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Research Progress on Chinese Medicine Derived Bioactive Monomers in Breast Cancer Resistance and Programmed Cell Death

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ABSTRACT

Therapeutic responses in breast cancer are jointly shaped by molecular subtype, clonal evolution, and the tumor microenvironment. Endocrine therapy, chemotherapy, radiotherapy, and targeted therapy can all select for acquired resistance. Bioactive monomers derived from Chinese medicinal materials have defined chemical structures and frequently act on interconnected signaling networks. They may influence drug efflux, epithelial-mesenchymal transition, tumor stemness, and cell-death thresholds by modulating PI3K/AKT/mTOR, MAPK, NF-kappaB, AMPK/HIF-1alpha, and Wnt/beta-catenin signaling. This review evaluates representative compounds, including curcumin, shikonin, baicalin, baicalein, berberine, resveratrol, tanshinone IIA, and dihydroartemisinin, with emphasis on apoptosis, ferroptosis, necroptosis, autophagy-related processes, and restoration of treatment sensitivity. It further examines microenvironmental barriers formed by hypoxia, cancer-associated fibroblasts, tumor-associated macrophages, regulatory T cells, and immune checkpoints. Preclinical studies of shikonin-induced immunogenic cell death, berberine-mediated GSDME pyroptosis, and natural-polyphenol combinations that reshape immune infiltration provide a mechanistic bridge to immunotherapy; however, they do not establish these compounds as substitutes for, or routine partners of, immune-checkpoint inhibitors. Most evidence derives from cell lines and animal models, and opposite effects may occur with different doses, formulations, or treatment schedules. Future work should establish target causality in subtype-defined patient-derived models, quantify pharmacologic synergy, match experimental exposure to achievable human exposure, and use rigorously designed clinical trials to define the population likely to benefit and the boundaries of safety.

1. Introduction

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Breast cancer is not a single disease. Hormone receptor-positive, HER2-positive, and triple-negative breast cancers differ substantially in oncogenic signaling, treatment selection, and patterns of relapse [1]. Clinical resistance may be primary, when effective response is absent at treatment initiation, or acquired, when pre-existing resistant subclones expand or adaptive changes emerge under treatment pressure. Relevant mechanisms include target alteration, bypass signaling, increased drug efflux, enhanced DNA-damage repair, epigenetic remodeling, epithelial-mesenchymal transition, cancer stem-like states, and microenvironmental protection [2]. These mechanisms frequently converge on a survival advantage and an elevated threshold for cell death. Restoring programmed cell death is therefore central both to explaining resistance reversal and to experimentally identifying sensitizing compounds.

Chinese medicine-derived bioactive monomers are chemically defined compounds isolated and characterized from medicinal plants or Chinese medicinal materials; they should not be conflated with multi-herb formulas, crude extracts, or dietary supplements. Their multitarget pharmacology may disrupt compensatory resistance networks, but it also increases uncertainty regarding off-target effects, dose dependence, and drug interactions. This narrative review prioritizes studies with direct breast-cancer evidence that connect a resistance phenotype with a molecular mechanism and a programmed-death process. Cellular, animal, and human evidence is discussed separately. Here, sensitization means an increased response to a specified treatment under defined experimental conditions and does not by itself indicate proven clinical benefit.

2. Mechanisms of Breast Cancer Resistance and Programmed Cell Death

2.1 Reprogramming of Receptor Signaling and Activation of Bypass Survival Pathways

After prolonged endocrine therapy, estrogen receptor-positive tumors may acquire ESR1 alterations, remodeling of ER coregulators, and compensatory growth-factor signaling. PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways can sustain protein synthesis, cell-cycle progression, and anti-apoptotic protein expression when ER signaling is inhibited. Receptor tyrosine kinases such as HER2, EGFR, and IGF-1R can also engage in bidirectional crosstalk with ER [2]. A compound that lowers AKT, ERK, or NF-kappaB activity while increasing caspase cleavage may reduce the survival threshold of resistant cells. Nevertheless, reduced protein phosphorylation alone does not establish that the pathway is required; gene knockdown, target rescue, or pharmacologic rescue with a selective inhibitor remains necessary.

2.2 Drug Efflux Hypoxic Adaptation and Tumor Stemness

ATP-binding cassette transporters, including ABCB1/P-glycoprotein, ABCG2/BCRP, and ABCC1/MRP1, reduce intracellular drug exposure and are associated with stem-like phenotypes in breast cancer [4]. Hypoxia promotes metabolic reprogramming, angiogenesis, and transporter expression through HIF-1alpha, enabling survival under agents such as anthracyclines. Epithelial-mesenchymal transition and CD44-high/CD24-low or ALDH-high phenotypes are associated with migration, dormancy, and risk of recurrence. A decrease in transporter expression or sphere-forming capacity indicates that resistance-associated traits have changed; it does not prove reversal of resistance. Stronger evidence requires dose-response comparisons between parental and resistant cells, intracellular drug-accumulation measurements, clonogenic assays, and in vivo rechallenge.

2.3 Classification and Interconversion of Programmed Cell Death

Cell-death nomenclature should be based on mechanism rather than a single morphology or

biomarker [3]. Mitochondrial apoptosis generally involves BAX/BAK-mediated mitochondrial outer-membrane permeabilization, cytochrome c release, and activation of caspase-9 and caspase-3/7. Death-receptor signaling activates caspase-8 through receptors such as FAS and TRAIL receptors. Ferroptosis is driven by iron-dependent phospholipid peroxidation, and its sensitivity is determined by the SLC7A11-GSH-GPX4 axis, the FSP1-CoQ10 axis, and iron homeostasis [24]. Necroptosis depends on RIPK1/RIPK3/MLKL signaling. Autophagy is fundamentally a lysosomal degradation process: it can buffer metabolic and oxidative stress but can also contribute to death in specific contexts. Increased LC3-II may indicate enhanced autophagy or impaired degradation and must be interpreted with flux measurements and genetic perturbation. Because death programs compensate for and convert into one another, increased ROS, reduced BCL-2, or reduced GPX4 alone is insufficient to define the mode of death.

3. Bioactive Monomers and Resistant Phenotypes

3.1 Curcumin

Curcumin is a major polyphenolic constituent of Curcuma longa. In antiestrogen-resistant MCF-7/LCC2 and MCF-7/LCC9 cells, curcumin inhibited NF-kappaB, Src, and AKT/mTOR signaling; reduced BCL-2, BCL-XL, and EZH2; and acted synergistically with 4-hydroxytamoxifen [5]. That study linked survival-pathway suppression with G2/M arrest and apoptosis. However, the 10-30 micromol/L concentrations used exceed the unbound plasma concentrations generally attainable with conventional oral formulations and therefore cannot be directly extrapolated to clinical adjunctive treatment. Other findings suggest that curcumin attenuates H19-associated epithelial-mesenchymal transition, indicating a possible effect on the plasticity of resistant cells.

Curcumin can also induce ferroptosis in breast-cancer cells. Cao et al. [13] observed increased lipid reactive oxygen species, malondialdehyde, and Fe2+ in MCF-7 and MDA-MB-453 cells. Inhibitor experiments and SLC1A5 knockdown supported a mechanism linking glutamine uptake, lipid peroxidation, and ferroptosis, while xenograft growth was also suppressed. These results provide mechanistic evidence for non-apoptotic death, although the dependence on SLC1A5 across subtypes, nutrient conditions, and microenvironments remains uncertain. Importantly, curcumin is not consistently sensitizing: an earlier cellular and animal study reported that dietary curcumin reduced apoptosis induced by selected chemotherapeutic agents [20]. Its antioxidant and pro-oxidant effects may therefore vary with dose, sequence, and drug mechanism.

3.2 Shikonin

Shikonin is a naphthoquinone derived from Lithospermum species. In tamoxifen-resistant MCF-7R models, shikonin upregulated the long noncoding RNA uc.57, reduced BCL11A, inhibited PI3K/AKT and MAPK signaling, and restored tamoxifen sensitivity in cells and xenografts [6]. The inclusion of uc.57 overexpression and BCL11A knockdown provided a more coherent causal chain than correlation alone. Shikonin combined with 4-hydroxytamoxifen also enhanced apoptosis and suppressed xenograft growth [16], supporting simultaneous effects on endocrine resistance and evasion of cell death.

In MDA-MB-231 triple-negative breast-cancer cells, shikonin promoted cIAP1/2 autoubiquitination and proteasome-dependent degradation, reduced RIPK1 ubiquitination, and induced apoptotic and necrotic-like death [15]. A subsequent nanodelivery study used RIPK3/MLKL activation and inhibitor rescue to support necroptosis and immunogenic cell death

[25]. Free shikonin and nanoparticle formulations, however, differ in pharmacokinetics, tissue distribution, and immune activity. Effects of a delivery system should not be attributed automatically to the free compound, and the redox activity and possible normal-tissue toxicity of shikonin require assessment within a defined therapeutic window.

3.3 Baicalin and Baicalein

Baicalin is a flavonoid glycoside from Scutellaria baicalensis, whereas baicalein is its aglycone. The two differ in solubility, absorption, metabolism, and cell permeability. In breast-cancer cells, baicalin increased ROS and the BAX/BCL-2 ratio, inhibited NF-kappaB expression and nuclear translocation, reduced survivin and BCL-2, and increased docetaxel sensitivity. In 4T1 subcutaneous and lung-metastasis models, it also suppressed tumor growth and dissemination [10]. These findings implicate NF-kappaB-associated anti-apoptotic signaling in the combination effect. Because the study did not systematically compare clinically derived docetaxel-resistant cells, chemotherapy sensitization is a more precise description than reversal of patient resistance.

In MDA-MB-231/IR cells generated by repeated irradiation, baicalein increased IFIT2; reduced ABCG2, Oct3/4, sphere formation, and the CD44-high/CD24-low population; and enhanced sensitivity to radiation, doxorubicin, and cisplatin while promoting apoptosis [11]. This model combines radioresistance with drug-tolerant features and provides a link between stemness and death evasion. However, the prognostic association of IFIT2 was derived from database analysis; patient-derived samples and in vivo limiting-dilution experiments are still needed to determine whether IFIT2 is a decisive target.

3.4 Berberine

Berberine is an isoquinoline alkaloid found in Coptis chinensis and related medicinal materials. In MCF-7/TAM cells, berberine combined with tamoxifen increased p21, reduced the BCL-2/BAX ratio, and strengthened G1 arrest and apoptosis [7]. In a hypoxia-induced MCF-7 resistance model, low-dose berberine increased doxorubicin sensitivity by suppressing the AMPK-HIF-1alpha-P-glycoprotein axis, whereas higher doses directly induced apoptosis through p53, BAX, cytochrome c, and caspase cascades. Xenograft findings were consistent with the in vitro trend [12]. This dose stratification illustrates how the same compound may function as either a sensitizer or a directly cytotoxic agent.

Berberine also enhanced death-receptor signaling in TRAIL-resistant breast-cancer cells and strengthened the antitumor and antimetastatic effects of an anti-DR5 antibody in the 4T1 model [17]. Its combination effects are not uniformly beneficial, however. Low-dose berberine can activate AMPK-dependent autophagy and NRF2 antioxidant responses, thereby weakening the cytotoxicity of 5-fluorouracil or camptothecin [19]. Equating autophagy induction with increased tumor-cell death can therefore lead to the wrong mechanistic conclusion. Autophagic flux and the net contribution of autophagy to survival should be tested using ATG-gene perturbation or lysosomal inhibitors.

3.5 Resveratrol Tanshinone IIA and Dihydroartemisinin

In MCF-7/DOX cells and xenografts, resveratrol increased apoptosis and restored doxorubicin responsiveness by inhibiting PI3K/AKT signaling [8]. In MCF-7/ADR cells, it also modulated SIRT1/beta-catenin signaling, partly reversed epithelial-mesenchymal transition, and enhanced doxorubicin-mediated inhibition of proliferation and migration [14]. The two studies explain sensitization through survival signaling and cellular plasticity, respectively, but both focused on a

single resistant system. Rapid metabolism and low systemic exposure remain major translational limitations for resveratrol.

Tanshinone IIA reduced P-glycoprotein, BCRP, and MRP1 expression, increased intracellular doxorubicin accumulation in MCF-7 and MCF-7/DOX cells, and affected a breast-cancer stem-like population [9]. A recent study reported that dihydroartemisinin promoted ferroptosis and increased radiosensitivity in breast-cancer cells and mouse models by downregulating hsa_circ_0001610 and relieving miR-139-5p-mediated regulation of SLC7A11 [26]. These observations point, respectively, to increased effective drug exposure and removal of an anti-ferroptotic defense, but the models, doses, and delivery approaches still require replication across laboratories.

4. Integrated View of Bioactive Monomers and Programmed Cell Death

4.1 Apoptosis as a Common Endpoint of Sensitization Studies

Most sensitization studies assess apoptosis using the BAX/BCL-2 ratio, mitochondrial membrane potential, cytochrome c release, caspase cleavage, and Annexin V staining. Curcumin, shikonin, baicalin, berberine, and resveratrol can each lower the apoptotic threshold in selected models. PI3K/AKT, NF-kappaB, and ERK regulate BCL-2 family proteins as well as cell-cycle progression and protein synthesis, making a sequence of pathway suppression, restoration of apoptosis, and drug sensitization biologically plausible. Evidence is stronger when resistant comparators are included, a combination effect exceeds simple additivity, and target rescue reverses the phenotype. A decrease in viability alone should not be labeled apoptosis and cannot establish reversal of clinical resistance.

4.2 Ferroptosis May Expose Metabolic Vulnerabilities in Resistant Cells

Ferroptosis is closely linked to cystine uptake, glutathione synthesis, GPX4 activity, membrane-phospholipid unsaturation, and the labile iron pool [24]. Resistant cells frequently reinforce the SLC7A11-GSH-GPX4 defense to buffer therapy-induced oxidative stress, potentially creating an exploitable metabolic dependency. Curcumin induces ferroptosis through SLC1A5-associated glutamine metabolism, whereas dihydroartemisinin acts through regulation of SLC7A11, suggesting that natural compounds can intensify lipid peroxidation through distinct entry points. A rigorous ferroptosis study should combine lipid-peroxidation assays, iron dependence, rescue with specific inhibitors, and perturbation of nodes such as GPX4, SLC7A11, or ACSL4. Total ROS, malondialdehyde, or morphology alone cannot exclude apoptosis or nonspecific oxidative damage.

4.3 Autophagy and Necroptosis Are Context Dependent

Curcumin plus berberine has been reported to induce apoptosis and autophagy-associated death through the JNK/BCL-2/Beclin 1 axis [18], whereas autophagy induced by low-dose berberine can protect tumor cells and antagonize chemotherapy [19]. The direction of the effect depends on stress intensity, treatment sequence, and metabolic context; activation of autophagy must be distinguished from death that depends on autophagy. Shikonin-induced RIPK1/RIPK3/MLKL signaling offers a potential route around caspase resistance, but necroptosis may also provoke inflammation and immune effects, so in vivo interpretation cannot rely on tumor volume alone. Immunogenic cell death should be supported by calreticulin exposure, ATP and HMGB1 release, dendritic-cell maturation, and evidence of immune dependence rather than by a single damage-associated molecule.

5. Tumor Microenvironment and Immunotherapy

5.1 Microenvironment-Mediated Resistance and Immunosuppression

The breast-cancer microenvironment comprises tumor cells, cancer-associated fibroblasts, vascular and lymphatic endothelial cells, extracellular matrix, and diverse immune populations. Hypoxia and lactate accumulation stabilize HIF-1alpha, promote angiogenesis and glycolysis, and impair effector T-cell function. Dense matrix and abnormal vasculature restrict drug and lymphocyte entry. Cancer-associated fibroblasts secrete mediators such as TGF-beta and CXCL12, while tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells establish an immunosuppressive network through IL-10, TGF-beta, arginine metabolism, and checkpoint signaling [27]. These processes can raise the apoptotic threshold and reduce the efficacy of chemotherapy, radiotherapy, and immunotherapy. Studies claiming resistance reversal by natural compounds should therefore examine matrix remodeling, hypoxia, myeloid composition, and CD8+ T-cell infiltration, activation, and exhaustion in addition to tumor-cell-intrinsic signaling.

Microenvironmental effects differ by molecular subtype. Triple-negative breast cancers generally have more tumor-infiltrating lymphocytes and greater immune-checkpoint expression than most hormone receptor-positive tumors, yet immune-inflamed, immune-excluded, and immune-desert states still occur within the same subtype. Increased PD-L1 or lymphocytes does not necessarily indicate effective antitumor immunity. Checkpoint blockade may fail when CD8+ T cells remain confined to the stroma, Treg or suppressive myeloid populations rise concurrently, or antigen presentation and type I interferon signaling are defective. Natural-compound studies therefore require spatial and cell-type resolution; bulk tumor RNA or the proportion of splenic lymphocytes cannot substitute for local immune function.

5.2 Programmed Cell Death Can Link Tumor Elimination to Immune Priming

The immune consequence of programmed cell death depends on the mode and site of death and on accompanying signals. Immunogenic death commonly includes cell-surface calreticulin, ATP release, and HMGB1 release, which promote antigen uptake and maturation of dendritic cells and initiation of tumor-specific T-cell responses. Shikonin directly interfered with hnRNPA1 and enhanced immunogenic-death signals in 4T1 and MDA-MB-231 mammary tumor cells. Dendritic cells loaded with lysates from shikonin-treated 4T1 cells produced antimetastatic and survival effects in mice [29]. A recent orthotopic 4T1 study also found that shikonin decreased splenic Treg and increased CD8+ T-cell proportions [32]. These findings suggest coordinated effects on tumor-cell death and host immunity, but tumor-lysate vaccines, ex vivo dendritic-cell treatment, intravenous administration, and routine systemic therapy are not interchangeable and do not establish patient benefit.

Pyroptosis may convert an intracellular apoptotic signal into inflammatory immune stimulation. A 2025 study reported that berberine induced caspase-3/GSDME-dependent pyroptosis in 4T1 cells, promoted dendritic-cell maturation and macrophage remodeling, enhanced local and systemic antitumor immunity in an immunocompetent orthotopic model, and suppressed lung metastasis [30]. This expands the mechanistic profile of berberine from direct apoptosis to remodeling of the immune microenvironment. Pyroptosis is not intrinsically beneficial, however: excessive inflammation may injure normal tissue, GSDME expression is influenced by epigenetic state, and the immune biology of 4T1 tumors does not fully represent human breast cancer. GSDME knockout, immune-cell depletion, and tumor-rechallenge experiments are needed to separate direct cytotoxicity from immune-dependent efficacy.

5.3 Evidence Boundaries for Combination With Immune Checkpoint Therapy

Immune-checkpoint inhibitors have changed treatment for selected triple-negative breast cancers. In the 1,174-patient KEYNOTE-522 trial of stage II-III triple-negative breast cancer, neoadjuvant pembrolizumab plus platinum-containing chemotherapy followed by adjuvant pembrolizumab improved overall survival compared with chemotherapy alone; estimated 60-month overall survival was 86.6% versus 81.7% [28]. This phase III evidence sets an appropriate clinical benchmark. A claim of enhanced immunotherapy sensitivity should demonstrate more than altered PD-L1 or CD8 markers: the natural compound should add to anti-PD-1/PD-L1 efficacy in a well-controlled immunocompetent model, with assessment of immune-related toxicity, interactions with chemotherapy, and durable immune memory.

Evidence for natural products remains preclinical. A combination of curcumin, resveratrol, and quercetin increased T-cell recruitment in 4T1-bearing mice, reduced neutrophil and macrophage accumulation, and suppressed immunosuppressive Th2 cells, N2 tumor-associated neutrophils, and M2 tumor-associated macrophages [31]. Because three compounds were administered together, the contribution of each monomer cannot be isolated, and synergy with checkpoint inhibition was not tested directly. Natural compounds may increase immune visibility of a cold tumor by reducing hypoxic or metabolic suppression, inducing immunogenic death, improving antigen presentation, or remodeling myeloid populations. At present, however, high-quality randomized evidence for combining a natural monomer with anti-PD-1/PD-L1 therapy in patients with breast cancer is lacking.

6. Comparison of Representative Studies

Compound	Resistance Model or Combination	Principal Mechanism and Death Phenotype	Evidence Level and Main Limitation	Reference
Curcumin	MCF-7/LCC2 and LCC9; 4-hydroxytamoxifen	NF-kappaB, Src, AKT/mTOR, and EZH2 inhibition; G2/M arrest and apoptosis	Cellular evidence; effective concentrations exceed typical oral human exposure	[5]
Curcumin	MCF-7, MDA-MB-453, and xenografts	SLC1A5-associated glutamine uptake, lipid peroxidation, and ferroptosis	Cellular and animal evidence; subtype and formulation dependence remain uncertain	[13]
Shikonin	MCF-7R; tamoxifen combination	uc.57/BCL11A axis; PI3K/AKT and MAPK inhibition	Genetic perturbation and xenografts; one resistant system	[6]
Shikonin	MDA-MB-231, 4T1, and dendritic-cell vaccine models	cIAP1/2-RIPK1, RIPK3/MLKL, and hnRNPA1; necroptosis and immunogenic death	Cellular and animal evidence; delivery, vaccine, and free-compound effects are not equivalent	[15,25,29,32]
Baicalin	Breast-cancer cells; docetaxel; 4T1	NF-kappaB, survivin, and BCL-2 inhibition; mitochondrial apoptosis	Cellular and animal sensitization; not a clinical acquired-resistance model	[10]
Baicalein	Radio- and chemoresistant MDA-MB-231/IR	IFIT2 induction; reduced ABCG2 and stemness; apoptosis	Resistant-cell evidence; limited in vivo resistance validation	[11]
Berberine	MCF-7/TAM; tamoxifen	Increased p21, reduced BCL-2/BAX; G1 arrest and apoptosis	Cellular evidence; pharmacokinetics and selectivity unknown	[7]
Berberine	Hypoxic MCF-7 model; doxorubicin	AMPK/HIF-1alpha/P-glycoprotein inhibition; high-dose p53-dependent apoptosis	Cellular and xenograft evidence; marked dose dependence	[12]

Compound	Resistance Model or Combination	Principal Mechanism and Death Phenotype	Evidence Level and Main Limitation	Reference
Berberine	Immunocompetent orthotopic 4T1 model	Caspase-3/GSDME pyroptosis; dendritic-cell maturation, macrophage remodeling, systemic immunity	Cellular and animal evidence; no checkpoint-combination or human evidence	[30]
Resveratrol	MCF-7/DOX or MCF-7/ADR; doxorubicin	PI3K/AKT inhibition or SIRT1/beta-catenin modulation; apoptosis and EMT suppression	Cellular and limited animal evidence; low systemic exposure	[8,14]
Tanshinone IIA	MCF-7/DOX; doxorubicin	Reduced P-glycoprotein, BCRP, and MRP1; increased intracellular drug accumulation	Cellular evidence; direct target of transporter regulation incompletely defined	[9]
Dihydroartemisinin	Breast-cancer radiosensitization model	circ_0001610/miR-139-5p/SLC7A11 axis; ferroptosis	Cellular and animal evidence; independent replication and exposure validation needed	[26]

7. Translational Challenges

7.1 Combination Effects Require Standardized Quantification

A decrease in cell viability after two agents are administered together does not automatically demonstrate synergy. Studies should use a complete dose matrix and quantify interaction with the Chou-Talalay combination index, Bliss independence, or Loewe additivity, while reporting sequence and exposure time. Resistance-reversal studies should compare changes in IC50 between parental and resistant cells and report the resistance fold and reversal fold, avoiding the misclassification of intrinsic compound cytotoxicity as specific sensitization. In vivo experiments require monotherapy, combination, and vehicle controls and should assess body weight, hematologic indices, liver and kidney function, cardiac toxicity, and histopathology.

7.2 Bioavailability and Formulation Determine Translatability

Polyphenols and alkaloids are frequently limited by low aqueous solubility, rapid first-pass metabolism, extensive protein binding, and uncertain tissue distribution. Sustained exposure to tens of micromolar concentrations in vitro is often impossible to reproduce with a conventional oral supplement. Nanoparticles, liposomes, cyclodextrin inclusion complexes, and prodrugs may improve solubility or tumor accumulation, but the carrier itself can alter cellular uptake, immune responses, and toxicity. Formulation studies cannot therefore be treated as simple repetitions of free-compound studies. Future work should report the parent compound and major metabolites concurrently and define the relationships among plasma and tumor exposure, target engagement, and pharmacodynamic effect.

7.3 Human Evidence Is Inconsistent and Pharmacokinetic Interactions Are Plausible

Curcumin provides the most developed human evidence, but results are inconsistent. A randomized double-blind study of 150 patients with advanced or metastatic breast cancer reported a higher short-term objective response rate with intravenous curcumin plus paclitaxel than with placebo plus paclitaxel [21]. By contrast, a randomized phase II study of oral curcumin plus docetaxel found no improvement in objective response, overall survival, or time to progression in an interim analysis of 37 patients and was stopped for futility [22]. Differences in route, formulation, chemotherapy regimen, sample size, and endpoint prevent direct comparison, and neither trial supports routine use.

Safety evaluation must extend beyond the absence of additional common adverse events. In patients receiving tamoxifen, curcumin reduced exposure to endoxifen, with a greater reduction

when piperine was coadministered [23]. This change may be clinically relevant in patients whose exposure is already near an effective threshold. Natural compounds may also affect CYP2D6, CYP3A4, UGT enzymes, and transporters such as P-glycoprotein and BCRP. Without adequate clinical evidence, patients should not be advised to self-administer high-dose monomer preparations with endocrine therapy, CDK4/6 inhibitors, chemotherapy, or immunotherapy.

7.4 Priorities for Future Research

Future studies should validate effects separately in ER-positive, HER2-positive, and triple-negative breast cancer and prioritize patient-derived organoids, patient-derived xenografts, immunocompetent syngeneic models, and humanized models when appropriate. CRISPR knockout, target rescue, and death-inhibitor rescue should establish causality and distinguish direct engagement of a critical node from nonspecific oxidative stress. Immunotherapy studies should include anti-PD-1/PD-L1 monotherapy, natural-compound monotherapy, and combination groups. CD8+ T-cell or macrophage depletion, spatial immune phenotyping, T-cell receptor clonal expansion, and tumor rechallenge should determine whether efficacy depends on adaptive immunity. Doses and schedules must reflect achievable human exposure, and pharmacokinetic-pharmacodynamic evaluation should distinguish parent compounds, active metabolites, and delivery systems. Clinical trials should prespecify molecular subtype, resistance mechanism, biomarkers such as PD-L1 and tumor-infiltrating lymphocytes, the combination regimen, and clinically meaningful endpoints including response, progression-free survival, overall survival, and immune-related adverse events rather than relying on a single peripheral-blood marker.

8. Conclusion

Chinese medicine-derived bioactive monomers may alter breast-cancer treatment response through survival signaling, drug efflux, hypoxic adaptation, tumor stemness, redox homeostasis, and the immune microenvironment. Studies of curcumin, shikonin, baicalin, baicalein, berberine, resveratrol, tanshinone IIA, and dihydroartemisinin indicate that restoration of apoptosis, induction of ferroptosis, and activation of necroptosis or pyroptosis may contribute to overcoming resistance. Immunogenic cell death, dendritic-cell maturation, and myeloid remodeling provide a mechanistic link between natural compounds and immunotherapy. Multitarget activity, however, does not imply high selectivity, and a change in immune markers does not establish sensitization to checkpoint inhibition. These compounds are best regarded as lead molecules with value for mechanistic research and drug development, not as substitutes for standard breast-cancer therapy or immunotherapy. Entry into reproducible and clinically testable combination strategies will require systematic validation of target causality, immune dependence, achievable human exposure, drug interactions, and subtype-specific benefit.

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