the protocol, the first draft of the manuscript, and the study's analyses. Saravanakumar Arthanari: Literature search; Gowtham Rajendran and Hemapriya Anbalagan: Data collection, writing, review, and editing. Jegadheeshwaran Murugan, Komaleshwaran Ramesh, Sangeetha Saravanan, Pradeep Nagarajan, and Parthiban Periyasamy: Data collection, writing, Sivakumar Ponnu, and Manivasakam Prakash: review, and editing. All authors have read and agreed to the published version of the manuscript.