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Molecular Mechanisms and Therapeutic Potential of Soy Isoflavones in Breast Cancer: A Narrative review

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ABSTRACT

Breast cancer remains a multifaceted disease requiring deeper understanding of dietary interventions. Soy isoflavones represent a promising area of investigation. Despite extensive research, a synthesis of evidence from laboratory, animal, and human research to elucidate mechanisms by which soy isoflavones could be used for preventing and treating breast cancer remains lacking. This review analyses findings from laboratory, animal and human research to clarify molecular mechanisms of soy isoflavones in breast cancer prevention and treatment. Soy isoflavones, particularly genistein and daidzein, influence cell proliferation, cell cycle regulation, apoptosis induction, epigenetic modifications, cell signalling pathways, angiogenesis, and metastasis in breast cancer models. These compounds modulate expression of crucial genes and proteins participate in these processes and disrupt essential cancer signalling pathways. Soy isoflavones impacts breast cancer cell metabolism, particularly glucose, lipid, and nucleotide metabolism, through effects on the pentose phosphate pathway. These compounds were also reported to have immunomodulatory properties, altering immune cell recruitment and signalling in the breast cancer microenvironment. While soy isoflavone effects vary based on dose, timing of exposure, and tumour subtype, evidence suggests their potential as chemo preventive agents, warranting further clinical investigation.

INTRODUCTION

Soy isoflavones are natural compounds found in soybeans and soy-based products such as tempeh, tofu, soy milk, as well as other foods fortified with soy. These phytoestrogens have attracted a considerable number of interests because of their various health advantages including menopausal symptom relief, gastrointestinal, bone, cardiovascular health and breast cancer risk reduction [1,2]. However, the benefit of isoflavone in breast cancer prevention and treatment has remained controversial due to its dual effect in breast cancer growth and proliferation as it exerts both pro-oestrogenic- and anti-oestrogenic effect through interaction with estrogen receptor or other pathway independently of estrogen receptor [3,4].

Isoflavone levels in food exhibit considerable variation, and these levels are significantly influenced by geographic region, harvest time, soybean variety, and soybean processing methods. Soy flour possesses the highest isoflavone content of 0.1-5 mg/g protein, compared to tofu at 0.1-2 mg/g protein and tempeh at 0.3 mg/g protein [5]. The primary constituents of isoflavones are genistein and daidzein, both of which are metabolized by intestinal microflora into their respective metabolites, p-ethyl phenol and equol. These compounds are detectable in human blood, plasma, and urine [6]. Daily consumption of soy isoflavones for 30 days significantly increases plasma concentrations of genistein and daidzein compared to the placebo group [7].

Studies exploring the impact of isoflavone consumption on breast cancer risk across Asian and Western populations have reported mixed outcomes. Boker et al examined whether dietary isoflavone intake influences breast cancer risk and reported no significant protective effect among Western women [8]. Nevertheless, some argue that prolonged consumption of soy isoflavones, beginning at a young age, may lower breast cancer risk [9]. Unlike the results reported by Boker et al., a cohort study conducted in Japan showed that regular intake of soy and soy-derived foods was associated with a reduced risk of breast cancer during a 9-year observation period, particularly among postmenopausal women [10]. Furthermore, a meta-analysis in China identified a significant correlation between diet and breast cancer risk in Chinese women, suggesting diet abundant in vegetables, fruits, soy, and processed foods might lower the risk of breast cancer, whereas consuming a diet high in fat could potentially raise it [11]. The inconsistent finding between Western and Asian women might be stem from difference in both eating habits and daily isoflavone consumption. As reported by Huser et al, Isoflavone intake among Chinese and Japanese individuals averages between 16-70 mg per day, far exceeding the average intake of around 2 mg per day in Europe and the United States [12]

Extensive research has explored soy's potential to reduce the risk of breast cancer, with results showing a link to the amount consumed [13–16]. This protective effect is achievable through consistent consumption for Asian population, with an isoflavone intake ranging from 25 to 50 mg [17]. The collection of evidence from population-based studies on the effect of genistein consumption is summarized in table 1.

Table 1. Outcome of population-based study on the effect of genistein consumption.

Study population	Intervention	Dose of soy isoflavone	Outcome measured	Result	References
132 of invasive breast cancer patients	Subjects consumed two daily packets of soy powder, or milk protein as a placebo, for up to 30 days before surgery	25.8 gr/pack	pre- and post-soy isoflavone plasma level, gene expression changes in tumour biopsy samples and surgical specimens before and after soy treatment	There was a statistically significant rise in plasma genistein and daidzein levels, increasing by roughly seven-fold and four-fold, respectively. Cell-cycle–related genes were upregulated as observed in tissue samples in the soy group compared with the placebo group	[7]
15555 participants that were recruited during breast cancer screening program	daily intake of isoflavone	0.4mg/day	Breast cancer incidence after 5.2 yrs follow-up	Breast cancer was newly diagnosed in approximately 1.8% of participants during follow-up. With a hazard ratio of 1.0, the level of daily isoflavone intake studied did not influence breast cancer risk	[8]

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17 case-control studies and 7 cohort studies were involved in meta-analysis	daily intake of isoflavone	10mg/day	Breast cancer risk estimation based on daily isoflavone intake	At this intake level, daily isoflavone consumption was linked to an 11.7% lower breast cancer risk	[18]
Eight longitudinal studies were involved for meta-analysis	daily intake of isoflavone	up to 15mg/day (low intake) and >15mg/day (high intake of isoflavone)	breast cancer incidence	Individuals with higher isoflavone intake had a lower risk of being diagnosed with breast cancer, whereas those with lower intake showed a higher risk	[19]
616 breast cancer patients were involved in a prospective cohort study	isoflavone consumption	~ 17.32 mg/day	5yrs survival of patients	At this level of isoflavone intake or higher, individuals had a 29% lower risk of breast cancer–related death after five years of follow-up	[20]

The finding presented in the table suggest that both the dosage and duration of daily intake of soy isoflavone may affect the breast cancer risk.

In terms of genistein safety, Marini et al investigated the long-term safety of genistein aglycone supplementation in postmenopausal women over a three-year period. Their study found no significant changes in breast density or endometrial wall thickness, while beneficial effects on bone density were observed in osteopenic women [15]. This indicates that genistein does not promote breast cell proliferation and is considered safe for this population. In contrast, a randomized phase II trial conducted by Khan found that six months of soy isoflavone intervention did not significantly supress breast epithelial cell proliferation, suggesting limited potential for breast cancer prevention. [21]. Further scientific exploration of soy's beneficial properties is warranted, with the potential for its application in reducing breast cancer prevention.

A cohort study involving breast cancer survivors receiving tamoxifen therapy found that long-term intake of high levels of Daidzein significantly reduced cancer recurrence without compromising the effectiveness of tamoxifen [22]. Comparable finding indicates that moderate consumption of soy isoflavone may help reduce recurrence risk in pre-menopausal women and patients with triple negative breast cancer [23]. A separate study found that postmenopausal women treated with anastrazole, an adjuvant endocrine therapy, showed decrease recurrence rates when they consumed high amount of soy-isoflavone over a five-year follow-up [24]. Collectively, these studies imply that moderate and high consumption of soy isoflavone is associated with a decrease likelihood of cancer recurrence.

Given these inconsistencies and gaps in the literature, this paper aims to explore the underlying molecular mechanism of soy isoflavone in breast cancer prevention or treatment, as detailed in the following sections.

METHOD

This review utilized a narrative method to compile information on molecular mechanisms and therapeutic potential of soy isoflavones in breast cancer. Literature searches were conducted in PubMed, Scopus, Web of Science, and Google Scholar using terms: "soy isoflavones", "genistein", "daidzein", "breast cancer", "molecular mechanism", "cell signalling", "cell metabolism", "epigenetics", "angiogenesis" and "therapeutic potential". Articles were searched within time frame 1994-2025. 73 articles were used in this narrative review upon selection of all authors. The selected paper should be in English, open access, focused on soy isoflavones and breast cancer, and explored mechanisms like apoptosis, cell proliferation,

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angiogenesis, epigenetic effect, or immune regulation. In vitro, in vivo and human studies were also retrieved for this review. Findings were organized thematically covering mechanisms of soy isoflavone to cell proliferation and cell cycle, epigenetic effects, cell signalling pathways, angiogenesis and metastasis, and immune modulation.

RESULTS AND DISCUSSION

Molecular mechanisms of isoflavone and its effect on breast cancer

Multiple prior investigations have revealed various molecular mechanisms believed to underpin the protective effects of isoflavone against breast cancer. These mechanisms encompass isoflavone's influence on cell proliferation regulation, cell cycle control, apoptosis induction, epigenetic modifications, cell signalling pathway modulation, angiogenesis inhibition and metastasis, cell metabolism and immune cells (Figure 1).

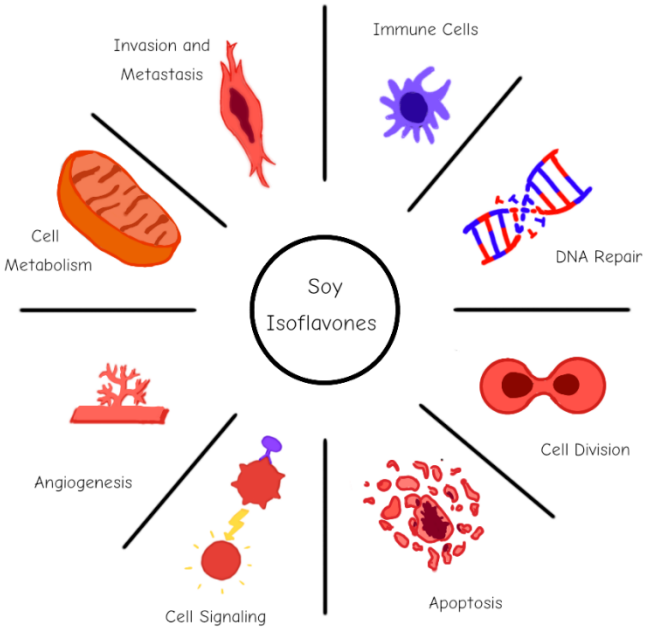

Figure 1. Multiple targets of isoflavone towards cancer hallmarks.

Isoflavone Effect on Cell Proliferation and Cell Cycle

The effect of isoflavone in breast cancer development is still controversial, where several previous studies in vitro and in vivo reported the impact of inhibition or acceleration of breast cancer development at the molecular level depending on the dose and ER status [25,26]. Isoflavones can promote cancer cell growth by forming a complex with oestrogen receptors. This complex binds to oestrogen response elements (EREs) in gene promoter regions, activating the transcription of genes involved in cell proliferation and cancer progression [27]. However, at doses >10μM genistein, ERE activity is reduced so that there is an inhibition

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of cancer cell growth [28]. Numerous findings of *in vitro* and *in vivo* study evidence of isoflavone effect to breast cancer cells growth and proliferation were listed in table 2.

Table 2. Invitro and in vivo study on isoflavone effects to breast cancer cells growth, proliferation and cell cycle

In vitro study population	Intervention	Dose of soy isoflavone	Outcome measured	Result	References
Normal and malignant breast cancer cell line	various dose of genistein were given to the tested cells	45uM and 90uM	cell cycle arrest and cells apoptosis	Malignant breast cancer cells exhibited greater G2/M arrest and apoptotic response than normal breast cells following treatment with 90 µM genistein	[29]
Triple negative breast cell line	various dose of genistein were given to the tested cells	0,5, 10 and 20uM	cell cycle arrest and cells apoptosis	G2/M arrest and apoptosis were induced by genistein in a dose-dependent manner, with higher concentrations leading to greater proportion of cells arrested at G2/M cell cycle phase.	[30]
ER+ breast cancer cell line	various dose of genistein were given to the tested cells	50uM and 100uM	cell growth, cell cycle dynamics	inhibition of cell growth, G2/M cell accumulation and reduction of cells number in S phase were observed at both dosage of genistein.	[31]
ER+ and triple negative breast cancer cell line	genistein and sulforaphane were administered to the tested cell line either individually or in combination	ranging from 5uM to 15 uM	cell viability, apoptosis and cell cycle arrest	combination of genistein and sulforaphane treatment led to the significant reduction of viable cells and increment of apoptotic cells number. G2/M cells arrest was more prominent in TNBC, whereas G1 cell arrest was observed in ER+ breast cancer cells	[32]

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MCF-7 and MDA-MB-231 cells	Genistein diluted in DMSO	60 and 100uM	cell viability, global DNA methylation level, DNMT activity and DNMT1 enzyme expression	Genistein reduced cell viability in both tested cell lines. At concentrations of 60 and 100 µM, it was also associated with demethylation of several tumour suppressor genes, likely through suppression of DNMT activity and reduced DNMT1 expression	[33]
Breast cancer cell line	genistein and daidzein treatment vs control	18.5uM and 78.5uM respectively	methylation status of tumour suppressor gene BRCA1 and BRCA2	At this dose, both genistein and daidzein were associated with reversal of gene methylation, leading to increased expression of these genes	[34]

In vivo study population	Intervention	Dose of soy isoflavone	Outcome measured	Result	References
Breast cancer mouse model	Isoflavone and broccoli sprout were administered to transgenic mice either individually or in combination	~ 2gr of isoflavone and around 2 serving cup/day of broccoli sprout were routinely given to the mouse model from the very early age (~4 weeks old) to 20-25 weeks	tumour incidence and tumour size	Isoflavone–broccoli sprout combination therapy significantly delayed tumour development and produced the smallest tumours among all treatment groups as observed in transgenic mouse.	[32]
athymic nude mouse bearing MCF -7 cells with different menopausal status	administration of soy isoflavone with various doses	6.25g/kg, 12.5g/kg and 25g/kg for 16 weeks	tumour growth	regardless of menopausal status of the animal model, soy isoflavone extracted at dose 6.25 and 12.5g/kg were significantly stimulating breast tumour growth	[35]

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Breast cancer mouse model	The mouse models were grouped and treated with genistein, daidzein alone and combination of both	10 mg/kg body weight for each substrate used and combination of both. It was administered three times a week until day 77	tumour growth and metastasis	Treatment with genistein alone slowed tumour growth by approximately 33% and reduced metastasis to the bone and liver. In contrast, daidzein accelerated tumour growth by about 38% and increased metastatic spread to the heart and lung. When genistein and daidzein were administered together, no clear effect on primary tumour growth was observed, although metastatic dissemination was induced	[36]
Ovariectomized female nude mice bearing MCF-7 human breast cancer xenografts	genistein and genistein treatment for 11 weeks	750 ppm for genistein and 1250 ppm for genistein	tumour area measurement every week and regression	both genistein and genistin were stimulating mammary tumour growth and retrieval of both from diet led to tumour regression	[37]
Female transgenic mouse model	endogenous estrogen level modification through ovariectomy of transgenic mice and treated with isoflavone until 60 weeks of age	0.26 g isoflavone/100gr soybean	incidence of breast cancer	breast cancer incidence was more frequently observed in mice group treated with isoflavone and with low estrogen level than those seen in control with high estrogen level.	[38]

In vitro and *in vivo* findings that were shown in the table 2 suggested that the effect of isoflavone to breast cancer cells growth was dose dependent. However, the differing effects observed between humans and experimental animals suggest variations in isoflavone metabolism, resulting in higher plasma isoflavone concentrations in animal models and consequently differences in breast cancer risk [39]. This finding also indicating the need of appropriate animal model that mimicking human body environment for laboratory experiment to study isoflavone effect in breast cancer.

Interestingly, synthetic isoflavone derivatives, like their natural counterparts, exhibit anti-proliferative effects, albeit at lower concentrations. Research by Sarkar et al 2006 demonstrated that synthetic isoflavone derivatives achieved a 50% reduction in the proliferation of various cancer cells, including those of breast cancer, in both in vitro and in vivo settings. This effect was noted at a concentration of 10 µM. a significantly lower dose compared to natural isoflavones (30-50 µM), without inducing toxicity. Moreover, apoptosis was triggered at 15 µM, whereas natural isoflavones required >70 µM. These findings suggest that synthetic isoflavone derivatives may hold greater potential for cancer treatment than natural isoflavones [40]. The mechanism is thought to involve the inactivation of cell survival and apoptosis pathways, such as NF-kB and AKT [40]. However, recent study confirms that isoflavones regulate genes and proteins engaged in cell division, apoptosis and cell progression at

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transcriptomic and proteomic level. These changes can lead to either stimulation or inhibition of cell proliferation, depending on the context either estrogen positive or negative [26,41].

Isoflavone effect on cell signalling

The cell signalling cascade plays an important role in regulating cell growth, including breast cells. Hyperactivation of this cell signalling cascade results in abnormal and uncontrolled cell growth, as well as disruption of the apoptosis pathway. Some signalling pathways which are commonly hyperactive in breast cancer were downregulated following soy isoflavone treatment as evidenced from transcriptome data analysis of breast cancer cell lines [26]. MAPK/ERK signalling was deactivated following genistein treatment in a time- and dose-dependent manner as seen in TNBC cell line led to cell growth inhibition. The treatment was also induced apoptotic pathway through activation of apoptotic-protein expression and modulation the BAX/BCL2 ratio [42,43]. In addition, genistein treatment was also inhibited Nf-Kb pathway which function in cell survival [26,30,42]. This inhibition may interfere with its ability to bind to the promoter region of its target gene leading to the decrease of that gene. In addition, crucial cell proliferation regulator, TGF-beta signalling, along with its downstream, was deregulated in cells treated with soy isoflavone. In contrast, tumour suppressor, TP53 signalling was upregulated under the same treatment [26].

In the ER+ breast cancer cell line, genistein administration resulted in a reduction of ER-alpha expression at certain doses and inhibited cell proliferation. The underlying explanation for this result may lie in the downregulation of ER-alpha signalling upon genistein treatment, which impacts the transcription of its target gene, such as cyclin D which known for its role in cell cycle regulation and proliferation.(CHOI et al., 2014). Proteomic analysis of MCF-7 and MDA-MB-231 cell line showed that some of signalling pathways were also deregulated with distinct pattern following soy isoflavone treatment in a dose dependent manner, including tyrosine kinases signalling, lipid and phospholipid catabolism, ECM degradation and cytoskeleton organization. These signalling pathways were crucial for facilitating cancer progression and metastasis [41]. Proteomic analysis result suggests that treating breast cancer cells with isoflavone may hinder cancer development and spread by altering the expression of key proteins involved in cell proliferation signalling.

In summary, the signalling effect of isoflavones are significantly influenced by the ER status and the dosage of isoflavone, making these factors should be considered when customizing adjuvant breast therapy for personalised medicine.

Isoflavone Effect on Epigenetic Regulation

DNA methylation and histone protein modification, which are epigenetic processes that occur without any alterations to DNA base sequences, are closely associated with the regulation of gene expression. Changes in these epigenetic mechanisms can affect the level of gene expression, thereby directly influencing gene function. DNA methylation involves the attachment of a methyl group to the cytosine base of DNA, primarily at CpG sites, resulting in the repression of gene expression[44]. Histones, proteins around which DNA is coiled for organizational purposes, play a crucial role in determining gene activation or repression. These histones can undergo chemical modifications that alter the degree of DNA packing. Such modifications impact the accessibility of transcription machinery to the DNA for gene transcription; specifically, tightly packed DNA results in gene repression, whereas loosely packed DNA facilitates gene activation [45].

Numerous investigations have documented the influence of isoflavone administration on epigenetic processes. For instance, Shike and colleagues investigated how soy isoflavone affects the expression of genes linked to breast cancer. They analysed the expression of 202 genes involved in breast cancer pathways in tumour tissues obtained before (via core biopsy) and after (through surgery) from two groups: patients who regularly consumed soy protein powder for 7-30 days and those administered a placebo. The findings revealed an upregulation of 21 genes involved in cell cycle, cell proliferation, and growth factors, particularly FGFR2, especially in patients with elevated genistein levels [7]. These results suggest that soy protein may stimulate breast cancer growth. However, it is important to note that this study only

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investigated the short-term effects of large doses (g) of soy protein and did not explore the long-term consequences of consuming small doses (mg) of soy protein, which is more representative of typical consumption patterns.

Soy isoflavones have been shown to influence the expression of important enzymes related to epigenetic regulation, such as DNA methyltransferases (DNMTs) [33] and histone deacetylases (HDACs), histone methyltransferases (HMTs) thereby impacting DNA methylation levels and histone modification processes [46–48]. Epigenetic mechanisms have a substantial impact on estrogen receptor expression and treatment outcome. Genistein has been reported to counteract methylation-mediated suppression of ER expression in TNBC cells [47,49,50] which subsequently increases tamoxifen sensitivity [50,51]. Estrogen receptor status plays a crucial role in breast cancer management because the presence or absence of ER expression strongly affects treatment decision and therapeutic outcome. These findings suggest a potential role for soy isoflavone in the treatment of TNBC cells type.

Epigenetic mechanism can also silence tumour suppressor genes expression like BRCA1 ([34,49,51] and BRCA2 [34] in TNBC cells. The expression of both genes was restored after treatment with genistein and daidzein through demethylation effect, indicating the potential role of these compounds as demethylating agents. Notably, genistein produced a more pronounced effect and required lower concentration than daidzein to achieve comparable outcomes. The addition of 5-Azacytidine, a demethylating agent, further enhanced the reactivation of these genes, whereas budesonide, a methylating agent, produce the opposite effect. This study provides insight into the epigenetic influence of genistein and daidzein on BRCA1 and BRCA2 modulation [34].

Donovan and colleagues reported that genistein inhibits the activity of AHR (aryl hydrocarbon receptor), which is often excessively activated in TNBC. Activated AHR supresses BRCA1 transcription by inducing promoter hypermethylation through the recruitment of DNA methyltransferases. Genistein counteract this mechanism by reducing hypermethylation, thereby restoring RCA1 transcription and elevating BRCA1 expression in TNBC [51]. In breast cancer cell line, co-treatment with genistein and sulforaphane derived from cruciferous vegetables was found to influence the activity of epigenetic enzymes, including HDACs and HMTs, thereby altering the epigenetic profile and potentially regulating genes related to cell proliferation and programmed cell death [32]. This therapeutic combination appears to hold significant promise for breast cancer treatment and prevention, emphasizing the need for further clinical evaluation.

From an epigenetic perspective, genistein affected the methylation state and expression of *ATM, APC, PTEN*, and *SERPINB5* genes in breast cancer cells[33]. The study found that genistein treatment reduced methylation of these genes' promoters and increased their mRNA expression. ATM involved in DNA damage response and cell cycle checkpoint and reduced expression of this gene is associated with increased breast cancer risk[52]. APC act as tumour suppressor and is hypermethylated and silenced in 49% breast cancer tissues. Loss of function of this gene lead to the activation of WNT/b-catenin pathway thus uncontrolled cell growth, facilitating cell adhesion and cell migration [53]. Promoter methylation of this gene is linked to risk of breast cancer and adverse clinicopathological parameters like advance stages and lymph node metastasis as indicated from meta-analysis study that involved 29 studies [54]. PTEN, as tumour suppressor gene, negatively regulate the PI3K/AKT signalling pathway, which is crucial for cell survival and proliferation. SERPINB5 involved in cell adhesion, invasion and angiogenesis thus downregulation of SERPINB5 is correlated with progression and metastasis of breast cancer. The reactivation of these crucial tumour suppressor genes through demethylation by genistein could potentially help in suppressing breast cancer growth and progression.

Soy Isoflavone Impact on Cancer Cell Metabolism.

The metabolic pathways of cancer cells, including breast cancer cells, play a crucial role in supporting their rapid proliferation and survival. One of these pathways is called Pentose Phosphate Pathway (PPP) and is frequently overactivated in cancer. This pathway provides building blocks of nucleic acid and energy necessary for cell rapid growth and survival, making it a target for therapeutic intervention [55]. Not only PPP, lipid and phospholipid metabolism are also crucial for cell viability and survival.

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The metabolic effect of soy isoflavone has been extensively characterized in vitro through integrated metabolomic and proteomic approaches, providing valuable insight into the molecular mechanisms underlying their biological activity. Metabolomic study have revealed that genistein and daidzein exert dose-dependent modulatory effect on cellular metabolic pathways, resulting in either stimulation or inhibition depending on the concentration administered. Soy isoflavone exposure produced differential metabolic responses in ER+ and ER- breast cancer cell lines. In ER+ cells, stimulatory doses enhanced the abundance of key PPP metabolites, including 6-phosphogluconate and ribose 5-phosphate, suggesting increased PPP activity. Conversely, in ER- cells, isoflavone treatment supressed glutamine uptake, leading to impaired protein biosynthesis and altered cellular energy metabolism [56]. In addition, proteomic analyses have demonstrated that isoflavone treatment increases the expression of proteins involved in lipid and phospholipid catabolism in ER- cell line [41]. Given that phospholipid constitute essential structural component of cellular membranes, enhanced phospholipid catabolism may compromise membrane integrity and stability. Consequently, these alterations could disrupt critical cellular function and adversely affect cell viability and survival. Collectively, these results indicate the metabolic effects of soy isoflavone are modulated by estrogen receptor status and exhibit a dose-dependent pattern. By modulating critical pathways for cell growth and survival, offering insight into soy isoflavone role in cancer chemoprevention and therapy [56–58]. Having explored the influence of soy isoflavones on cancer cell metabolism, it is also crucial to understand their role in other critical processes such as angiogenesis and metastasis, which are instrumental in cancer progression.

Soy Isoflavone Effect to Angiogenesis and Metastasis in Breast Cancer

Angiogenesis is a fundamental process in cancer progression, enabling tumour to acquire an adequate blood supply that support rapid growth and facilitates metastatic spread. For this reason, targeting this has emerged as well-established approach in anticancer therapy. Evidence from in vitro study showed that soy isoflavone exert its anti-angiogenic effect in breast cancer cells primarily through the suppression of signalling pathways such as NF-κB and HIF1α [59] , both of which are closely associated with cell survival, migration and invasiveness. Notably, docking analysis showed that Genistein directly interact with the inhibitor site of HIF1α, a major regulator of angiogenesis under hypoxic condition, thereby reducing its expression [60]. This suppression leads to reduced VEGF expression, an important component in the angiogenic pathway and is downstream target of HIF1α and consequently limits tumour neovascularization [60] and microvessel density [61].

In addition to its direct effect to cancer cells, genistein also exert biological effects on endothelial cells, which are key mediator of angiogenesis. Specifically, genistein may impair endothelial sprouting and invasion into the surrounding extracellular matrix, two critical events required for neovascularization. Evidence from in vitro studies indicate that these effects are mediated through the suppression of VEGF-induced signalling, including the inhibition of the MAPK pathway activation and protein tyrosine kinase activity in HUVECs. This finding suggests that genistein may interfere with the endothelial response to pro-angiogenic stimuli. Thus, limiting angiogenesis and cancer progression [62].

In terms of metastasis, degradation of the extracellular matrix (ECM) facilitates cancer cell migration and invasion through which tumour cells can penetrate surrounding tissues and enter the vasculature. A critical step in this process is the epithelial-mesenchymal transition (EMT), during which epithelial cells acquire a more motile and invasive mesenchymal phenotype. Genistein has been shown to modulate the expression of several proteins involved in EMT, including the upregulation of E-cadherin, and the downregulation of P-cadherin and N-cadherin. These alterations supress the EMT process and may consequently limit the cancer cells dissemination. [63]. Furthermore, genistein has been reported to reduce the expression and activity of matrix metalloproteinases (MMPs) [61,64,65] thereby inhibiting extracellular matrix remodelling and decreasing the migratory and invasive potential of cancer cells. Evidences from animal model corroborate these observations, demonstrating that genistein attenuates tumour-associated angiogenesis and metastatic progression in vivo, likely by impairing tumour cell migration and protease-mediated extracellular matrix degradation [66] However, some recent in vivo studies suggest that dietary soy isoflavones might increase lung metastasis in breast cancer models with bone micro-tumours,

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underscoring the need for caution and further research, particularly concerning their use in breast cancer survivors with existing micro-metastases [67]. Collectively, the diverse impacts of genistein highlight its promise as both a preventive and therapeutic agent in breast cancer models by effectively inhibiting both angiogenesis and metastasis.

Modulation of Immune Response by Soy Isoflavone

Immune cells play a crucial role in eliminating cancer cells, particularly cytotoxic T lymphocytes (CTLs). These cell function as a surveillance system that identifies and distinguishes cancer cells from normal cells and subsequently targets them for destruction. However, the ability of CTLs to perform this function can be impaired when cancer cells expressing programmed death-ligand 1 (PD-L1) bind to programmed death-1 (PD-1) receptors on T cells. This interaction supresses T-cell activity, allowing cancer cells to evade immune recognition and destruction.

PD-L1 was found to be highly expressed in 20.9% TNBC samples based on IHC staining [68]. Similar observation has been reported from TCGA data and cancer cell line encyclopaedia, where TNBC tissues and MDA-MB-231 cell line exhibited higher expression of PD-L1 than other breast cancer type [69] . The PD-L1 and PD-1 interaction may also induce the activation of regulatory T cells (Tregs), which possess immunosuppressive function. Knockdown of PD-L1 in this breast cancer subtype restore CTL activity as evidenced by increase infiltration of pro-inflammatory cells and suppression of Tregs populations. This shift creates a more anti-tumour environment which lead to increased number of apoptotic cells, as confirmed by flowcytometry analysis.

Isoflavone supplementation has been shown to decrease the CD4+/CD8+ ratio in the peripheral blood, as determined by flow cytometry in experimental rat model. This modulation of immune cells population was associated with suppression of breast tumorigenesis. Female rats treated with carcinogenic agent and receiving isoflavones with certain doses developed significantly fewer tumour nodules, with tumour incidence reduced by up to 33%, whereas rats exposed to carcinogenic agent without isoflavone supplementation exhibited a 100% tumour formation rate [70]. Another study reported that genistein modulates the tumour microenvironment by supressing the recruitment of M2 macrophages, a subtype strongly associated with tumour progression. This modulation contributed to the inhibition of breast cancer growth in animal models [71]. Altogether these results depict how isoflavone can create a more favourable immune environment and a decrease likelihood of tumour formation.

In a recent study, Song et al observed a reduction in IL-6 levels among breast cancer participants with higher soy isoflavone consumption [72]. This finding is supported by a meta-analysis demonstrating the effects of soy isoflavones in reducing inflammatory markers, including IL6 and TNF-α, following long-term supplementation at doses below 100mg/day [73]. Given the established role of chronic inflammation in cancer progression, the observed reduction in these inflammatory markers may contribute to attenuating tumour progression. Collectively, these findings suggest that soy isoflavones exert broad immunomodulatory effects on immune cells and cytokine profiles, which may attenuate chronic inflammation, a key process strongly associated with cancer progression.

CONCLUSION

Overall, soy isoflavones have shown promising potential in modulating various molecular and cellular pathway associated with breast cancer prevention and therapy. However, their effectiveness depends on multiple variables such as dose, tumour subtype, exposure duration, and intestinal microbiota activity. These factors should be carefully evaluated before applying isoflavones in clinical approach aimed at personalized medicine. Establishing optimal dosage strategies remains difficult, particularly because human studies face challenges in differentiating the impact of long-term and short-term intake while maintaining precise dietary control. Moreover, inconsistencies among studies may arise from variations in methodology, population demographic and sample sizes. Consequently, further rigorous and standardised research is required to better define the therapeutic potential of soy isoflavone in breast cancer treatment.

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Author Contributions

Dewi Rusnita: Conceptualization, methodology, writing-original draft preparation. Siti Nurhajjah: literature search, writing-Reviewing and editing. Nur Afrainin Syah: Supervision, writing-Reviewing and editing.

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