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REVIEW ARTICLE

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Mechanism of action of genistein on breast cancer and differential effects of different age stages

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ABSTRACT

Context: Genistein, a soy-derived isoflavone, exhibits structural similarities with 17β-estradiol and demonstrates antioxidant, anti-inflammatory, and estrogenic properties. Despite its low bioavailability limiting its clinical application, it shows potential for breast cancer prevention and treatment.

Objective: This review aims to summarize the pharmacological effects and molecular mechanisms of genistein in breast cancer, focusing on its therapeutic potential, strategies to overcome bioavailability limitations, and its role in personalized medicine. Differential impacts among population subgroups are also discussed.

Methods: A systematic review was conducted using PubMed, ScienceDirect, and Google Scholar databases. Studies were selected based on their focus on genistein's mechanisms of action, strategies to enhance its bioavailability, and interactions with other therapies.

Results: Genistein exerted anticancer effects by modulating estrogen receptor β (ERβ), inhibiting angiogenesis, arresting the cell cycle, and inducing apoptosis. Its antioxidant properties help mitigate tumor-associated oxidative stress. Bioavailability enhancement strategies, such as nanoparticle and lipid-based formulations, show promise. Age-dependent effects were evident, with distinct responses observed in prepubertal, menopausal, and postmenopausal populations, underscoring its potential for personalized therapies. Furthermore, genistein influences epigenetic modifications, including DNA methylation and miRNA expression, bolstering its anticancer efficacy.

Conclusion: Genistein is a promising candidate for breast cancer therapy, particularly for personalized treatment. Strategies to enhance bioavailability and further clinical research are essential to optimize its therapeutic potential and evaluate its efficacy in combination therapies.

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Introduction

Breast cancer is a major global health challenge and remains the leading cause of cancer-related deaths among women (National Cancer Institute 2024). While advances in early detection and treatment have improved survival rates, the recurrence of tumors, resistance to conventional therapies, and significant side effects continue to hinder treatment effectiveness. As a result, some natural compounds have garnered increasing attention for their potential to not only significantly reduce cancer incidence and progression, but also lower mortality rates with minimal side effects (Bandera et al. 2011; Barnes et al. 2011).

Genistein, a soy-derived isoflavone, has garnered considerable attention owing to its structural similarity to 17β-estradiol and its estrogenic effects. Genistein has emerged as a promising candidate for breast cancer therapy, owing to its potent antioxidant, anti-inflammatory, and estrogenic properties. A 2014 report by the American Institute for Cancer Research and the World Cancer Research Fund concluded that although research on this topic is limited, there is sufficient evidence suggesting that isoflavones, including genistein, can positively impact breast cancer survival rates. However, some studies (Yang et al. 2015) have reported conflicting results, indicating that genistein may stimulate cancer progression in certain cell and animal models. Therefore, the overall effect of genistein on breast cancer remains a topic of ongoing debate.

In addition to its estrogenic activity, genistein also exerts anti-cancer effects through apoptosis induction, inhibition of angiogenesis, and modulation of the cell cycle. However, its clinical application has been hindered by low bioavailability, which limits its effectiveness. Recent efforts have focused on improving bioavailability using advanced drug delivery systems such as nanoparticles and lipid-based formulations. Additionally, growing evidence suggests that the therapeutic response to genistein may differ across various patient populations, particularly prepubertal, menopausal, and postmenopausal women, emphasizing the need for personalized therapy.

This review examines the pharmacological mechanisms of genistein in breast cancer, explores strategies to enhance its bioavailability, and investigates its differential effects in various populations. It also discusses the potential of incorporating genistein into personalized treatment regimens to optimize clinical outcomes in breast cancer therapy.

Methods and materials

This section outlines the methods and materials employed to ensure the scientific rigor and reproducibility of the study. A

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thorough literature search and screening strategy were implemented to ensure data reliability and relevance. Validation entailed using the keyword 'genistein' in databases such as PubMed, ScienceDirect, and Google Scholar, alongside results from pertinent clinical trials. Data were sourced from specialized books and online resources, adhering to clear inclusion and exclusion criteria. The search strategy spanned multiple databases and adhered to PRISMA guidelines (PRISMA 2020). To exclude reproducible studies and meta-analyses Figure 1 shows the literature screening process.

Genistein: structure and origin

Genistein flavonoids were first identified in *Genista tinctoria L.(Fabaceae)*, which is the origin of its name. Genistein is prevalent in leguminous foods, seeds, fruits, and vegetables, with soybean being the primary source (Mei et al. 2019). In plants, isoflavone synthases generate genistein from the flavanone naringenin through ring migration (Bitto et al. 2010; Fan et al. 2013), serving functions such as UV filtration, phytochrome deposition, and symbiotic nitrogen fixation.

The initial synthesis of genistein was documented in 1928 by Baker and Robinson (Chang et al. 1994), who synthesized the 2-methyl precursor of genistein from a single-carbon homolog of a deoxybenzoin substrate. Genistein, with the formula 4′,5,7-trihydroxyisoflavone (C15H10O5), is structurally similar to estradiol and binds to Estrogen Receptor(ER) receptors (Yoon et al. 2014). Consequently, genistein exhibits estrogenic activity by binding to and stimulating relevant receptors during metabolism, impacting biological endocrinology, and possessing various biological activities. The structure of the dynein lignin is shown in Figure 2.

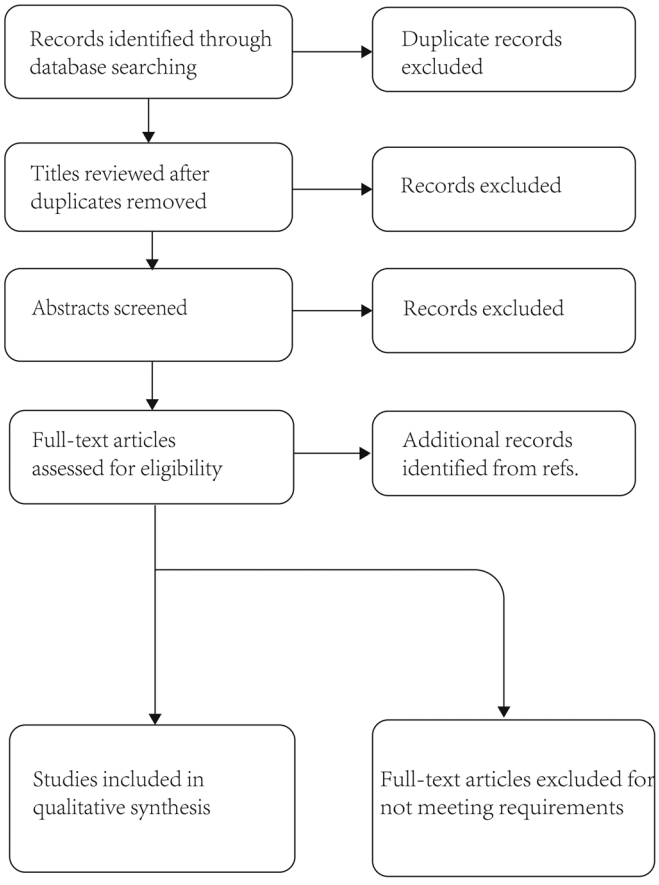

Figure 1. PRISMA study flow chart combination.

Bioavailability and biometabolism of genistein

Bioavailability refers to the amount of a substance absorbed by an organism, which is crucial for assessing the effectiveness of a chemical in the human body. In a typical diet, genistein is primarily absorbed in its glycoside form. Studies (Steensma et al. 2006) have shown that both free and glycoside forms of genistein are bioavailable, with genistein detectable in rat plasma 15 min post-administration, yielding Area Under Curve(AUC) values (0–24 h) of 54 and 24 μmol-h/L, respectively. Peak plasma concentrations of ingested genistein in adults occur at 4–7 h, whereas β-glycosides peak at 8–11 h (Cederroth et al. 2012).

The general metabolism of dietary genistein is shown in Figure 3. Genistein metabolism primarily occurs in the intestine (Setchell 1998), where it binds to glucuronic acid during intestinal transport. Some genistein reaches the liver, where it is excreted in the bile and re-enters the small intestine, allowing secondary absorption and metabolism (Steensma et al. 2006). Genistein is hydrolyzed to genistein flavonoids by β-glucosidase and phenol sulfatase; these flavonoids are lipophilic and active, either absorbed directly or further metabolized by intestinal flora (Friend and Chang 1984; Day et al. 1998). Specific colonic bacteria, such as Escherichia coli HGH21 and Gram-positive strain HGH6, convert genistein to 5-hydroxymarinol, which inhibits the proliferation, migration, and invasion of SMMC-7721 and HepG2 cells *in vitro* (Lee et al. 2017).

Various metabolites of genistein, including dihydrogen genistein flavonoids, soy flavonoids, and 6′-hydroxy-O-desmethyl angiopogonanol, have been identified in human and animal blood and excreta (Strassburg et al. 1998; Heinonen et al. 2003; Izukawa et al. 2009). Differences in the intestinal flora among

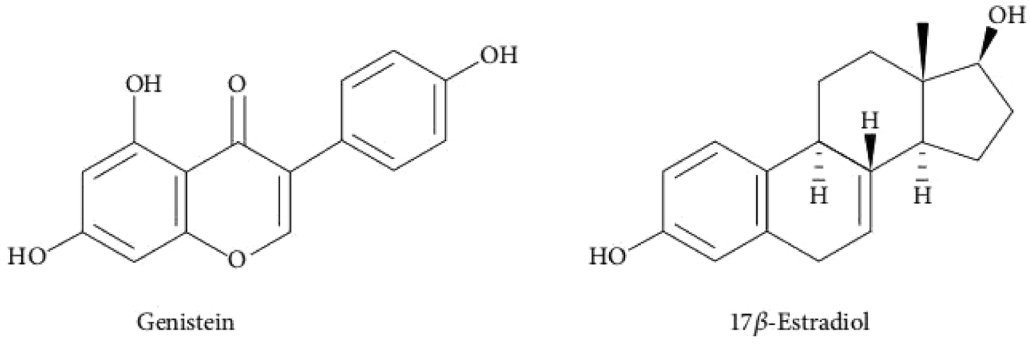

Figure 2. Chemical structures of genistein and 17β-estradiol.

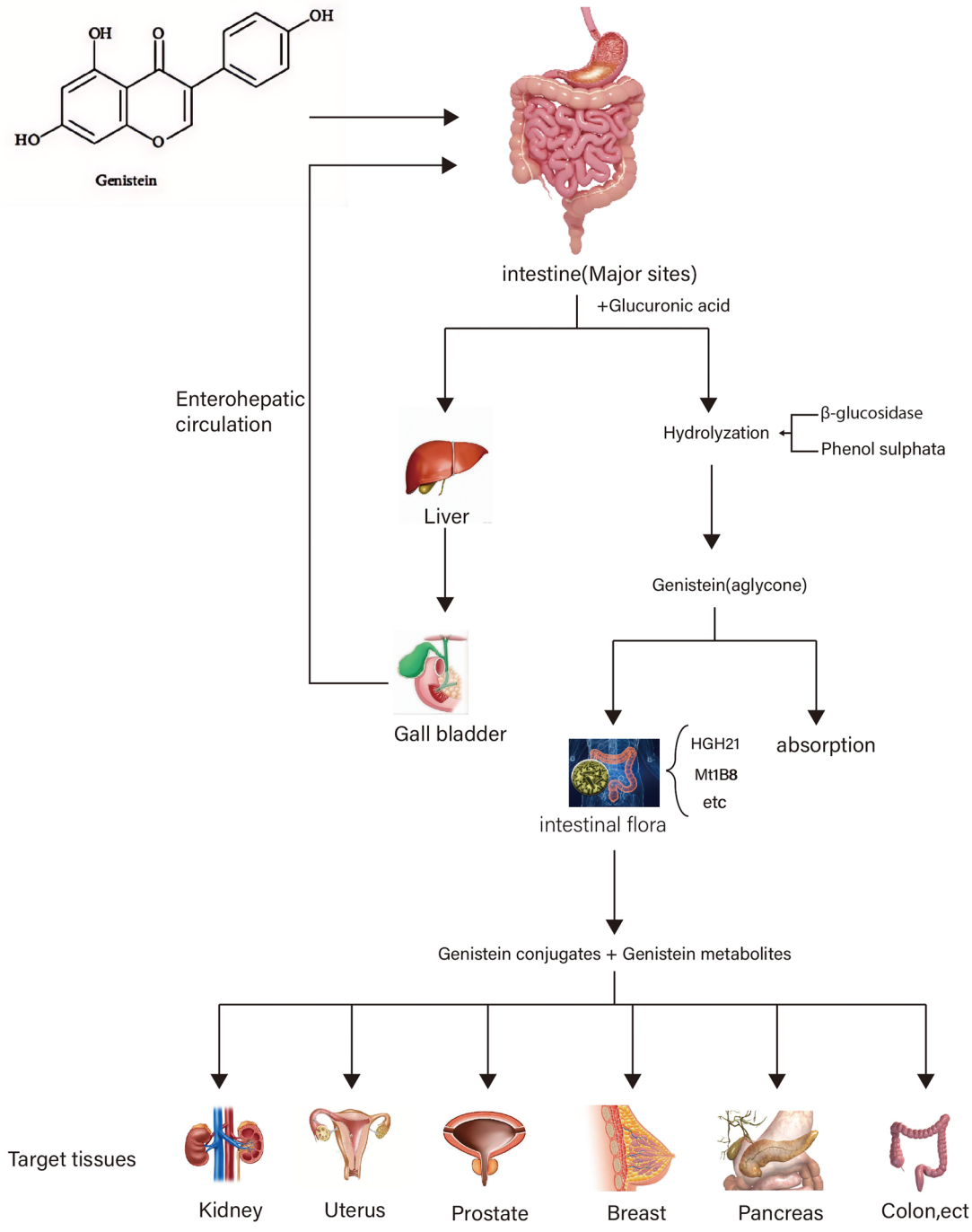

Figure 3. Metabolism of genistein in humans. This figure illustrates the metabolic pathways of genistein, including enterohepatic circulation, hydrolyzation in the intestine by β-glucosidase and phenol sulphatase, and subsequent interactions with intestinal flora.HGH21, an *E. coli* strain; Mt1B8, a gram-positive rod-shaped bacterium identified as a member of the family *coriobacteriaceae*. This figure was created by the authors, based on data from related studies (Friend and Chang 1984; Setchell 1998; Steensma et al. 2006; Lee et al. 2017).

individuals may significantly affect their responses to genistein. This suggests that the therapeutic efficacy of genistein in breast cancer can be optimized through dietary modifications or probiotic supplementation. The metabolism of genistein in humans is depicted in Figure 3.

Advances in nanotechnology for genistein delivery

The clinical application of genistein has been limited by its poor solubility, low bioavailability, and rapid metabolism (Jaiswal et al. 2019). Recent advancements in nanotechnology have introduced innovative delivery systems that address these limitations, significantly improving the therapeutic potential of genistein. This section explores four promising nanotechnology-based approaches: niosomes, folate-targeted systems, Solid Lipid Nanoparticles (SLNs), and Polymeric Micelles.

Niosomal delivery

Niosomes are bilayer vesicles formed from non-ionic surfactants, known for their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic compounds (Akbarzadeh et al. 2022).

When combined with phytoestrogens, niosomes enhance their solubility, stability, and bioavailability, enabling controlled drug release (Moghtaderi et al. 2022). Niosomes enhance the therapeutic potential of genistein in cancer treatment by optimizing targeted delivery and significantly reducing the systemic side effects.

Folate-targeted systems

Folate-targeted systems are advanced delivery platforms functionalized with folic acid, leveraging the overexpression of folate receptors (FRs) in cancer cells to achieve receptor-mediated endocytosis (Zwicke et al. 2012). These systems provide enhanced targeting capabilities, minimize off-target effects, and improve therapeutic precision (Zwicke et al. 2012; Patra et al. 2022).

Some studies have shown that folate-conjugated chitosan nanoparticles (FGCN) significantly improve the cellular uptake and cytotoxicity of genistein while achieving better-controlled drug release. FGCN enhanced the specificity of genistein delivery by interacting with FR-α, which is overexpressed in breast cancer cells (Cai et al. 2017). Experimental results revealed that FGCN reduced the 50% Inhibitory Concentration(IC50) of Genistein from 33.8 μg/ml to 14.6 μg/ml compared to non-targeted systems, demonstrating superior anticancer activity. Further apoptosis studies confirmed that FGCN outperformed unmodified systems and free genistein in inducing cancer cell death.

Solid lipid nanoparticles

SLNs are biocompatible lipid-based nanoparticles designed to enhance the delivery of lipophilic drugs, such as genistein (Scioli Montoto et al. 2020). By encapsulating genistein within SLNs, these systems improve their solubility, stability, and bioavailability while providing controlled and sustained release profiles, making them particularly effective for cancer therapy (Ferreira et al. 2022).

Some studies have shown that SLNs have the potential to reverse multidrug resistance (MDR) in breast cancer. Experiments with SLNs in drug-resistant breast cancer cells (MCF7/ADR) have demonstrated significantly enhanced intracellular drug uptake through caveola-mediated endocytosis (Xu et al. 2018). When caveolin-1 activity is inhibited by genistein, the uptake of SLNs is markedly reduced, indicating the critical role of this pathway in SLN-mediated delivery (Xu et al. 2018). By leveraging these mechanisms, SLNs can bypass efflux pumps in MDR cells, thereby improving the efficiency of drug delivery. Additionally, SLNs enable targeted delivery and sustained therapeutic levels in the tumor microenvironment, further enhancing the anticancer efficacy of genistein (Dobrzynska et al. 2020).

Polymeric micelles

Polymeric micelles are nanoscale delivery systems composed of amphiphilic block copolymers that self-assemble into a hydrophobic core and hydrophilic shell (Ghosh and Biswas 2021). This unique structure enhances the solubility and stability of poorly water-soluble drugs, such as genistein, protecting them from premature degradation and facilitating efficient drug delivery.

Some studies have shown that a novel genistein-loaded mixed micelle (GEN-M) system, composed of a polymeric solubilizer and Vitamin E derivative (TPGS), effectively addresses the solubility and bioavailability challenges of genistein (Shen et al. 2018). Optimized GEN-M micelles exhibited a mean particle size of 184.7 ± 2.8 nm, a narrow polydispersity index (PDI) of 0.162 ± 0.002, and a zeta potential of −2.92 ± 0.01 mV. The system achieved a high entrapment efficiency of 97.12 ± 2.11% and drug loading of 3.87 ± 1.26%. Encapsulation increased Genistein's aqueous solubility to 1.53 ± 0.04 mg/mL, a significant improvement over free Genistein. Additionally, the GEN-M system demonstrated sustained drug release *in vitro* and enhanced permeability across a Caco-2 cell monolayer. Pharmacokinetic studies showed a 2.42-fold increase in oral bioavailability compared with free genistein.

Collectively, these delivery systems provide transformative solutions for overcoming the pharmacokinetic challenges of genistein, unlocking their full therapeutic potential in cancer therapy. Future studies should focus on integrating these systems with personalized medical approaches and exploring their applications in combination therapies to maximize clinical outcomes.

Mechanisms involved in the treatment of breast cancer with genistein

Relationship between genistein and estrogen

Genistein, a phytoestrogen structurally similar to 17β estradiol, mimics estrogen by binding to and activating estrogen receptors, leading to reduced estrogen production (Fritz et al. 2013; Chen et al. 2014; Ziaei and Halaby 2017). Unlike endogenous estrogens, which do not preferentially bind to either ER receptor, genistein, and S-oxynivalenol typically bind to ERβ rather than ERα (Kuiper et al. 1998; Muthyala et al. 2004). Activation of ERα is linked to breast cancer cell proliferation, whereas ERβ activation has the opposite effect (Treeck et al. 2010; Thomas and Gustafsson 2011; Jiang et al. 2013). Although genistein can activate ERα, its strong affinity for ERβ and competitive inhibition of estrogens suggests an inhibitory effect on breast cancer cell proliferation at specific doses (Sotoca et al. 2008; Pons et al. 2014; Lecomte et al. 2017).

Genistein may have different effects on various breast cancer subtypes, such as ER-positive and triple-negative cancers, due to its selective ERβ binding, warranting further investigation (Pons et al. 2014; Lecomte et al. 2017).

Genistein also reduces breast cancer cell growth through estrogen receptor-independent mechanisms, including inhibition of DNA topoisomerases and tyrosine kinases (Messina et al. 1994; Barnes and Peterson 1995), and suppresses the expression of invasive genes S100A8 and S100A9 in ERβ-overexpressing MCF-7 cells, which are associated with poor prognosis (Chang et al. 2008; Miller et al. 2017; Puar et al. 2018).

Effects of genistein on angiogenesis

Angiogenesis involves the growth of blood vessels within and around a tumor, primarily through the proliferation and migration of endothelial cells, forming a new lumen, nerve plexus, and vascular network (Puar et al. 2018; Salehi et al. 2021).

Genistein demonstrated unique antioxidant and antiangiogenic effects at specific doses, attributed to particular groups in its molecular structure. Further research (Kousidou et al. 2005) is needed to explore these structure-function relationships through molecular simulations and experimental validation. In T47D cells, genistein treatment reduced the expression of MMPs 2, 3, and 15, thereby inhibiting angiogenesis and metastasis through the transcriptional regulation of cancer-related genes and reducing breast cancer cell invasiveness. Another study (Latocha et al. 2014) indicated that genistein has a dual effect on angiogenesis, promoting angiogenesis at low (0.001–1 μM) and

high (25–100 μM) concentrations. An animal (Danciu et al. 2014) experiment using genistein and a genistein-cyclodextrin mixture on chicken allantoic membranes (CAM) showed a reduction in both intra-egg and extra-egg angiogenesis, with more pronounced results for genistein alone.

Bioinformatics studies (Shukla et al. 2020) have confirmed that genistein inhibits angiogenesis through the Akt, HIF-1α, and VEGF signaling pathways. Combined evidence from bioinformatics, cell experiments, and animal studies support the role of genistein in inhibiting angiogenesis (Draut et al. 2017; Mukund et al. 2019).

Antioxidant effects of genistein

Cellular oxidative processes lead to various types of cancer (Loh et al. 2019). Studies have indicated that genistein has antioxidant properties (Javanbakht et al. 2014; Chang et al. 2015; Lopes de Azambuja et al. 2015; Rahman Mazumder and Hongsprabhas 2016), which inhibit erythrocyte hemolysis caused by diuric acid or hydrogen peroxide (Gyoergy et al. 1964; Patlolla et al. 2000). Genistein also inhibits hepatic mitochondrial microsomal lipid peroxidation, NADH oxidase, and the respiratory chain (Jha et al. 1985; Thannickal et al. 1998).

Researchers have attributed the anti-cancer, anti-inflammatory, cardioprotective, and enzymatic effects of genistein to its antioxidant properties. Giles and Wei (1997) found genistein to be an effective hydrogen peroxide scavenger, inhibiting hydrogen peroxide formation by 12-O-13-acetate (TPA) in HL-60 cells differentiated from dimethyl sulfoxide (DMSO). 1 and 5 mmol genistein significantly prolonged tumor latency and reduced tumor diversity by approximately 50% (Wei et al. 1995). Another controlled experiment (Foti et al. 2005) demonstrated the protective effects of isoflavones against oxidative DNA damage by supplementing Jurkat cells and primary lymphocytes with the two isoflavones. Isoflavones protect against oxidative DNA damage at concentrations below 2 mM. These antitumor properties may stem from genistein's anti-priming and anti-promoting effects, blocking DNA adduct formation, and inhibiting oxidative and inflammatory events *in vivo*.

Genistein affects cell cycle arrest, antiproliferative mechanisms

Cell cycle arrest is a crucial anti-cancer mechanism that inhibits cancer cell proliferation, induces apoptosis, enhances chemotherapy and radiotherapy sensitivity, and prevents tumor recurrence and metastasis. The cell cycle is meticulously regulated and each phase is monitored by specific checkpoint proteins. Thirty years ago, using omics methods, researchers discovered that genistein suppresses protein kinases and regulates 183 proteins (Yan et al. 2010).

Research (Shao et al. 1998; Lin et al. 2000) indicates that Genistein inhibits breast cancer cell proliferation by arresting the G2/M phase, inducing $p21^{WAF/CIP1}$ expression, and promoting apoptosis. Genistein induces G2 cell cycle arrest by downregulating Cdc25C phosphatase, upregulating p21Waf11/Cip1 expression, and consequently reducing Cdc2 kinase activity (Frey et al. 2001). Another study (Rahal and Simmen 2010) found that genistein lowered breast cancer risk by activating the PTEN pathway and inducing PTEN-p53 interactions in breast epithelial cell nuclei.

Additionally, genistein inhibits EGF-stimulated invasion in breast cancer by decreasing phosphorylated Akt, inhibiting the NF-κB pathway downstream of Akt, and modulating the PI3K/Akt and EGFR/Akt/NF-κB pathways (Brown et al. 1998; Pavese et al. 2010), which promote cellular differentiation and cancer cell death.

Bioinformatic analysis (Mukund et al. 2019) confirmed active site binding and interaction, highlighting the importance of lysine, serine, and aspartate residues. Further studies (Lamartiniere et al. 2002; Robillard and Segar 2006) have also suggested that combining genistein with chemotherapeutic agents may enhance chemotherapy efficacy by further inhibiting cell cycle proteins and promoting apoptosis.

Genistein induces cell apoptosis

Programmed cell death is a tightly regulated process triggered by stimuli such as tissue remodeling, cell detachment, genomic damage, and hypoxia (Adams 2003; Danial and Korsmeyer 2004; Adams and Cory 2007). Dysregulation of apoptosis can lead to cancer, while its induction in cancer cells inhibits cancer progression.

The Bcl-2 protein family is a key apoptosis regulator, and modulation of these proteins effectively controls apoptosis. Genistein has been shown to lower the anti-apoptotic protein Bcl-xl and increase the pro-apoptotic proteins Bax and caspase 3 in breast cancer cells (Li et al. 1999; Upadhyay et al. 2001; Po et al. 2002; Tophkhane et al. 2007). It downregulates Bcl-2, upregulates Bax, and disturbs the Bax to Bcl-2 ratio. Genistein regulates NF-κB, which has a binding site in the Bcl-2 promoter, indicating that genistein flavonoids may modulate Bcl-2 expression through NF-κB, thereby controlling apoptosis (Park et al. 2019).

Genistein also inhibited cell growth and induced apoptosis *via* the MEK5/ERK5 pathway, reducing MEK5, total ERK5, and phosphorylated ERK5 protein levels in a concentration-dependent manner, consistent with growth inhibition and apoptosis induction (Park et al. 2019). Genistein exposure leads to a concentration-dependent decrease in NF-κB/p65 protein levels and NF-κB DNA-binding activity. Additionally, genistein induces apoptosis through Ca2+ regulatory activity, generating Ca2+ through phytoestrogen interactions with ER receptors, similar to vitamin D receptors (Sergeev 2004). It activates the Ca2+-dependent pro-apoptotic proteases, μ-calpain and caspase-12, inducing apoptosis in breast cancer cells (Hsiao et al. 2019).

Alterations in oncoprotein phosphatase 2 A (CIP2A) may also contribute to genistein-induced growth inhibition and apoptosis. In genistein-treated T47D and MCF-7-C3 breast cancer cells, CIP2A oncoprotein expression was abnormal (Zhao et al. 2016). Furthermore, genistein can block the G2/M phase of breast cancer cells *via* multiple pathways, leading to ROS-dependent apoptosis (Kaushik et al. 2019). The signaling pathways influenced by genistein are summarized in Figure 4.

Epigenetic mechanisms of genistein in breast cancer

Epigenetic modifications, such as DNA methylation and miRNA regulation, play a pivotal role in breast cancer progression by silencing tumor suppressor genes (TSGs) or activating oncogenes (Dworkin et al. 2009; Jovanovic et al. 2010). These reversible modifications present promising therapeutic targets for restoring normal gene expression. Genistein, a natural isoflavone, has demonstrated significant antitumor effects by modulating these epigenetic mechanisms, highlighting its therapeutic potential.

Genistein selectively inhibits DNMT1 activity and expression, a key enzyme in maintaining DNA methylation patterns (Baylin

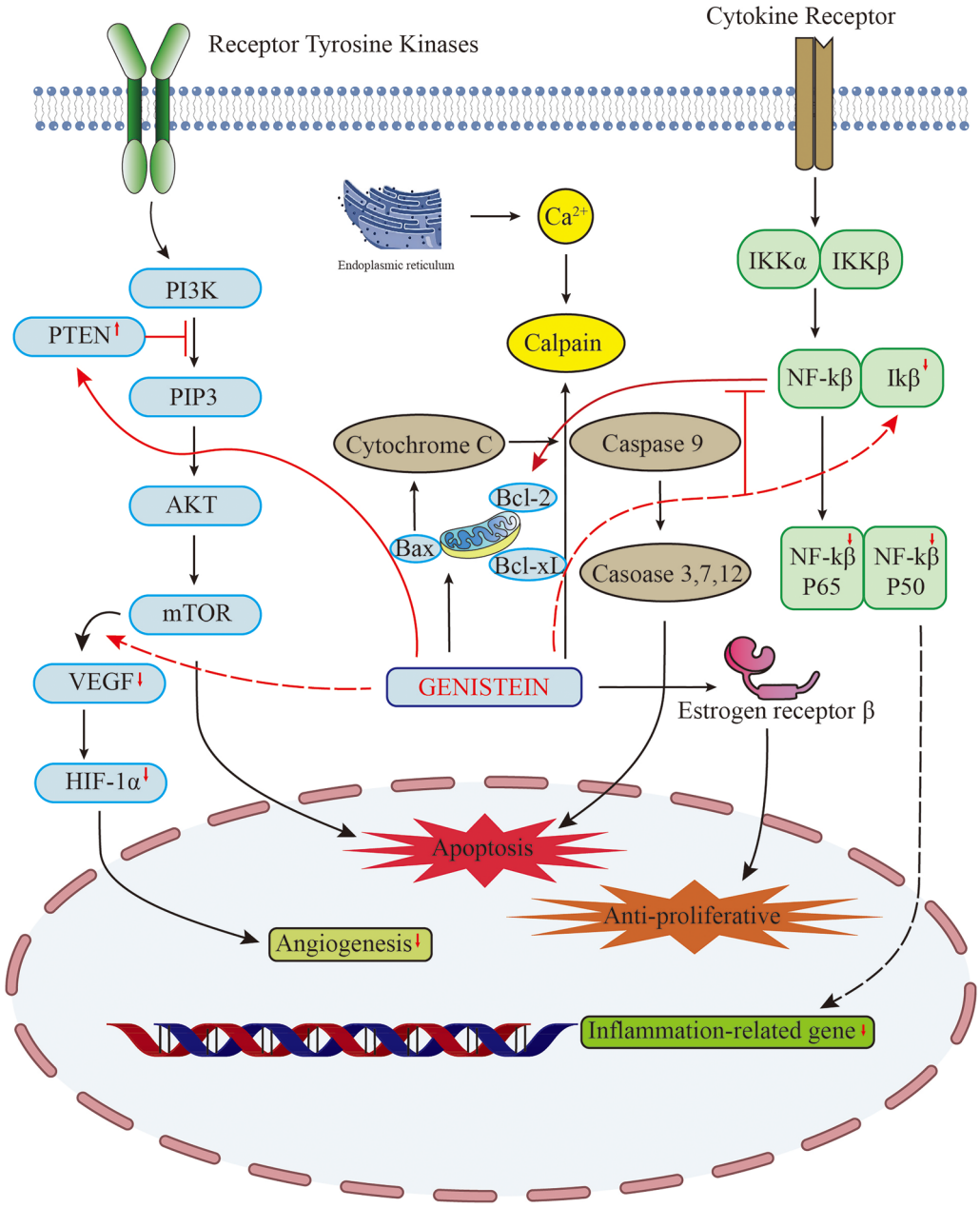

Figure 4. Genistein induces apoptosis, anti-tumor proliferation, anti-angiogenesis, and reduction of inflammation-related gene production through some of the signaling pathways it affects. PTEN: phosphatase and tensin homolog; PI3K: Phosphoinositide 3-kinases; mTOR: the mammalian target of rapamycin; PIP3: Phosphatidylinositol (3,4,5)-trisphosphate; Akt: Protein kinase B. Dashed lines represent inhibition, solid lines represent promotion. This figure was created by the authors, based on data from related studies (Adams 2003; Danial and Korsmeyer 2004; Zhao et al. 2016; Park et al. 2019).

and Ohm 2006). Molecular docking studies reveal that genistein binds directly to DNMT1's catalytic domain, competitively blocking its interaction with hemimethylated DNA, thereby reducing global methylation levels in breast cancer cells (Xie et al. 2014). This reactivates silenced TSGs such as ATM, PTEN, and SERPINB5, promoting apoptosis and reducing metastasis. Notably, genistein exhibits gene-specific effects; for instance, no changes were observed in SFN methylation or expression levels, underscoring its targeted epigenetic modulation.

Genistein also influences miRNA expression, which plays a critical role in tumor progression. Differential miRNA expression between tumor and non-tumor cells has been linked to angiogenesis, metastasis, and poor treatment outcomes in breast cancer (Li et al. 2012; Lyng et al. 2012). In MCF-7 cells, genistein upregulated miR-23b, enhancing adhesion spot attachment, reducing pseudopodia formation, and decreasing cell migration and invasion by regulating PAK2-mediated cytoskeletal reorganization (Pellegrino et al. 2013). Moreover, genistein induced apoptosis in metastatic MDA-MB-435 and Hs578t cells at low physiological concentrations, with pro-apoptotic miR-155 targeting FOXO3, PTEN, and p27 upregulated following treatment (de la Parra et al. 2016; Carbognin et al. 2019).

These findings demonstrate that genistein acts through dual epigenetic mechanisms: reversing aberrant DNA methylation by inhibiting DNMT1 and reactivating silenced TSGs, while simultaneously modulating miRNA networks to suppress tumor progression. This multifaceted epigenetic modulation underscores genistein's potential as a therapeutic agent for breast cancer. Further research should explore its combinatory use with other therapies and its molecular interactions to optimize clinical application.

Genistein and mammary stem cells

Mammary tissues contain numerous long-lived, self-renewing, and pluripotent mammary stem cells (MaSCs) that differentiate into luminal and basal epithelial cell lineages (Stingl et al. 2001; Ercan et al. 2011; Koren and Bentires-Alj 2015). Alterations in MaSCs are linked to environmental signals, and their proper interaction and response drive mammary gland changes during puberty, menstruation, and pregnancy (Ercan et al. 2011).

Owing to their stem cell properties, MaSCs are susceptible to mutations that can lead to tumor formation (Tharmapalan et al. 2019; Khan et al. 2021), with these mutated cells known as breast tumor stem cells (BCSCs) (Kakarala and Wicha 2008; Lim et al. 2009; Liu et al. 2014; Bao et al. 2015; Zhang et al. 2020). These cancer stem cells can repopulate and mirror the heterogeneity of the original tumor's heterogeneity (Macias and Hinck 2012; de la Parra et al. 2016), contributing to poor prognosis, tumorigenesis, metastasis, recurrence, and therapy resistance (Charafe-Jauffret et al. 2009; Creighton et al. 2009; Ricardo et al. 2011; Yin and Glass 2011; Bartucci et al. 2015; Li et al. 2017; Palomeras et al. 2018; Rabinovich et al. 2018; Zhang et al. 2020).

Genistein inhibits BCSCs by directly interfering with stem cell growth and differentiation pathways or through paracrine signaling from adjacent cells. It influences differentiation *via* the PI3K/Akt and MEK/ERK pathways, and inhibits mammosphere formation by altering paracrine secretion (Montales et al. 2012; Liu et al. 2016). This inhibition is linked to AKT suppression and PTEN upregulation (Montales et al. 2012). Animal studies (Montales et al. 2013) have shown that genistein inhibits mammary adipogenesis by activating ERβ and suppressing PPARγ expression, thereby inhibiting mammosphere formation in breast cancer cells. In nude mice with MCF-7 xenografts, genistein reduced BCSCs by blocking the Hedgehog-Gli1 pathway and decreasing SMO and/or Gli1 protein levels (Fan et al. 2013).

MaSCs localize to terminal end buds (TEBs) (Macias and Hinck 2012). However, differentiation and a reduced number of TEBs are correlated with increased resistance to chemical carcinogenesis (Macias and Hinck 2012). Prepubertal genistein exposure enhances the differentiation of mammary epithelial cells, increases differentiated lobular alveolar structures, and reduces breast tumor incidence by eliminating TEBs (Thomsen et al. 2006), thereby decreasing breast tissue sensitivity to carcinogens (Cabanes et al. 2004; Peng et al. 2009; 2010; Jadhav et al. 2017). Further studies (Iorio et al. 2005; Guttilla and White 2009; Li et al. 2012) have suggested that genistein inhibits breast cancer development and progression by modulating BCSC-associated miRNAs.The anticancer effects of genistein are summarized in Table 1.

Synergy of genistein with other breast chemotherapeutic agents

Genistein interacts with drugs and carcinogens. When combined with anti-breast cancer drugs, genistein induces synergistic apoptosis in MDA-MB-231 and BT-474 cells, reducing chemotherapeutic resistance (Satoh et al. 2003; Mai et al. 2007).

In MCF-7/Adr cells, the combination of doxorubicin and genistein synergistically inhibited HER2/neu expression and increased the intracellular accumulation of doxorubicin, thereby decreasing chemoresistance (Xue et al. 2014). Cytochrome P450 1B1 (CYP1B1) is crucial for the activation of environmental carcinogens and endogenous estrogen during breast cancer cell development (Kunnumakkara et al. 2020). At 5 μM, genistein significantly inhibited the expression of Cytochrome P450 1B1 (CYP1B1) induced by the environmental carcinogen 7,12-dimethylbenzanthracene (DMBA), thereby reducing its carcinogenic metabolism and alleviating oxidative DNA damage, thus playing a crucial role in the prevention and treatment of breast cancer (Leung et al. 2009).

Breast cancer endocrine treatment typically involves three drug types: (1) aromatase inhibitors (AI), (2) selective estrogen receptor modulators and down-regulators such as tamoxifen, and (3) LHRH analogs for ovarian deprivation. These medications, which regulate estrogen levels, along with oral glucocorticoids used for over six months, are more likely to cause calcium loss, reduced bone density, and a higher risk of osteoporosis (Javed et al. 2025). Phytoestrogens theoretically mitigate bone loss owing to higher ER-β expression in bone tissue (Greenwood et al. 2000). A meta-analysis (Ma et al. 2008) indicated a significant reduction in spinal bone loss after six months of daily 90 mg isoflavone supplementation. Amato et al. (Amato et al. 2013) found that, while daily intake of 120 mg isoflavones did not prevent localized bone loss, it reduced the loss of systemic bone mineral density.

Genistein with different populations

Although genistein is considered a natural compound that can effectively target breast cancer, its effects can vary among people of different ages and living conditions.

Intake and population breast cancer incidence rate

A meta-analysis (Boutas et al. 2022) exploring the link between soy intake and breast cancer revealed that only 25% of the 9699 diagnosed patients were in the high intake group, with most consuming 0–15 mg per day of genistein. The forest plot assessing the impact of low/high genistein intake on breast cancer diagnosis showed an odds ratio (OR) of 7.01 (95% CI = 6.58–7.47), indicating that individuals consuming >15 mg/d had a lower breast cancer rate than those consuming 0–15 mg/d. This pattern also held for menopausal women, where 0.35% of those developing breast cancer had an intake of >15 mg/d, versus 1.37% with 0–15 mg/d, with an OR of 3.91 (95% CI = 3.71–4.13). These findings suggest that, while menopause is a risk factor for breast cancer, it does not diminish the benefits of genistein intake in reducing breast cancer risk. Details about the intake and population-level breast cancer incidence rates are provided in Table 2 (Yamamoto et al. 2003; Kang et al. 2010; 2012; Zhang et al. 2012; Morimoto et al. 2014; Baglia et al. 2016; Zhang et al. 2017; Wei et al. 2020).

Genistein and the menopausal population

Menopause is an aging process that can cause a variety of symptoms including hot flashes, sweating, and mood changes. Currently, hormone replacement therapy (HRT) is the most effective way to alleviate menopausal syndromes. However, the Women's Health Initiative (Krebs et al. 2004) showed that HRT increased the development of coronary heart disease, stroke, and breast cancer in postmenopausal women. With recent studies of natural plant replacement therapies, phytoestrogens have gradually gained attention.

Table 1. Anticancer effects of genistein in *in vivo*/*in vitro* studies.

Research	Cancer Model	Study Dose	Effect	References
Estrogen receptor action	MCF-7 (ERβ)	50 μM, 100 μM	Inhibits breast cancer cell proliferation	Chen et al. 2003
	Breast cancer specimens from 417 stage I–III patients (2004–2006, Michigan).	N/A	Inhibits S100A8, S100A9 expression through ERα signaling	Pons et al. 2014
Antiangiogenic effect	Mouse breast cancer model	50 mg/kg	Inhibits angiogenesis through VEGF and HIF-1α pathways.	Draut et al. 2017; Mukund et al. 2019
	T47D breast cancer cell line	N/A	Inhibits angiogenesis, metastasis by downregulating MMPs.	Latocha et al. 2014
	T47D breast cancer cells	Low: 0.001–1 μM; High: 25–100 μM	Promotes angiogenesis at low doses, inhibits at high doses.	Berndt et al. 2018
	Chicken embryo chorioallantoic membrane (CAM)	3 μL (10 mM each)	Genistein inhibits angiogenesis in CAM model.	Danciu et al. 2014
Antioxidant effect	Jurkat cells, lymphocytes, and healthy subjects.	<2 mM	Protects DNA from oxidative damage.	Foti et al. 2005
	Mouse skin tumor model	1 and 5 μmol	Prolongs tumor latency, reduces multiplicity.	Wei et al. 1995
	HL-60 cells	N/A	Inhibits TPA-induced HL-60 cell differentiation	Wei et al. 1995
Cell cycle arrest	MCF-10F non-neoplastic breast epithelial cells	19–22 μM(IC50)	Downregulates Cdc25c, upregulates p21, induces G2/M arrest.	Frey et al. 2001
	MCF-10A non-tumor mammary epithelial cells	N/A	Enhances PTEN expression and p53 binding, promotes cell cycle arrest.	Rahal and Simmen 2010
	Cancer cells (e.g., MCF-10A)	Low concentration (dietary intake)	Regulates cell cycle and Akt proteins, inhibits tumor growth, promotes apoptosis.	Pavese et al. 2010
Apoptotic mechanisms	MCF-7 breast cancer cells	Bcl-2 overexpression	Regulates Bcl-2 proteins and MEK5/ERK5, induces apoptosis, inhibits growth.	Park et al. 2019
	MCF-7 breast cancer cells	50 μM	Activates μ-calpain, caspase-12, induces apoptosis in breast cancer cells.	Sergeev 2004
	MCF-7, T47D breast cancer cells	0–60 μM	Downregulates CIP2A, promotes apoptosis, inhibits growth.	Zhao et al. 2016
miRNAs and cancer progression	Breast cancer cells (MCF-7, MDA-MB-231)	N/A	Altering miRNA expression	Pellegrino et al. 2013
	MDA-MB-435, Hs578T breast cancer cells	Low physiologically relevant concentratio	Upregulates miR-155, targets FOXO3, PTEN, casein kinase, and p27, inhibits viability, induces apoptosis.	Carbognin et al. 2019
Mammary stem cells	MCF-7 and MDA-MB-231 mammary spheres	2 μM, 40 nM	Regulates PI3K/Akt, induces ER-β stem cell differentiation.	Liu et al. 2016
	SV40-transformed MSF and MCF-7 cells.	40 nM	Activates ERβ, inhibits PPARγ, reduces mammary fat and mammosphere formation.	Montales et al. 2013
	MCF-7 breast cancer cells	15 μM, 30 μM	Reduces $CD44^+/CD24^-$ cells, breast cancer stem cells, and mammography volume.	Fan et al. 2013
	Nude mouse (MCF-7 transplantation)	20 mg/kg, 50 mg/kg	Blocks Hedgehog–Gli1, reduces SMO, Glil, and BCSCs in tumors.	Fan et al. 2013
Combination therapy	MCF-7/Adr breast cancer cells	30 μmol/L; Different doses of DOX	Enhances DOX accumulation, downregulates Her2/neu, promotes G2/M arrest and apoptosis.	Xue et al. 2014.

Vasomotor syndrome

Vasomotor syndrome (VMS) encompasses symptoms such as hot flashes and sweating due to disrupted vasoconstriction and diastole after menopause. Epidemiological studies (Reed et al. 2013) have revealed that the incidence of postmenopausal hot flashes in women from Asian countries with high soy consumption, including China, Japan, and South Korea, is significantly lower (10%–25%) than that in Western countries (60%–90%).

A small prospective study (Cheng et al. 2007) indicated that menopausal women taking 60 mg/d of isoflavones for 12 weeks experienced a 57% decrease in the severity and frequency of hot flashes. Another study (Welty et al. 2007) by Welty et al. confirmed a reduction of over 40% in hot flashes in all menopausal women.

Osteoporosis

Postmenopausal osteoporosis (PMO) is a prevalent age-related condition linked to aging. Estrogen deficiency is the primary cause of PMO. Severe postmenopausal estrogen deficiency increases osteoclast activity, reduces bone density, increases bone turnover, disrupts calcium salt deposition, enhances bone resorption, and causes significant bone loss culminating in PMO.

Genistein, through its phytoestrogenic effects and specific affinity for the ERβ receptor, can effectively affect PMO development, similar to its influence on osteoporosis during chemotherapy (Greenwood et al. 2000; Ma et al. 2008; Amato et al. 2013).

Metabolic syndrome

Postmenopausal changes in metabolism may lead to obesity, which in turn may lead to a higher incidence of cardiovascular disease. One study (Jain et al. 2022) showed that genistein significantly reduced glucose concentration and increased sensitivity in postmenopausal women with metabolic syndrome or type 2 diabetes. Genistein also reduced blood pressure and triglyceride concentrations as well as circulating insulin levels in postmenopausal women with metabolic syndrome. In addition, adipocyte differentiation is mediated by the Erß signaling pathway, and genistein can inhibit adipogenesis by activating ERβ and suppressing PPARγ expression (Montales et al. 2013).

Other progress

Some studies have discussed the effects of genistein on cognitive function, but there are reservations about the need for genistein because it has less of an overall effect or is not the most effective alternative.

Table 2. Summary data for selected studies.

Study	Country	Participants n	Daily soy isoflavones consumption								Total BC BC cases, n
			BC cases, n		Pre-menopausal, n			Post-menopausal, n			
			0–15 mg/day	>15 mg/day	0–15 mg/day	>15 mg/day	BC	0–15 mg/day	>15 mg/day	BC	
Kang et al. 2010	China	524	132	392			248			276	524
Kang et al. 2012	China	288	187	101			107			181	288
Zhang et al. 2012	China	616	397	219			326			290	616
Baglia et al. 2016	China	70,578	852	182	246	27	273	606	155	761	1034
Wei et al. 2015	China	300.852	2031	258	1004	116	1120	1.027	142	1.169	2289
Yamamoto et al. 2003	Japan	21,852	94	85	50	39	89	43	44	87	179
Morimoto et al. 2014	USA	84.550	3578	1191	507	150	657	3.071	1.041	4112	4769
Zhang et al. 2017	USA,Canada, Australia	6,235	4597	1.524	2210	846	3056	2.462	714	3176	6235

BC: Breast cancer.

Genistein and the early developmental population

Prepuberty and genistein contact can induce increased differentiation of mammary epithelial cells to increase the number of differentiated lobular alveolar structures, reducing the incidence of breast tumors by eliminating terminal buds (Thomsen et al. 2006). Researchers (Lamartiniere et al. 2002; Peng et al. 2010) have found that rats must be exposed to genistein between birth and prepubertal mammary gland development in order to reduce the risk of breast cancer. Thus, genistein can enter adolescent human life as a breast cancer-preventive agent during the prepubertal stage.

Genistein and the fetus

Many chronic human diseases and disorders, including breast cancer, have developmental origins (Robillard and Segar 2006). Fetal epigenetic genes are particularly vulnerable to dysregulation during early development and are sensitive to environmental factors. Research (Hilakivi-Clarke and de Assis 2006) indicates that breast cancer may originate in the fetal environment. Consequently, maternal diets with epigenetic regulatory properties could influence the epigenetic reprogramming process, causing permanent changes in the offspring that affect breast cancer susceptibility.

Genistein, a recognized dietary epigenetic modulator, is considered a safe and effective preventive agent against breast cancer (Dolinoy et al. 2006; Li et al. 2009; Li and Tollefsbol 2010; Li et al. 2013). Long-term maternal treatment with a genistein diet can induce epigenetic inheritance of key tumor-related genes, potentially aiding in breast cancer prevention in their offspring (Chen et al. 2022).

Risks and other impacts of genistein use

Genistein and reproduction

Genistein, a phytoestrogen, binds to estrogen receptors (ERα and ERβ) and disrupts testosterone biosynthesis in humans, causing hormonal imbalance. Its interaction with endocrine disruptors impairs testicular function. A study (Haun et al. 2018) of 12 men consuming 56 g/d of soy protein for four weeks revealed a 19% reduction in serum testosterone levels.

In women, high doses of genistein affect ovarian activity *via* multiple pathways, resulting in both estrogenic and antisteroidogenic effects that diminish ovarian function. This isoflavone has shown benefits in treating polycystic ovary syndrome (PCOS) (Guelfi et al. 2023). The effects of genistein on pregnancy are unclear and vary according to species, administration route, and dosage.

Genistein and the thyroid gland

Genistein shows potential as an anti-menopausal syndrome treatment, but some studies indicate it may affect thyroid disorders by inhibiting thyroid peroxidase (TPO) activity, which is crucial for synthesizing triiodothyronine (T3) and thyroxine (T4). Up to 10% of postmenopausal women might develop undetected hypothyroidism, raising concerns about the estrogen-like effects of genistein (Doerge and Sheehan 2002).

A meta-analysis (Otun et al. 2019) on the impact of soy consumption on thyroid function found significant changes in TSH levels, but not in fT3 and fT4 levels, suggesting that the adverse effects of soy on thyroid function in healthy adults may not be clinically significant. However, two studies (Sathyapalan et al. 2017a, 2017b) observed significant increases in TSH and decreases in fT4 after 12 weeks of soy protein and isoflavone supplementation, without resulting in subclinical or significant hypothyroidism.

A randomized trial (Sathyapalan et al. 2011) with 60 subclinical hypothyroidism patients who consumed 16 mg of phytoestrogen daily for six months found that 11.5% progressed to significant hypothyroidism, a rate three times higher than the low-dose group [standardized ratio 3.6 (95% CI = 1.9,6.2)].

Thus, while genistein has less impact on those without subclinical hypothyroidism, further research and caution are needed for its use in pregnant women, infants, and patients with subclinical hypothyroidism.

Genistein and allergy

Genistein, a soybean metabolite, can cause allergic reactions (allergies). Soy allergy usually begins in childhood and presents as an allergic reaction to soy infant formula. Symptoms include paresthesia, eczema, itchy skin, wheezing, diarrhea, stomachache, vomiting, and red skin. However, most children overcame the soy allergies. Although soybean allergies can cause discomfort, the results are not serious and do not lead to fatalities (Warren et al. 2020).

Discussion

The anticancer potential of genistein, a natural phytochemical, against breast cancer has been confirmed in numerous studies. As an isoflavone, genistein shares a structure similar to that of

estrogen and can regulate the proliferation, apoptosis, and migration of breast cancer cells through the estrogen receptor pathway, tyrosine kinase inhibition, and antioxidant effects. Compared with traditional chemotherapeutic drugs, genistein exhibits a milder and more diverse mechanism of action, showing distinct advantages in inhibiting cancer cell proliferation, inducing apoptosis, and suppressing tumor invasion.

Although genistein has demonstrated strong anticancer potential *in vitro*, its clinical application has faced challenges. This discrepancy is closely related to the bioavailability of genistein, which is characterized by low absorption rates and rapid metabolism *in vivo*, limiting its anticancer effects in clinical settings. However, recent advancements in drug delivery systems, such as nanocarriers and liposomes, have significantly enhanced the concentration of genistein in cancer cells, thereby improving its anticancer efficacy. With these advancements, the issue of low bioavailability may no longer pose a significant barrier to its clinical application.

The anticancer mechanism of genistein in breast cancer involves multiple molecular pathways, including regulation of the cell cycle, antioxidant and anti-inflammatory activities, binding to hormone receptors, and modulation of cytochrome P450(CYP450) enzymes. Additionally, genistein activates key signaling pathways such as MAPK/ERK, which support tumor cell growth and survival. Despite gradual elucidation of genistein's mechanism of action, several unresolved questions remain. For example, studies have reported variability in the effects of genistein across different cell lines, dosages, and administration methods, suggesting that its mechanism of action may be context-dependent and complex. Moreover, there is still no consensus regarding the differential effects of genistein on various breast cancer subtypes.

Furthermore, according to available clinical research, the effect of genistein as a single therapeutic agent remains limited. The heterogeneity of breast cancer complicates the use of genistein as a monotherapy. Therefore, future research should focus on exploring the potential of genistein for breast cancer prevention, particularly in high-risk groups. Additionally, investigating the synergistic effects of genistein with conventional chemotherapeutic drugs, targeted therapies, and immunotherapies will be a key area for future study. Combination therapy with genistein may enhance the efficacy of chemotherapeutic drugs, overcome chemotherapy resistance, improve immune responses, and reduce chemotherapy side effects. This approach is expected to offer new strategies for individualized breast cancer treatment and facilitate the broader clinical application of genistein.

The incidence of breast cancer is significantly higher in Western countries than in Asian countries (Sung et al. 2021). Traditionally, this disparity has been attributed to established risk factors such as early menarche, late first pregnancy, and delayed menopause (Collaborative Group on Hormonal Factors in Breast Cancer 2012). However, recent studies have suggested that dietary habits may play a critical role (Wan et al. 2022). The dietary preference for soy-based foods among Asian populations may be a key factor contributing to their lower incidence of breast cancer. Against this backdrop, genistein, a natural compound, has gained attention owing to its potential role in breast cancer prevention and treatment. For instance, in postmenopausal women with low estrogen levels, genistein may modulate hormone receptors *via* alternative pathways, reducing dependence on estrogen, and potentially influencing breast cancer progression. Additionally, its effect on metabolically active breast tissue during adolescence warrants further investigation to better understand its role in breast cancer risk. Therefore, genistein holds significant promise as a bioactive supplement in future research and applications.

Another challenge is the potential side effects of genistein. The research by Sathyapalan et al. shows that although it is relatively low in toxicity, high doses may lead to hormone imbalances, reduced testosterone synthesis, and potential thyroid dysfunction. Further clinical data are needed to confirm the safety of its long-term use.

Future research should focus on the following key areas:1. Conduct in-depth studies on the mechanism of genistein, particularly regarding its differential effects in various subtypes of breast cancer.2.Explore the clinical therapeutic effects of genistein in combination with chemotherapeutic agents and targeted therapies, such as genistein and taxanes, especially in overcoming chemotherapy resistance.3.Additional clinical trials are required to evaluate the efficacy and safety of genistein in patients of different ages and physiological conditions.

Conclusions

This review highlights the anticancer potential of genistein in breast cancer, particularly in combination therapies with chemotherapeutic agents, targeted therapies, and immunotherapies. Despite promising results in various experiments, the clinical application of genistein faces challenges, particularly because of its low bioavailability. However, advancements in drug delivery systems have offered potential solutions for enhancing their therapeutic efficacy.

The innovative contribution of this review is its comprehensive exploration of the therapeutic effects of genistein across different regions and physiological states, including its use in various populations, such as prepubertal, menopausal, and postmenopausal women. This review also highlights the potential of genistein as a preventive agent and its synergistic effect with conventional treatments. Furthermore, it analyzed both the benefits and risks of genistein use, providing valuable insights for personalized breast cancer treatment strategies.

Future research should focus on optimizing the bioavailability of genistein, further exploring its clinical applications, and conducting extensive trials to confirm its safety and efficacy in diverse patient populations, especially in high-risk groups.

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No potential conflict of interest was reported by the author(s).

Author contributions

CRediT: **Zhebin Xiang**: Conceptualization, Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing; **Bo Ma**: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing; **Xiujun Pei**: Data curation, Investigation; **Wenjie Wang**: Data curation, Investigation, Methodology; **Weilun Gong**: Investigation, Visualization, Writing – review & editing.

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Data availability statement

The data supporting the findings of this review were collected from publicly available sources, including PubMed, ScienceDirect, and Google Scholar, following the PRISMA guidelines. These data consist of published research studies and clinical trial results on genistein and its effects on breast cancer. No new datasets were generated during this study. All data are available in the cited references and can be accessed through the respective databases.

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