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Molecular Mechanisms of Genistein in Breast Cancer: From Oxidative Stress to Oncogenic Pathway Inhibition

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Abstract: Genistein (GT), a soy-derived isoflavone, have received attention due to their possible anticancer effects. The present research is designed to explore the anticancer potential of GT in the therapeutic management of breast cancer (BC) with molecular mechanisms. For this, data have been collected from plausible different online databases, including PubMed, Web of Science, Google Scholar, PubChem, ScienceDirect, Scopus, Springer Link, and Wiley Online. The findings highlight GT's potential to reduce oxidative damage, induce apoptosis, and modulate the cell lifecycle in BC cells. It inhibits cancer cell proliferation by affecting the human epidermal growth factor receptor 2 (HER2), phosphoinositide 3-kinase/ protein kinase B (PI3K/ AKT), and hedgehog regulatory pathways. Moreover, GT exhibits promising pharmacokinetic properties, including high intestinal absorption (95.5%) and strong Caco-2 permeability, with metabolism primarily via CYP1A2 and CYP2C19. However, its poor blood-brain barrier (BBB) permeability and low water solubility present difficulties to the systemic bioavailability. Toxicological investigations demonstrate a dose-dependent effect of GT, with large dosages causing toxicity and low concentrations showing therapeutic potential. Clinical studies emphasize its complex involvement in BC, with differing findings on benefits and risks, indicating the need for additional safety and efficacy study.

Keywords: Genistein; isoflavone; oxidative stress; breast cancer; cytotoxicity; botanical sources.

1. Introduction

Cancer is defined as a process of uncontrolled cell growth with no useful function or capacity to invade other organs or interfere with the body's normal cells (Greaves, 2001). Cancer is a severe worldwide burden on health as well as one of the top causes of death (Ma & Yu, 2006). 10 million fatalities in 2020 were linked to cancer, which is the second-largest cause of death globally (Cao et al., 2021). BC is one of the most prevalent kinds of cancer diagnosed in women globally, and it is the leading cause of mortality among them. In 2020, there were an anticipated 2.3 million new cases of BC (1 in 4 new cases) and 685,000 cancer deaths (1 in 6 deaths) related to BC (2.26 million cases) (Khazaei et al., 2023). The total number of instances of newly identified BC is anticipated to climb by more than 40% by 2040, exceedingly around three million instances per year (Arnold et al., 2022).

Normally, interactions between cells maintain homeostasis and a balance between the cell division and deaths of cells (Gómez-López et al., 2014). The balance is thrown off in cancer, and the cell starts to grow out of control (Sarkar & Li, 2006). Certain malignant disorders are caused by common mechanisms that cause DNA damage, while specific DNA damage causes cancer (Alhmoud et al., 2021). The risk of BC rises with the period of menarche, time at menopause, number of children, and the duration of breastfeeding (Sayed et al., 2021). About 5–10% of BC cases include a genetic or hereditary component, such as BRCA1 or BRCA2 mutations; nevertheless, eight out of nine female patients diagnosed with BC do not have a first-degree female family member who is impacted (Feng et al., 2018).

A group of genes known as proto-oncogenes are responsible for the development of cancer when they are changed from healthy cells (Brown, 2021). An oncogene is defined as a mutated proto-oncogene. Thus, a major molecular target for the creation of anti-cancer medications is oncogenes, and the kind and stage of cancer determine the course of treatment (Sarfati et al., 2016). BC is categorized into three subgroups depending on ERBB2 gene amplification and the existence of an estrogen or progesterone

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receptor in the cell. All of the three subtypes have their own risk assessment and medication plan (Łukasiewicz et al., 2021).

For non-advanced BC, surgery is the preferred course of treatment; adjuvant therapies such as hormone therapy, chemotherapy, and radiation are also beneficial in reducing the chance of relapse and enhancing long-term survival (Ciria-Suarez et al., 2021). These therapies affect a person's individuality, appearance, self-worth, social interactions, and sexual performance by altering their physical characteristics and sexuality as well as the rate of fertility (Brierley et al., 2019). Fatigue, hair loss, cytopenia, muscle discomfort, neurocognitive disability, and chemo-induced peripheral nerve damage are among the early adverse effects of chemotherapy that occur within the first six months of treatment. Cardiomyopathy, subsequent malignancies, early menopause, sterility, and psychological impacts are among the long-term or delayed adverse effects (occurring after 6 months of therapy) (Burguin et al., 2021). Many anticancer medications are available with various restrictions that are vital to the treatment of cancer, including paclitaxel, imatinib, rituximab, tamoxifen, cisplatin, and bevacizumab (Mitra et al., 2015). Present-day conventional anticancer drugs not only inhibit the development of cancer cells but also negatively impact the proliferation of healthy, non-proliferative cells (Billy & Clairambault, 2013). Women are beating BC more often, but because of therapy, up to 90% of them get unanticipated long-term side effects (Lovelace et al., 2019). BC survivors may have physical, practical, sentimental, and psychological problems that greatly impact their overall state of life (De Ligt et al., 2019). Because of the limits of standard therapies and the abundance of costly anticancer therapy technologies now accessible, discovering a novel anticancer medication is crucial to saving lives.

Management of BC as a whole is fraught with difficulties when it comes to predictive diagnostics, risk assessment, focused management of metastatic disease, suitable treatment alternatives, and the economic viability of used strategies (Mazurakova et al., 2022). As rates of incidence rise in developing nations throughout the world, the global burden of BC will undoubtedly increase, but a short lifespan does not have to be an unavoidable result (Wilkinson & Gathani, 2022).

Phytochemicals, which are secondary metabolites produced by plants, are non-nutrient chemical compounds that serve as a significant source of medicinal agents owing to their wide range of pharmacological properties (Islam et al., 2025; Jahan et al., 2025). Numerous biological actions, such as antimicrobial, immunomodulatory, anti-inflammatory, antioxidant, and anticancer effects, are exhibited by phytochemicals, either in isolation or in blends with whole plant diets (Das et al., 2021). Furthermore, phytochemicals are frequently accessible, reasonably priced, and may have few adverse effects. Morphine from the opium poppy, quinine from the cinchona tree, digoxin from the foxglove plant, and L-DOPA from the velvet bean are used in managing severe pain, malaria, congestive heart failure, atrial fibrillation, and Parkinson's disease, respectively (Roy et al., 2019). The phytochemicals vinblastine, vincristine, paclitaxel, etoposide, and camptothecin are common anticancer drugs that are derived from different plants.

Genistein (GT) (C15H10O5) is a flavonoid group of polyphenolic isoflavones that is frequently present in a variety of dietary plants, including fava and soybeans (Jaiswal et al., 2019). It is extensively dispersed within the Fabaceae family and was initially isolated from Dyer's Genista tinctoria L., a broom plant. Mammal GT acts like estrogen when used as isoflavone (Tuli et al., 2019). GT's antiviral, antioxidant, antibacterial, and angiogenesis-promoting capabilities, as well as its pharmacological effects on lipid metabolism and diabetes, have all been demonstrated in preclinical study (Sharifi-Rad et al., 2021). It is described as an angiogenesis inhibitor and a phytoestrogen (Bhat et al., 2021). Since isoflavones have been linked to a number of advantageous outcomes, including the reduction of menopausal symptoms, breast and prostate cancers, cardiovascular disease, osteoporosis, obesity, diabetes, and viral infections, the market for soy-based products has expanded significantly (Sharifi-Rad et al., 2021). This review emphasizes the anticancer activity of GT in BC. For this goal, we have compiled the most recent information on this promising anticancer agent for BC.

2. Methodology

2.1. Search strategy

An up-to-date (12 March 2025) search was made in the various databases, such as PubMed, Web of Science, Springer Link, Google Scholar, Wiley Online, and ScienceDirect, with the popular term "genistein," which then became associated with "tumor," "anticancer activity," "cancer," "antiproliferation activity," "chemical features," "antitumor activity," "cytotoxic activity," "human cancer," "pharmacological effects," "biological activities," "pharmacological activities," "biological sources," "in vitro studies", or "in vivo studies". The search parameters did not include any time or language limits. The complete assessment of the studies included the sources, test system, dose/concentration, proposed action mechanism, overall result, and recommendations.

2.2. Inclusion criteria

(1) Studies conducted in vivo, in vitro, or ex vivo with or without the use of laboratory animals such as rats, mice, rabbits, and human beings, as well as tissues or cells produced from them. (2) Research that suggests potential mechanisms of action or does not. (3) Studies on GT's botanical sources and anticancer properties. (4) When combined with other chemicals, GT shows synergistic effects.

2.3. Exclusion criteria

(1) Research showed duplicate data and titles and/or abstracts that didn't fit the requirements for inclusion. (2) GT appears in other research that does not address that particular issue. (3) Papers authored in languages apart from the English language. (4) Studies that aren't fully available. (5) Letters, opinions, commentary, and case reports.

3. Results

3.1. Botanical sources of genistein

A natural substance is a secondary metabolic product produced by living things that is recognized for its unique chemical variety and therapeutic qualities (Elshafie et al., 2023). Natural substances have long been used to develop anticancer drugs due to their structural diversity and biological activity (Naeem et al., 2022). Many chemotherapeutic drugs, such as camptothecin from Camptotheca acuminata and paclitaxel from Taxus brevifolia, have been developed from plants, demonstrating their potential in cancer treatment (Newman and Cragg, 2020). In addition, marine organisms, fungi, and microbes have led to the creation of novel anticancer medicines, such as actinomycin D from Streptomyces species and trabectedin from Ecteinascidia turbinate (Atanasov et al., 2021). The success of these natural substances emphasizes their importance in identifying lead compounds for modern anticancer therapeutics, particularly through mechanisms like induction of apoptosis, cell cycle arrest, and prevention of angiogenesis (Cragg and Pezzuto, 2016). GT can effectively treat various kinds of illnesses (Sharifi-Rad et al., 2021; Wegrzyn et al., 2010). GT, a bioactive phytochemical, is found in many plant species. Pueraria lobata root showed anti-inflammatory and antioxidant effects (Jin et al., 2012). Numerous studies assess pharmacological therapies

for chronic disorders, emphasizing the importance of investigating alternative therapy options such as natural cures derived from medicinal plants (Goyal et al., 2024). The fruit and seed of P. corylifolia are commonly used in traditional Chinese medicine for skin diseases and as a tonic (Mahajan et al., 2022). However, all botanical sources are arranged in **Table 1.**

3.2. Physicochemical properties and pharmacokinetics

Pharmacokinetics (PKs) is vital in drug discovery as it improves ADME features of promising candidates (Theil et al., 2003). The goal is to produce a candidate for clinical use with an appropriate concentration-time pattern in the human body, resulting in optimal efficacy and safety (Reichel & Lienau, 2016). A well-defined ADME profile ensures the best medication concentration at the target site while avoiding toxicity and adverse effects (Dahan et al., 2017). Poor absorption or quick metabolism may elevate to subtherapeutic levels, although slow clearance might cause drug buildup and toxicity (Roberts & Buckley, 2007; Singh & Malhotra, 2004). Furthermore, factors like the binding of proteins, tissue permeability, and metabolic pathways alter a drug's bioavailability and half-life, influencing its dosing regimen (Stielow et al., 2023; Benedetti et al., 2009). Understanding pharmacokinetics is vital for optimizing lead compounds and regulatory approval, as ADME studies assess clinical suitability. Advances in modeling and in vitro screening aid early prediction, reducing failures and improving drug design (Roy & Nandi, 2019; Pantaleão et al., 2016). Oral administration of GT causes absorption of this chemical with a t1/2 of 8 hours and tmax of 5–6 hours (Setchell et al., 2003; Chandrasekharan & Aglin, 2005; Setchell et al., 2001). Only 20-40% of oral GT is absorbed from the gastrointestinal tract and enters the enterohepatic cycle. Hence, the oral absorption of GT from the GI tract is relatively poor, resulting in low bioavailability (Yang et al., 2012). GT spreads fast across the body and crosses the placenta as well as BBB, with the largest concentrations found in the gastrointestinal system and liver. A human investigation discovered that its mean volume of distribution, standardized for bioavailability, clearance rate, and half-life, was 258.76 L, 21.85 L/h, and 7.77 h, respectively (Chandrasekharan & Aglin, 2013). The low water solubility of GT is generally the cause of its limited bioavailability following oral dosing (de Oliveira, 2016; Motlekar et al., 2006). The area under plasma concentration (AUC) of GT is 31,269.66 ng h/mL, while its maximum plasma concentration (Cmax) is 4,876.19 ng/mL (Kwon et al., 2007). Conversely, our ADME prediction examines GT's pharmacokinetics and bioavailability, essential factors for clinical application. With a molecular weight of 270.24 g/mol and moderate lipophilicity (log Po/w = 2.67), GT exhibits drug-like properties and complies with Lipinski's Rule of Five. The compound exhibits high intestinal absorption at 93.387%, demonstrating efficient uptake through the gastrointestinal tract. Its low skin permeability, with a log Kp value of –2.735, indicates minimal absorption through the skin. Additionally, it does not interact with P-glycoprotein, which facilitates cellular uptake. However, its limited central nervous system (CNS) penetration is reflected by its low BBB permeability (log BB = –0.71), and its restricted tissue distribution is suggested by a low volume of distribution (–0.066 log L/kg). The compound is metabolized by enzymes, including CYP1A2 and CYP2C19, which influences its metabolic profile and potential for drug-drug interactions. It demonstrates moderate clearance, with a log value of 0.151 ml/min/kg, and does not act as a substrate for renal OCT2, suggesting moderate excretion rates. These pharmacokinetic properties are crucial for evaluating its therapeutic effectiveness and safety profile. **Table 2** presents the predicted PK parameters of GT as analyzed by SwissADME and pkCSM.

Table 1. The botanical sources, plant parts and extraction methods of Genistein.

Plant name	Plant part	Extraction method	References
Trifolium pratense	Leaf	HPLC	Delmonte et al., 2006
Chenopodium quinoa Willd.	Seed	HPLC	Lutz et al., 2013
Lupinus luteus L.	Root	HPLC	Kneer et al., 1999
Vicia faba	Seed	Solvent Extraction	Kaufman et al., 1997
Psoralea corylifolia	Fruit	-	Shinde et al., 2009
Sophora japonica L.	Fruit	HPLC	Tian et al., 2004
Lupinus albus	Seed	Solvent Extraction	Kaufman et al., 1997
Desmodium gangeticum L.	Seed	HPTLC	Patil et al., 2016
Flemingia vestita	Tuberous root	HPTLC, HPLC	Shailajan et al., 2014
Psoralea corylifolia	Leaves	Solvent Extraction	Kaufman et al., 1997
Glycine max	Fruit	-	Pomfrey, 2013
Pueraria lobata	Root	Solvent Extraction	Kaufman et al., 1997
HPLC: High-performance liquid chromatography; HPTLC: High performance thin layer chromatography			

3.3. Anticancer effects of genistein: Underlying mechanism of action

3.3.1. Induction of oxidative stress

Inducing oxidative stress (OS) has been identified as a novel approach in cancer therapy. This technique enhances anti-cancer effects by increasing OS levels within tumors or certain organelles and chemicals found in cancer cells. Consequently, it significantly reduces the oxidative damage to normal tissues (Jiang et al., 2023). Several signaling pathways associated with the development of tumors can also control the metabolism of reactive oxygen species (ROS) through direct or indirect means (Gorrini et al., 2013).

The presence of molecular oxygen causes the reoxidation of Cu (I) to Cu (II), resulting in the production of ROS (Ahmad et al., 2000). Elevated amounts of ROS can exceed the antioxidant capacity of cells, resulting in permanent damage and programmed death of cells (apoptosis) (Kong et al., 2000).

Ullah et al. (2011) found that the use of GT at a concentration of 50 μM caused the death of BC cells (MDA-MB-231 and MDA-MB-468). This was achieved by activating the release of naturally occurring copper ions and the production of reactive oxygen species.

Superoxide dismutase, catalase, and thiourea, which are scavengers of ROS, were found to suppress the antiproliferative and apoptotic effects elicited by GT in both BC cell lines. During a separate inquiry, the utilization of GT caused a considerable increase in GPx expression and a substantial reduction in MnSOD, CuZnSOD, and TrxR mRNA expression. The manipulation of antioxidant enzyme and apoptotic signaling expression led to cell death in MCF-7 cells (Prietsch et al., 2014).

3.3.2. Cytotoxic effects

The cytotoxicity of a small molecule plays an important role in deciding its outcome in the drug discovery process (Sun et al., 2020). Cytotoxicity assays are commonly conducted to evaluate the potential toxicity of test chemicals, such as plant-derived extracts and purified compounds, which may be intended for pharmaceutical application. In this context, it is crucial to ensure low or no toxicity. Alternatively, the compounds can be formulated as anticancer medicines, necessitating the crucial need for specific cytotoxicity toward malignant cells (McGaw et al., 2014).

Table 2. Different pharmacokinetics parameters of Genistein.

Properties	Factors	Genistein
Physicochemical Properties	Formula	$C_{15}H_{10}O_5$
	MW (g/mol)	270.24 g/mol
	Heavy atoms	20
	Aromatic heavy atoms	16
	HB donors	3
	HB acceptors	5
	Molar refractivity	73.99
Lipophilicity	Log $P_{o/w}$ (XLOGP3)	2.67
Drug-likeness	Lipinski	Yes; 0 violation
	Bioavailability score	0.55
Water Solubility	Log S (ESOL)	−3.72
	Class	Soluble
Absorption	Caco2 permeability (log Papp in 10-6 cm/s)	0.9
	Intestinal absorption (human) numeric (% Absorbed)	93.387
	Skin permeability (log Kp cm/h)	−2.735
	P-glycoprotein I Inhibitor	No
	P-glycoprotein II Inhibitor	No
Distribution	BBB permeability (log BB)	−0.71
	CNS permeability (log PS)	−2.0488
	VDss (human) (log L/kg)	0.094
Metabolism	CYP1A2 Inhibitor	Yes
	CYP2C19 Inhibitor	Yes
	CYP2C9 Inhibitor	No
	CYP2D6 Inhibitor	No
	CYP3A4 Inhibitor	No
Excretion	Total clearance (log ml/min/kg)	0.151
	Renal OCT2 substrate	No
HB: Hydrogen bonds; MW: Molecular weight; BBB: Blood brain barrier; CNS: Central nervous system		

GT has been found to exhibit cytotoxic effects on several cell lines in multiple experiments. Given its cytotoxic qualities, it appears to be a promising option for investigating its potential anticancer effects. The potential of GT to induce cytotoxicity was assessed in a study conducted by Kim et al. (2019), using MDA-MB-231 and HCC1937 cells. The results showed promising effects of GT in causing cell death. GT demonstrated a cytotoxic effect (with an IC50 value of 56.8 ± 0.9 μM) against MCF-7, SK-BR-3, and MDA-MB-468 cell lines. However, when combined with equol (dose of 50 μM), GT exhibited a potent cytotoxic effect (IC50 value of 40.7±2.7 μM) specifically against MCF-7 cells, but not against SK-BR-3 and MDA-MB-468 cells (Ono et al., 2017). Various investigations have provided substantial evidence of GT's cytotoxic effects on different cancer cell lines, such as MDA-MB-435, Hs578t, MDA-MB-231, and MCF-7. The concentrations used in this research ranged from 2.5 to 100 μM, demonstrating its potential for cancer treatment (de la Parra et al., 2016; Fan et al., 2013; Xie et al., 2014).

3.3.3. Cell cycle arrest

The cell cycle is an extremely maintained biological procedure that closely governs cellular growth, development, and differentiation (Bai et al., 2017). It plays a crucial role in controlling cell proliferation and division and growth following DNA damage. The process regulates the shift from a state of inactivity (G0) to cell growth, and by means of its checkpoints, guarantees the correctness of the biological transcription (Schwartz and Shah, 2005). The cell cycle is frequently disrupted in cancer cells, leading to uncontrolled cell divisions. Consequently, targeting the cell cycle is a potential strategy for treating diseases characterized by excessive cell growth, such as cancer (Williams and Stoeber, 2012). Anti-cancer treatment disrupts the growth cycle of cancer cells by impeding or harming processes in the cell cycle, which

trigger checkpoints, halt cell division, and initiate programmed cell death (Manchado et al., 2012).

Research has shown that GT has the ability to suppress the development of tumor cells by interfering with different steps of the cell cycle. GT has the ability to interrupt the cell cycle of MCF-7 cells specifically at the G1 phase. However, when combined with equol, it stops the cells at the G2/M phase while eliminating the equol-induced G1 block. This suggests that GT acts as an antagonist to equol in the advancement of the cell cycle (Ono et al., 2017). GT (10 –100 μM) reduced the number of cells and caused cell cycle arrest in the G2/M phase by suppressing cyclin B1 expression in BRCA1-mutant cells (Kim et al., 2019). A study conducted by Fang et al. (2016) found that GT-induced cell cycle arrest in the G2/M phases of triple-negative BC (TNBC) cells resulted in anti-cancer effects. Zhao et al. (2016) found that GT exhibited anti-cancer properties by halting the G0/G1 phase of the cell cycle in the MCF-7-C3/CIP2A and T47D/CIP2A cancer cell lines. Multiple investigations have demonstrated that in two particular cell lines, it causes cell cycle arrest at the G2/M phase, namely MDA-MB-231 and SKBR3. The dose required for this effect ranges from 5 to 40 μM (Ye et al., 2018; Pan et al., 2012).

3.3.4. Apoptotic effects

Apoptosis, also defined as programmed cell death, is often defined by certain physical traits and metabolic activities that need energy (Elmore, 2007). Apoptosis, essential for growth and tissue balance, is triggered by intracellular signals like genotoxic stress or extracellular signals like ligand-receptor interactions (Pistritto et al., 2016). Both the inherent and external apoptotic pathways employ caspases to execute apoptosis by cleaving many proteins. In cancer, the process of programmed cell death, known as apoptosis, is usually hindered through various mechanisms, such as the excessive production of proteins that prevent apoptosis and the insufficient production of proteins that promote apoptosis (Pfeffer and Singh, 2018). Increasing data suggests that apoptosis plays a crucial role in cancer survival and has become a primary focus for the identification and creation of new anticancer medications (An et al., 2019).

Various mechanisms are involved in controlling apoptosis in cancer cells. The PI3K/AKT signaling pathway is a crucial intracellular mechanism that plays a significant role in controlling apoptosis and cell survival (Meng et al., 2017). The MAPK (mitogen-activated protein kinase) signaling pathways control several biological processes through numerous cellular mechanisms. MAPKs play a dual role in many processes, such as apoptosis, as they can function as either activators or inhibitors. The specific role they play depends on the kind of cell and the stimulus involved (Yue and López, 2017). The Notch signaling system can play a role in promoting cell survival or inducing cell death, stimulating cell proliferation or triggering apoptosis, facilitating the activation or inhibition of cell differentiation, and preventing the invasion or promoting the metastasis of cells (Aster et al., 2017). Also, numerous factors, primarily proteins, have been identified as crucial regulators of apoptosis. Among the most important are caspases, amyloid-B peptide, the Bcl-2 protein family, the p53 gene, and heat shock proteins (Papaliagkas et al., 2007).

Based on a research report, GT has been found to induce programmed cell death in MCF-7, T47D, and HEK 293T cell lines by reducing the expression of CIP2A. This reduction is linked to a drop in total caspase-3 levels and an increase in the cleavage of caspase-3 and PARP (Zhao et al., 2016). Another study additionally discovered the participation of GT in apoptosis and demonstrated GT's capacity to inhibit the expression of Skp2. Furthermore, the levels of p21 and p27 proteins were elevated in human MDA-MB-231 and SKBR3 cell lines (Ye et al., 2018). The results of a study conducted by Ono et al. (2017) showed that apoptosis was not very noticeable when GT was used alone. However, when GT was combined with equol, there was a significant increase in apoptosis. This rise was associated with an increased Bax/Bcl-xL expression ratio, although the activities of Akt and mTOR showed no change. Additionally, a separate study revealed that GT promoted apoptosis in MCF-7 human BC cells by suppressing HOTAIR expression via the PI3K/AKT signaling pathway (Chen et al., 2015b). GT triggered apoptosis in the MCF-7 cell line by activating the MAPK signaling pathway through the activation of calpain and caspase 7 (Shim et al., 2007). In addition, GT induced programmed cell death by increasing the expression of Bax and decreasing the expression of Bcl-2 in the MCF -7 cell line, leading to a significant decrease in the Bcl-2/Bax ratio (Chen et al., 2015a). At a concentration of 50 μM, GT triggered programmed cell death by downregulating the expression of the antiapoptotic protein Bcl-2 and upregulating the expression of the proapoptotic protein Bax and activating caspase 3 (Ullah et al., 2011). When tested on the cancer cell line MDA-MB-231, Pan et al. (2012) found that GT reduced the levels of cyclin B1, Bcl-xL, and Bcl -2. This effect may be due to the activation of NF-κB through the Notch-1 signaling pathway. In their study, Fang et al. (2016) observed that GT induces apoptosis in MDA-MB-231 cells by triggering DNA damage responses, specifically by activating the ATR and BRCA1 complexes (Fang et al., 2016). Multiple investigations have demonstrated that it promotes apoptosis in the MCF-7 cell line at concentrations ranging from 0.01 to 200 μM (Prietsch et al., 2014; Choi and Kim, 2013; Chinni et al., 2003).

3.3.5. Anti-proliferative effects

Proliferation is a crucial component of cancer initiation and advancement. This is evident by the modification of expression and/or function of proteins associated with the cell cycle. Activation of several signal transduction pathways leads to the stimulation of cell growth (Feitelson et al., 2015). The HER2 signaling pathway has significant functions in cell growth, survival, and differentiation, operating in a complicated manner (Tai et al., 2010). The PI3K/AKT signaling system governs various fundamental biological activities, such as cell proliferation, survival, growth, and motility, which play an important role in the growth of malignancies (Engelman, 2009; Downward, 2010; Luo et al., 2003; Gustafson et al., 2010), and additionally, it stimulates cellular proliferation in different mammalian cells, a process that is facilitated by insulin-like growth factor (IGF)-1 (Resnicoff et al., 1993). Investigation has established that the hedgehog signaling pathway plays a vital role in the formation of malignancies by influencing the growth, aggressiveness, dissemination, and increase in cancer stem cells at the level of molecules (Sari et al., 2018).

GT was discovered to possess the capacity to inhibit the growth of human HER2-positive malignancy cells by impeding the cellular proliferation process mediated by the HER2 signaling pathway (Shen et al., 2013). A separate study found that GT inhibited the growth of MCF-7 BC cells at concentrations ranging from 20 to 80 μM. The suppression was accomplished via the IGF-1R-PI3K/AKT pathway, which governs the cell cycle, cell growth, and cell proliferation (Chen et al., 2015a). GT inhibited the development of MCF-7 cells via the hedgehog regulatory pathway (Fan et al., 2013). Pan et al. (2012) found that GT treatment at a dosage of 15 mg/ml resulted in a significant decrease in the proliferation of MDA-MB-231 cells. This effect was achieved via increasing the expression of Cx43 protein. In Zhao et al. (2016), the MTT assay revealed that GT, at concentrations of 30 and 60 μM, effectively inhibited the growth of MCF-7 and T47D cells. GT, at concentrations ranging from 5 to 20 μM, decreased the methylation of BRCA1 CpG and the proliferation of MCF-7 cells. This effect was accompanied by an increase in p53 levels (Romagnolo et al., 2017). Prietsch et al. (2014) discovered that GT triggered the death of MCF-7 cells via altering the apoptosis

and autophagy pathways. GT inhibited cell proliferation by increasing ERα expression in MCF-7, MDA-MB-231, and MDA-MB-157 cells (Choi and Kim, 2013). Various studies have provided substantial evidence of GT's antiproliferative effects on different cancer cell lines, such as MDA-MB-231, SKBR3, MCF-7, T47D, and MDA-MB-468. These effects were observed at concentrations ranging from 5 to 100 μM, indicating the potential of GT as a therapeutic agent against cancer (Ye et al., 2018; Pan et al., 2012; Chen et al., 2015a; Ullah et al., 2011).

3.3.6. Autophagy

Autophagy is a biological mechanism that destroys proteins and organelles. It occurs through the engulfment of these components into autophagosomes, which are then destroyed in lysosomes. The purpose of autophagy is to recycle these materials in order to support cellular metabolism and maintain homeostasis (Yang et al., 2011). Autophagy in cancer biology has a dual function, both promoting and suppressing tumor growth, while also contributing to the formation and the proliferation of malignant cells (Lim and Staudt, 2013; Salminen et al., 2013). Certain antineoplastic medications have the ability to modulate autophagy. Autophagy-regulated chemotherapy can either increase cancer cell survival or cause cell death (Rosenfeldt et al., 2011; Gewirtz, 2014).

A current study proposed that GT may possess anticancer properties for the prevention of BC by stimulating autophagy. This phenomenon arises from the advancement of autophagy through the reduction of antiapoptotic survivin, an increase in the BAX/Bcl-2 ratio, and changes in the redox state of cancer cells (Prietsch et al., 2014).

3.3.7. Inhibition of invasion and migration

A recent study suggested that GT may have anticancer effects for treating BC via promoting autophagy. This process occurs due to the progression of autophagy, which is facilitated by the decrease in antiapoptotic survivin, an increase in the BAX/Bcl-2 ratio, and alterations in the redox state of cancer cells (Gattringer et al., 2023). Invasion and diffusion from primary solid tumors are crucial for the formation of deadly secondary metastases in distant organs (Polacheck et al., 2013). Multiple studies have substantiated the presence of two primary modes of cancer cell invasion: collective and individual cell migration. These mechanisms enable tumor cells to surmount obstacles within the extracellular matrix and disseminate into neighboring tissues (Krakhmal et al., 2015). Assessing the migratory and invasive abilities of tumor and stromal cells, as well as understanding the underlying mechanisms, is crucial for developing new approaches in cancer diagnosis, prognosis, medication development, and treatment (Kramer et al., 2013).

Research conducted by Ye et al. (2018) showed that GT, at concentrations of 20 or 40 μM, effectively hinders the movement and infiltration of MDA-MB-231 and SKBR3 cell lines. This inhibition is directly proportional to the dosage administered. According to a recent experiment, GT at doses between 10 and 100 μM inhibits colony formation and migration. Both MDA-MB-231 and HCC1937 cells exhibited decreased migration, with the reduction being more prominent in HCC1937 cells (Kim et al., 2019).

3.3.8. Genotoxic effect and mutagenic effects

Anticancer medications can also function by inducing genotoxic and mutagenic impacts on cancerous cells. These processes are also documented as cytotoxic (Asgharian et al., 2022; Buga et al., 2022). Recently, the efficacy of genotoxic drugs has been significantly enhanced through the identification and characterization of molecules that specifically target DNA damage and cell cycle checkpoints (Swift and Golsteyn, 2014). The ATR signaling pathway is crucial because it is necessary to address the replication stress resulting from both spontaneous DNA damage and challenging-to-replicate sections of the genome, such as fragile spots (Brown and Baltimore, 2003). Fang et al. (2016) reported that GT caused DNA damage in MDA-MB-231 cells and triggered the activation of BRCA1 -A and -B complexes through the ATR signaling pathway (Fang et al., 2016).

3.3.9. Miscellaneous effects

The secretion of growth factors by mammary adipose tissue has a significant role in the survival of cancer cells. Therefore, it is imperative to regulate the secretion of adipose tissue while designing anticancer drugs (Kothari et al. 2020). The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays critical roles in regulating development, xenobiotic metabolism, cell cycle progression, and cell death. Activation of the AhR by particular ligands can promote tumor suppression in several types of cancer (Elson et al., 2023).

GT was observed to decrease the size of breast adipocyte cells and increase the expression of PTEN and E-cadherin in the mammary gland. The study found that GT suppressed adipose development and reduced the creation of anchorage-independent mammospheres in human MCF-7 BC cells (Montales et al., 2013). According to Donovan et al. (2019), GT shows potential as a treatment drug for triple-negative BC (TNBC) with activated AhR via activating BRCA1 through epigenetic mechanisms.

This study demonstrates that GT has powerful anticancer properties by producing oxidative stress, causing apoptosis, and suppressing cancer cell proliferation, migration, and invasion. It interrupts the cell cycle throughout the G1 and G2/M phases, inhibits critical oncogenic pathways (HER2, PI3K/AKT, Notch, and MAPK), and promotes autophagy, resulting in cancer cell death. GT also causes genotoxic effects by activating the ATR and BRCA1 complexes, which inhibit DNA replication. Furthermore, it regulates epigenetic pathways and inhibits mammary adipose formation, which contributes to its anticancer properties. These results highlight GT's potential as a therapeutic agent for BC treatment. **Table 3** shows a detailed overview of the breast and mammary cancer activity of GT. Additionally, **Figure 1** illustrates its possible mechanism of action.

3.4. Overall mechanism of genistein's effects to signaling pathways

GT exerts its anti-cancer effects in BC by modulating several key cellular signaling pathways. It induces apoptosis by interfering with the PI3K/AKT, MAPK, and Notch signaling pathways, thereby promoting programmed cell death (Chen et al., 2015b; Shim et al., 2007; Pan et al., 2012). GT also causes cell cycle arrest primarily through the inhibition of Notch-1 signaling, halting uncontrolled cell proliferation (Pan et al., 2012). Additionally, it shows potent anti-proliferative effects by targeting the HER2, PI3K/AKT, and Hedgehog pathways, which are often dysregulated in BC (Shen et al., 2013; Chen et al., 2015a; Fan et al., 2013). Moreover, GT has been associated with genotoxic effects, potentially through the activation of the ATR pathway, which plays a role in DNA damage response (Fang et al., 2016). These multi-targeted actions make genistein a promising candidate for BC therapy.

3.5. Toxicological profile

Toxicological study is vital in drug research to assure medicine safety before clinical usage. It evaluates synthetic as well as natural chemicals for potential toxic effects (Arome & Chinedu, 2009). Natural substances can be beneficial, but they can also offer hazards

Table 3. Anticancer activity of GT in breast and mammary cancer

Compound	Cell line/ model	Dose/Conc	Efficacy, IC_{50} (exposure time)	Mechanism of action	References
Genistein	MDA-MB-231	0.5–15 mg/ml	-	↓Proliferation, ↑Cx43 protein expression	Conklin et al., 2007
	MCF-7, T47D and HEK 293T	30–60 μM	-	↓CIP2A, E2F1, proliferation, total caspase-3, cell cycle (G0/G1) ↑cleavage of caspase-3, PARP, apoptosis,	Zhao et al., 2016
	MDA-MB-231 and SKBR3	20–40 μM	-	↓Skp2, proliferation, invasion, migration, cell cycle (G2/M), ↑apoptosis, P21, P27	Ye et al., 2018
	MCF-7 and MDA-MB-231	60–100 μM	-	↓DNA Methylation, binding of hemimethylated DNA, ↑Cytotoxicity, mRNA expression of genes	Xie et al., 2014
	MCF-7, MCF-7/Her2 and BT-474	1–10 μg/ml	-	↓Proliferation, HER2, AKT kinase, ESR1 CpG methylation, BRCA-1, BRCA1 CpG methylation, cyclin D1,	Shen et al., 2013
	MCF-7 and UACC-3199	5–20 μM	-	↑P53, apoptosis, necrosis	Romagnolo et al., 2017
Equol + Genistein combination	MCF-7, SK-BR-3 and MDA-MB-468	50–100 μM	40.7 μM	↓Bcl-xL, cell cycle (G2/M), ↑Bax/Bcl-xL expression ratio, apoptosis, cytotoxicity, cleavage of PARP	Ono et al., 2017
Genistein		100 μM	56.8 μM	↓Cell cycle s phase ↑Cytotoxicity,	
	MCF-7 and CCD1059sK	0.01–100 μM	-	↓Proliferation, TrxR, CuZnSOD, MnSOD, ↑Apoptosis, autophagy, Bax/Bcl-2 ratio, GPx	Prietsch et al., 2014
	MDA-MB-231	5–20 μM	-	↓Proliferation, cell cycle (G2/M), NF-κB, cyclin B1, Bcl-2, Bcl-xl, ↑Apoptosis	Pan et al., 2012
	MCF-7	40 μM;	-	↓Mammary adiposity, ↑PTEN, E-cadherin, Erβ (Esr2)	Montales et al., 2013
	MDA-MB-231 and HCC1937	10, 25, 50, or 100 μM	-	↓GPR30, Akt phosphorylation, migration, colony formation, cyclin B1 expression, cell cycle (G2/M), ↑Nrf2, cytotoxicity	Kim et al., 2019
	MCF-7	20–80 μM	-	↓Proliferation, Bcl-2, IGF-1R proteins, P-Akt proteins, Bcl-2/Bax protein ratio, ↑Apoptosis, Bax,	Chen et al., 2015a
	MCF-7	2.5–70 μM	-	↓Proliferation, SMO, Gli1, ↑Apoptosis, cytotoxicity	Fan et al., 2013
	MCF-7, MDA-MB-231 and MDA-MB-157	5–50 μM	-	↓Proliferation, ↑Tumor latency, ERα expression,	Li et al., 2013
	MCF-7, SK-BR-3, ZR-75-1	1–200 μM	138.13 μM	↓Proliferation, cell shrinkage, ERα, c-erbB-2 expression ↑Apoptosis	Choi and Kim, 2013
	MCF7, UAC-C3199 and HCC38 BC	4–10 ppm	-	↓CpG methylation, AHR binding, (TCDD)-dependent localization of AHR, ↑BRCA1,	Donovan et al., 2019
	MDA-MB-231	40 μM	-	↓Cell cycle (G2/M), ↑apoptosis, ↑ATR signaling, ↑BRCA1-A and -B complexes.	Fang et al., 2016
	MDA-MB-435, Hs578t and MCF-7	1–25 μM	-	↓miR-155, ↑FOXO3, PTEN, casein kinase, P27, cytotoxicity, apoptosis	de la Parra et al., 2016

	MCF-7 and T47D	5–100 μM	-	↓Proliferation, HOTAIR expression, Akt phosphorylation, ↑Apoptosis	Chen et al., 2015b
	MCF-7	1–100 μM	-	↓Akt, BAD expression, Telomere length, ↑Apoptosis, $P21^{WAFI}$	Chinni et al., 2003
	MCF-7	25–150 μmol/l	27.5 μmol/l	↑Apoptosis, calpain, caspase 7, poly (ADP ribose) polymerase, P38 MAPK phosphorylation	Shim et al., 2007
	MDA-MB-231 and MDA-MB-468	50 μM	-	↓Proliferation, Bcl-2, ↑Apoptosis, Bax, caspase-3, ROS	Ullah et al., 2011

↑: Increase/stimulation/up-regulation/initiation; ↓: Decrease/inhibition/down-regulation/blocking; AHR: Aryl Hydrocarbon Receptor; ATR: Ataxia telangiectasia and Rad3-related protein; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra-large; BMI1: B cell-specific Moloney murine leukemia virus integration site 1; BRCA1: Breast Cancer 1; c-erbB-2: Cellular erythroblastic leukemia viral oncogene homolog 2; CIP2A: Cancerous Inhibitor of Protein Phosphatase 2A; c-MYC: Cellular myelocytomatosis oncogene; CuZnSOD: Copper-Zinc Superoxide Dismutase; Cx43: Connexin 43; DNMT: DNA methyltransferase; E2F1: E2F transcription factor 1; Erα: Estrogen receptor alpha; Erβ (Esr2): Estrogen Receptor Beta; ESR1: Estrogen Receptor 1; FOXO3: Forkhead box O3; Gli1: Glioma-associated oncogene homolog 1; GPR30: G protein-coupled receptor 30; GPx: Glutathione peroxidase; HOTAIR: HOX Transcript Antisense RNA; IGF-1R: Insulin-like growth factor 1 receptor; miR-155: microRNA-155; MnSOD: Manganese superoxide dismutase; mRNA: Messenger Ribonucleic Acid; Nrf2: Nuclear factor erythroid 2-related factor 2; PARP: Poly (ADP-ribose) polymerase; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; ROS: Reactive oxygen species;Skp2: S-phase kinase-associated protein 2; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; TrxR: Thioredoxin reductases

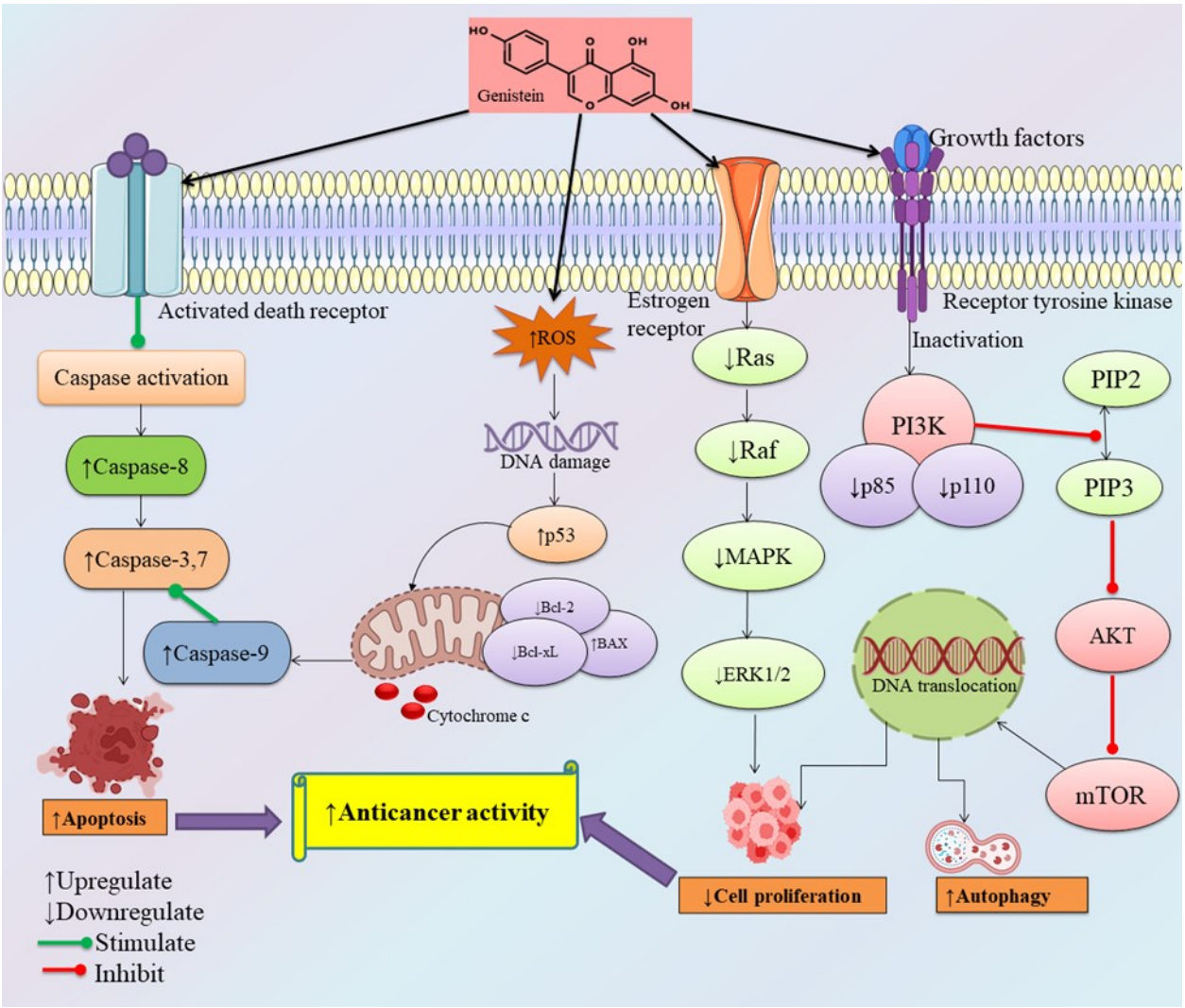

Fig. 1. Possible mechanism of anticancer activity of genistein. [The image illustrates that genistein demonstrates anticancer properties in BC by triggering apoptotic pathways via death receptor signaling, which results in caspase activation and the release of cytochrome c. It promotes the generation of reactive oxygen species (ROS), leading to DNA damage and the activation of p53. This, in turn, downregulates anti-apoptotic proteins such as Bcl-2 and Bcl-xL while upregulating the pro-apoptotic protein BAX. Additionally, GT inhibits the Ras/Raf/

MAPK/ERK1/2 pathway, thereby reducing cell proliferation, and suppresses the PI3K/AKT/mTOR pathway by deactivating receptor tyrosine kinases. This suppression results in decreased cell survival and increased autophagy. Together, these actions promote apoptosis and hinder the progression of BC. BAX: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra-large; ERK1/2: Extracellular signal-Regulated Kinases 1 and 2; p53: Tumor Protein 53; PI3K: Phosphoinositide 3-kinase; PIP2: Phosphatidylinositol-4,5-bisphosphate; PIP3: Phosphatidylinositol-3,4,5-trisphosphate; AKT: Protein Kinase B; Caspase-3: Cysteine Aspartate-Specific Protease-3; Caspase 7: Cysteine Aspartate-Specific Protease-7; Caspase-9: Cysteine Aspartate-Specific Protease-9; MAPK: Mitogen-Activated Protein Kinase; mTOR: mechanistic Target of Rapamycin; Ras: Rat sarcoma; Raf: Rapidly Accelerated Fibrosarcoma; ROS: Reactive Oxygen Species.]

. To evaluate safety and modify dosages, toxicity testing is required (Hussain et al., 2009). The use of in vitro and in silico approaches instead of traditional animal models aims to improve toxicity testing accuracy (Raies & Bajic, 2016; Patlewicz & Fitzpatrick, 2016). Numerous studies assess pharmacological therapies for chronic disorders, emphasizing the importance of investigating alternative therapy options such as natural cures derived from medicinal plants.

A study on zebrafish embryos exposed to high doses of GT demonstrated a dose-dependent reduction in heart rate, number of hatched embryos, and body lengths compared to vehicle-treated embryos. The study indicated that only roughly six out of ten embryos survived in the presence of 0.25×10^{-4} M of GT, and none in the presence of 1×10^{-4} M or 0.5×10^{-4} M of GT. Surviving embryos treated with 0.25×10^{-4} M GT showed physical abnormalities, including pericardial edema, yolk sac edema, and spinal kyphosis. Granular myocyte degeneration in skeletal muscle, as well as neural cell loss and apoptosis in the brain, was identified. The study found that large doses of GT have a strong teratogenic effect (Kim et al., 2009). Another study found that oral administration of 400 and 1,000 mg/kg GT had endocrine-disrupting effects in female rats, including mild vacuolation and mucinification. Male rats treated with GT had significantly higher prolactin levels in comparison to the control group (Okazaki et al., 2002). Sarasquete et al. (2018) assessed the toxicity profile of soy isoflavone using zebrafish embryos. GT and daidzein were discovered to have a considerable effect on zebrafish embryo hatching success and mortality rates. The median fatal value was 4.41 mg/l. GT also increased oestrogen, death receptor, and CYP1A transcript levels, as well as thyroid transcript signals in control zebrafish embryos and larvae. Research indicates that treating mucopolysaccharidoses (MPS) III patients with low dosages of GT produces varying neurocognitive effects and no significant adverse effects. In mice with MPS IIIB, high doses of GT (160 mg/kg/day) have been demonstrated to enhance behavioral phenotype and decrease neuroinflammation and heparan sulfate accumulation. High-dose oral GT treatment is safe and beneficial for MPS patients with neurological impairment; however, require more investigation (Kim et al., 2013). High doses of GT cause considerable toxicity, including teratogenic consequences, endocrine disruption, and higher mortality. In contrast, low doses have therapeutic promise with few side effects, particularly in neurocognitive disorders. Further investigation is needed to improve the dose for safe use.

3.6. Clinical evidence

Clinical studies, defined as investigations or trials carried out on human subjects, are an important component of the research process involved in producing a novel drug (Schultz et al., 2019; Bhuia et al., 2023a). Clinical trials are critical for identifying, diagnosing, and lowering the risk of disease, as well as discovering novel therapeutic techniques (Akhondzadeh, 2016). Furthermore, clinical trials provide insights into treatments that are based on evidence, safety, and accuracy (Bhuia et al., 2023b). The effect of soy consumption affects the proliferating rate of premenopausal women. After fourteen days of 60 g soy treatment (45 mg isoflavone), the soy group's serum levels of GT increased. This study found that eating soy for a short amount of time increased the expression of progesterone receptors and breast growth (McMichael-Phillips et al., 1998). Another study observed higher consumption of soy foods may reduce the probability of fibroadenomas and, consequently, BC. This study found an inverse relationship between the plasma isoflavones, including daidzein and GT, and the risk of fibroadenoma (Dijkstra et al., 2010). By evaluating the isoflavone concentrations of substances, compounds, and biological distribution to estradiol exposure, Bolca et al. (2019) investigated the impact of isoflavone ingestion on healthy breast tissue. LC-MS was used to examine samples of blood and healthy breast tissue that were taken after cosmetic breast reduction. Results indicated that isoflavone levels within the breast tissue that may have an effect on health were attained following consumption of soy milk as well as soy products high in GT. According to recent research, GT may raise the threat of BC while having no effect on the proliferation of breast epithelial cells.

Significant increases in gene expression were observed in the six months of the soy-treated group in research involving 98 women, suggesting limited preventative benefit and possible side effects in premenopausal women (Khan et al., 2012). The expression profile of genes of women with the initial stages of BC in their tumor tissue before and after receiving a placebo and a soy protein supplement. The authors found that genes associated with the process of the cell cycle and the proliferation were overexpressed in response to soy consumption and elevated plasma GT levels (Shike et al., 2014). These studies emphasize the complexities of GT's involvement in BC, with some data suggesting potential preventive effects and others cautioning against its usage, particularly in certain populations. Additional research is needed to determine its therapeutic potential and safety profile.

3.7. Limitations of this study

GT, despite its promising anticancer properties, has several limitations that hinder its clinical application, high doses can be toxic or even promote tumor growth in some models, while low doses may be therapeutic. While some studies suggest preventive benefits, others indicate no significant preventive effect and and potential risks in early-stage BC due to increased expression of proliferation-related genes. The most significant gaps in genistein research are well-designed clinical validation assessing genistein's efficacy and safety as a breast cancer therapeutic or preventive agent, low water solubility, and limited BBB penetration. Future research should prioritize clinical validation and formulation improvement.

4. Conclusion

GT is a promising phytochemical with multi-targeted anticancer effects in breast cancer models, including upregulation of oxidative stress, cytotoxicity, arresting of the cell cycle, apoptosis, downregulation of cell invasion and migration, genotoxic and mutagenic effects, miscellaneous effects, and antiproliferative effects. They promote anticancer treatment through altering multiple signaling pathways, including the PI3K/AKT, MAPK, and HER2 pathways. Mixed clinical outcomes suggest that benefits depend on dose, subtype, and menopausal status, while high doses may pose a risk of toxicity. Pharmacokinetic limitations (notably poor bioavailability and blood-brain barrier penetration), and

unresolved controversies regarding its safety, especially in hormone-sensitive and premenopausal populations. To optimize GT's potential in cancer treatment, future study should focus on refining its formulation, conducting large-scale clinical studies, and investigating its interaction with existing chemotherapeutic medicines.

Conflict of interest

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Authors' contributions

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