***Review Article***

**Impact of Dietary Phytoestrogens on the Prevention and Management of Breast Cancer : A Comprehensive Analysis**

**Abstract**

Breast cancer remains one of the most common cancers affecting women worldwide. Diet, particularly phytoestrogens—plant-derived substances with estrogen-like activity—has received increased interest in the prevention and treatment of breast cancer. This review thoroughly investigates the numerous forms of dietary phytoestrogens, including isoflavones, lignans, and coumestans, emphasizing their sources, methods of action, and potential impact on breast cancer risk and progression. Phytoestrogens influence a variety of physiological processes, including estrogen receptor activation, apoptosis, angiogenesis, and oxidative stress, making them intriguing candidates for breast cancer chemoprevention. Epidemiological, in vitro, and in vivo studies suggest that regular consumption of phytoestrogen-rich foods, particularly in early life, may lead to a lower incidence of breast cancer and better outcomes for survivors. Furthermore, incorporating phytoestrogens into clinical management regimens may provide a supplementary approach to traditional medications, with the potential to reduce therapy-related adverse effects and improve quality of life. However, results remain contradictory due to differences in food patterns, hereditary factors, and tumor subtypes, necessitating caution in making broad recommendations. This study emphasizes the role of dietary modification in cancer prevention and identifies phytoestrogens as an important component of nutraceutical methods. The findings are useful for doctors, researchers, and policymakers looking to develop integrated approaches to cancer care. Future research should concentrate on large-scale, longitudinal clinical trials to develop uniform dietary guidelines and evaluate the long-term efficacy and safety of phytoestrogen use in varied populations.

**Keywords**

**Phytoestrogens,** Isoflavones**,** Coumestans, Lignans,Genistein, **Hormone-Dependent Tumors,**

**1. Introduction**

Breast cancer is a major worldwide health concern, being the most commonly diagnosed cancer in women and the leading cause of cancer-related death. According to the World Health Organization, there were an estimated 2.3 million new cases and 685,000 deaths from breast cancer in 2020. A wide range of risk factors influence the incidence of this cancer, including non-modifiable elements like age, genetic predisposition, and family history, as well as modifiable lifestyle factors like reproductive history, alcohol consumption, physical inactivity, and obesity. The World Health Organization estimates that breast cancer caused 2.3 million new cases and 685,000 deaths globally in 2020. A wide range of risk factors influences the incidence of this cancer, including both non-modifiable elements like age, genetic predisposition, and family history, as well as modifiable lifestyle factors like reproductive history, alcohol consumption, physical inactivity, and obesity(Rietjens et al. 2017; Surico et al. 2017). Plant-based diets, such as the Mediterranean diet, have been linked to a lower incidence of breast cancer. In contrast, diets rich in processed foods, red meat, and bad fats have been related to an increased risk of cancer. Phytoestrogens, one of the bioactive substances found in plant-based meals, have received a lot of interest for their possible significance in breast cancer prevention and treatment (Murkies et al. 2000; Cappelletti et al. 2006; Barnes 2010; Mauny et al. 2022).

Phytoestrogens are naturally occurring plant-derived substances with structural and functional properties similar to endogenous estrogen. Phytoestrogens are classified into three types: isoflavones, which are mostly found in soy products; lignans, which are abundant in flaxseeds, whole grains, and some vegetables; and coumestans, which are found in legumes like alfalfa and clover. Because of their propensity to bind to estrogen receptors, phytoestrogens can have both estrogenic and anti-estrogenic effects, impacting breast cancer development and progression. The link between phytoestrogen use and breast cancer continues to be studied extensively. While some epidemiological studies indicate a preventive benefit, particularly when taken early in life, others have conflicting results. According to experimental investigations, phytoestrogens can affect cell signaling pathways, regulate the cell cycle, and trigger apoptosis in breast cancer cells. However, differences in metabolism, bioavailability, and gut microbiota composition add to the complexities of their biological effects (Keinan-Boker et al. 2004; Nechuta et al. 2012; Fritz et al. 2013; Messina 2014).

The purpose of this review is to give a complete investigation of the effect of dietary phytoestrogens on breast cancer prevention and management. We want to elucidate the potential function of phytoestrogens in breast cancer prevention by combining current epidemiological evidence, clinical trials, and molecular insights, as well as investigate their implications for dietary recommendations in at-risk populations.

**2. Types and sources of dietary phytoestrogens**

Phytoestrogens are naturally occurring plant chemicals that share structural and functional properties with endogenous estrogen. They can bind to estrogen receptors and have either estrogenic or anti-estrogenic actions, depending on the physiological setting. Phytoestrogens are divided into three categories: isoflavones, lignans, and coumestans as summarized in Table 1. Each of these classes has a distinct chemical structure, biological activity, and dietary sources(Kurzer and Xu 1997; Bacciottini et al. 2007).

**2.1. Isoflavones**

Isoflavones are a subclass of flavonoids found mostly in legumes, particularly soybeans. Genistein, daidzein, and glycitein are the most studied isoflavones, and they are found largely as glycosides in plant-based meals. In the gut, these glycosides are converted by enzymes, allowing them to be absorbed and then used biologically. Isoflavones can modify estrogenic pathways by binding to estrogen receptors, prompting substantial investigation into their potential protective effects against hormone-related malignancies, such as breast cancer.
Common dietary sources of isoflavones include Soy-based items including tofu, soy milk, tempeh, miso, and edamame. Legumes including chickpeas and lentils also come under this category (Horn-Ross et al. 2000; Adlercreutz 2002; Thompson et al. 2006).

**2.2. Lignans**

Lignans are polyphenols found in whole grains, seeds, and vegetables. Unlike isoflavones, lignans must undergo microbial metabolism in the stomach before being transformed into physiologically active chemicals, notably enterolactone and enterodiol. These metabolites have low estrogenic activity and may alter hormone-related illness risk via regulating estrogen metabolism and receptor signaling. Flaxseeds are the richest source of lignans, with up to 800 times more than any other plant food. Typical dietary sources of lignans include Flaxseed which has its highest concentration, Whole grains (wheat, oatmeal, rye, and barley), Legumes( lentils, chickpeas, and beans) as well as Fruits and vegetables (especially carrots, broccoli, and berries) (Mazur and Adlercreutz 1998; Setchell and Cassidy 1999; Messina 2014)

**2.3. Coumestans**

Coumestans, including coumestrol, are the least abundant type of phytoestrogen but have significant estrogenic activity. They are typically found in sprouted legumes and leafy greens. Coumestans may alter estrogen-dependent physiological processes due to their significant binding affinity for estrogen receptors, however, their dietary contribution is lower than that of isoflavones and lignans combined. Coumestans are commonly found in Legume sprouts (alfalfa, clover, and soybean sprouts) and leafy greens (spinach and b russels sprouts) (Lampe et al. 1999; Barcenilla et al. 2000; Thompson et al. 2006).

Phytoestrogen bioavailability and physiological effects are controlled by a variety of factors, including food processing processes, gut microbiota makeup, and dietary patterns. Understanding the different types and sources of dietary phytoestrogens is critical for assessing their potential health effects and incorporating them into disease prevention and promotion diets.

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| Type | Key compounds | Characteristics | Common dietary sources |
| Isoflavones | Genistein, Daidzein, Glycitein | Found mainly in legumes, especially soy. Exist as glycosides; converted by gut enzymes for absorption. | * Soy products: tofu, soy milk, tempeh, miso, edamame
* Chickpeas, lentils
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| Lignans | Enterolactone, Enterodiol (metabolites) | Found in whole grains, seeds, fruits, and vegetables. Require microbial metabolism in the gut. | * Flaxseeds (richest source)
* Whole grains: wheat, rye, barley, oats
* Legumes: lentils, chickpeas, beans
* Fruits & vegetables: carrots, broccoli, berries
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| Coumestans | Coumestrol | Least abundant; strong estrogenic activity; found in sprouted legumes and leafy greens. | * Legume sprouts: alfalfa, clover, soybean sprouts
* Leafy greens: spinach, Brussels sprouts
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**Table 1. Types of dietary phytoestrogens**

**3. Mechanisms of Action of Phytoestrogens in Breast Cancer**

Phytoestrogens are factory-grounded composites that act as estrogen in structure and have been studied for their eventuality in impacting crucial signaling pathways involved in the development and progression of bone cancer. These composites, including genistein, quercetin, enterolactone, and coumetarol, can interact with important pathways similar to PI3K- AKT- mTOR, MEK- ERK, Wnt/ β- catenin, and JAK- STAT, which play significant places in bone cancer. The **PI3K- AKT- mTOR pathway** regulates vital cellular functions, including growth and survival, and its dysfunction is linked to bone cancer. Genistein, an emulsion set up primarily in soybeans, has been shown to inhibit the activation of PI3K and AKT, reducing survival signals. Also, it suppresses mTOR exertion, which leads to a reduction in protein product and excrescence progression. Genistein also has the implicit to enhance the effectiveness of cancer treatments similar to tamoxifen,  prostrating resistance mechanisms in some bone cancer cases(Torrens-Mas and Roca 2020).

The **MEK- ERK pathway**, which is involved in cell proliferation and survival, can become hyperactive in numerous cancers, including bone cancer. Quercetin, a flavonoid set up in foods like apples, onions, and berries, has been shown to block this pathway by inhibiting the activation of the RAF- MEK- ERK  waterfall,  therefore decelerating cell proliferation. Quercetin also induces cell cycle arrest in the G2/ M phase, halting rapid-fire division, and reducing survival signals by downregulating Cyclin D1, making it a promising agent in targeting this pathway(Torrens-Mas and Roca 2020).

The **Wnt/ β- catenin pathway** is essential for the development of triadic-negative bone cancer (TNBC) and the conservation of cancer stem cells, which are linked to rush and resistance to treatments. Enterolactone, a lignan deduced from flaxseeds and whole grains, interferes with this pathway by precluding β- catenin from entering the nexus, which in turn reduces the expression of genes similar to c- Myc and Cyclin D1. This action impedes TNBC progression and reduces stem cell-like parcels, which could help rush. (Ministerial Meeting on Population of the Non-Aligned Movement (1993: Bali) 1994; Mali et al. 2018)**.**

Incipiently, **the JAK-STAT pathway**, actuated by hormones and cytokines, is pivotal for regulating colorful cellular processes, including proliferation and vulnerable responses. Coumestrol,  set up in alfalfa sprouts and clover, inhibits the phosphorylation of JAK2, which in turn reduces the activation of STAT3. This repression limits cytokine signaling that promotes excrescence growth and inhibits epithelial-mesenchymal transition( EMT), a crucial process in metastasis. By targeting this pathway, coumestrol could potentially reduce the spread of cancer cells (Sohel).

**4. Epidemiological and Clinical Evidence of Phytoestrogens in Breast Cancer**

Population-based studies on phytoestrogen consumption and breast cancer risk: Research suggests that phytoestrogens may help lower breast cancer risk, especially in Asian countries where soy-based foods are a dietary staple. The Shanghai Women's Health Study reported that women with higher soy intake had a 30% reduced risk of breast cancer**.** However, studies in Western populations have produced mixed results, likely due to variations in diet, genetics, and metabolism(Bilal et al. 2014).

Clinical trials evaluating phytoestrogens in breast cancer prevention and management: Some clinical trials suggest that soy isoflavones interact with estrogen receptors and may reduce breast density, a factor linked to lower cancer risk. When used alongside hormone therapies like tamoxifen, phytoestrogens have shown promise in easing menopausal symptoms and maintaining bone health, but their impact on cancer progression remains unclear (Valsecchi et al. 2008; Yao et al. 2019; Goh et al. 2022).

Controversies and inconsistencies in study findings: Findings on phytoestrogens remain inconsistent due to differences in study design, genetics, and individual metabolism. While some experts worry that these compounds could stimulate estrogen-sensitive breast cancers **(9) - (Please mention reference details in brief)** others argue that their effects depend on an individual’s gut microbiota and overall hormonal environment **(10) - (Please mention reference details in brief)** More well-controlled studies are needed to fully understand their role in breast cancer prevention and treatment(Patisaul and Jefferson 2010; Lalioti et al. 2024). Kindly refer to Figure 1 for an illustrative summary.



**Figure 1.** Epidemiological and clinical perspective of phytoestrogens in breast cancer

**5. Use of phytoestrogen for the prevention of breast cancer**

Their function in breast cancer prevention has piqued scientific curiosity, owing to their ability to regulate hormonal activity in the body. Phytoestrogens may help prevent breast cancer by preferentially binding to the estrogen receptor beta (ERβ). Unlike ERα, which encourages cell proliferation, this receptor is thought to inhibit tumors in breast tissue. Phytoestrogens can diminish estrogen-stimulated cell proliferation, a crucial factor in hormone-dependent breast malignancies, by increasing ERβ and reducing ERα activity (Fuentes and Silveyra 2019). Phytoestrogens also alter intracellular signaling pathways that control cell growth, apoptosis (programmed cell death), and metastasis. Compounds such as genistein, a prominent soy isoflavone, have been demonstrated to block the PI3K/Akt and MAPK pathways, both of which are required for cancer cell survival and proliferation. This interference may inhibit tumor formation and progression (Domínguez-López et al. 2020). Additionally, phytoestrogens influence the expression of genes involved in the cell cycle. They can repress oncogenes like cyclin D1 while upregulating tumor suppressor genes like p21 and p27. These alterations help to halt the cell cycle and limit the proliferation of possibly cancer-causing cells. Furthermore, they boost the expression of pro-apoptotic proteins such as Bax while inhibiting anti-apoptotic proteins such as Bcl-2, allowing damaged or altered cells to be eliminated naturally (Nguyen and Osipo 2022). Phytoestrogens may also lessen the risk of breast cancer by modifying estrogen metabolism. They can tip the balance of estrogen metabolites toward those that are less carcinogenic. For example, enhanced 2-hydroxylation of estradiol produces less toxic estrogen metabolites, reducing the estrogenic burden on breast tissue (Domínguez-López et al. 2020). Epidemiological studies add to the evidence supporting phytoestrogens' possible protective effects. Populations with significant soy diet, such as those in East Asia, have been shown to have lower rates of breast cancer than Western populations. These findings are more robust for people who have had early exposure to phytoestrogens, implying that timing may be important in their chemopreventive benefits (Yamamoto et al. 2003). However, the evidence is contradictory, with other research finding no significant link between phytoestrogen intake and breast cancer risk. Individual differences in gut microbiota (which alter phytoestrogen metabolism), genetic polymorphisms, and menopausal state all have the potential to influence outcomes As a result, while phytoestrogens show promise as dietary agents for breast cancer prevention, further research is needed to determine their efficacy and proper use in various groups (Ramakrishna 2013; Bilal et al. 2014).

**6. Use of phytoestrogen as adjuvant therapy with conventional treatments**

Phytoestrogens have been widely studied for their role in cancer prevention although their influence on treatment outcomes remains debated. Some studies indicate that they may affect the efficacy of anti-cancer drugs by modulating pathways such as oxidative stress. Certain phytoestrogens appear to shield healthy cells, potentially mitigating the side effects associated with cancer therapies (Torrens-Mas and Roca 2020). The combination of epigallocatechin gallate (EGCG) with doxorubicin produced synergistic effects stopping cell proliferation and metastasis in prostate cancer cells and in vivo models. Luteolin increased the effectiveness of doxorubicin and decreased its side effects by enhancing the antioxidant capacity of serum(Stearns and Wang 2011). Soy Isoflavones in high doses have been found to stimulate estrogen receptor-positive breast cancer cells. Their use is therefore discontinued in patients undergoing treatment with tamoxifen as they may antagonize tumor growth inhibition (Lin et al. 2008).

**7. Effects on hormone receptor-positive vs. triple-negative breast cancer**

Phytoestrogens promise a great deal as a potential therapeutic agent for triple-negative breast cancer (TNBC) by targeting key signaling pathways such as (AKT/PI3K/mTOR, NF-κB, 3Wnt/β-catenin), metastasis, tumor suppression, and regulating cell death. Some do reverse drug resistance and enhance chemotherapy. Nano-based phytoestrogens enhance drug accumulation and their efficacy while in silico studies show that it is very low toxic and confirms favorable pharmacokinetics making it a promising alternative for TNBC treatment until many effective drugs are available (Sohel).Phytoestrogens have an affinity for Erβ which may inhibit transcriptional activity of Erαeven though they can weakly bind to both. However, only saturating doses stimulating both receptors have been shown to bring upon growth inhibitory factors (Bilal et al. 2014). Phytoestrogens have also been shown to influence breast cancer cells by binding to G protein-coupled estrogen receptors (GPER), affecting proliferation and signaling (Huang et al. 2023). Consuming soybeans has been reported to show a decrease in cancer recurrence even in patients with ER+ breast cancer (Patisaul and Jefferson 2010) .

Phytoestrogens have been studied for their effects on hormone receptor-positive breast cancer but only these compounds can weakly bind to estrogen receptors. However their effect depends on the dose and certain phytoestrogen types (Patisaul and Jefferson 2010).   For Ex. Genistein, aprominent flavonoid phytoestrogen, has been shown to initiate the growth of ER+ breast cancer cells but only under certain conditions (van Duursen et al. 2013a). Kindly refer to Table 2 for a comparative analysis of the effects of phytoestrogens on hormone receptor-positive and triple-negative breast cancer.

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| Aspect | Hormone Receptor-Positive Breast Cancer (ER+/PR+) | Triple-Negative Breast Cancer (TNBC) |
| Receptor Interaction | Weak binding to estrogen receptors, mainly ERβ; high doses needed to stimulate ERα and ERβ simultaneously for inhibitory effects of estrogen | No dependence on ER, PR, or HER2; phytoestrogens act via alternative pathways |
| Effect on Cell Growth | Can stimulate or inhibit cell growth depending on type and dose; e.g., Genistein can promote ER+ cell growth under specific conditions | Inhibits tumor and growth, metastasis, and induces apoptosis via non-hormonal pathways |
| Mechanisms of Action |

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Binding to ERβ may inhibit ERα transcriptional activity; also binds to GPER affecting signaling | Targets AKT/PI3K/mTOR, NF-κB, Wnt/β-catenin pathways; inhibits metastasis and induces tumor suppressionPI3K/mTOR, NF-κB, |
| Mechanisms of Action | Limited evidence; that some phytoestrogens may interfere with hormonal therapies | Enhances chemotherapy efficacy; some reverse drug resistance; nano-formulations improve drug accumulation |
| Recurrence Impact | Soy consumption linked with reduced recurrence in ER+ patients  | Shows potential as an adjunct therapy where no hormonal targets are available |
| Toxicity and Pharmacokinetics | Dose-dependent; high concentrations may have adverse effects | Low toxicity and favorable pharmacokinetics shown in in-silico studies |

**Table 2.** Comparative Effects of Phytoestrogens on Hormone Receptor-Positive and Triple-Negative Breast Cancer

[**Abbreviations:** AKT – Protein Kinase B; ER – Estrogen Receptor; ER+ – Estrogen Receptor Positive; ERα – Estrogen Receptor Alpha; ERβ – Estrogen Receptor Beta; GPER – G Protein-Coupled Estrogen Receptor; HER2 – Human Epidermal Growth Factor Receptor 2; mTOR – Mechanistic Target of Rapamycin; NF-κB – Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; PR – Progesterone Receptor; TNBC – Triple-Negative Breast Cancer; Wnt – Wingless/Integrated]

**8. Safety considerations and potential interactions with medications**

High phytoestrogen intake could increase the risk of carcinogenesis and affect breast cancer recurrence, while others propose protective effects. Phytoestrogens often seen as beneficial can pose a risk in cancer contexts. They can mimic endocrine disruptors in hormone-sensitive cancers like breast cancer. Consulting a healthcare provider before increasing intake is usually suggested (van Duursen et al. 2011, 2013b).

**9. Interaction with Medications**

Phytoestrogens can decrease the efficacy of breast cancer treatment and may require dosage adjustment for breast cancer medications, like tamoxifen and aromatase inhibitors. Its anticancer properties are muted because phytoestrogens compete with the drugs’ mechanisms, by binding to estrogen receptors, changing drug metabolism, and blocking cellular signaling pathways. It is suggested that phytoestrogens have been implicated in the effectiveness of chemotherapeutic agents through modulation of reactive oxygen species (ROS), influencing drug absorption, and altering the body’s detoxification processes, potentially contributing to a decrease in cytotoxic effects of chemotherapy (de Lemos 2001; Torrens-Mas and Roca 2020).

**10. Conclusion**

Dietary phytoestrogens, due to their structural closeness to endogenous estrogens, represent a viable option for breast cancer prevention and therapy. Their capacity to interact with estrogen receptors, affect gene expression, and influence different cellular pathways including apoptosis, proliferation, angiogenesis, and oxidative stress demonstrates their diverse function in cancer biology. The addition of phytoestrogens to the daily diet, notably isoflavones, lignans, and coumestans, has demonstrated potential benefits in lowering breast cancer risk, particularly when introduced early in life or ingested regularly over time. Epidemiological and experimental research have provided solid evidence for their preventive role, but there are still uncertainties due to individual variability, tumor heterogeneity, and dietary changes among populations. While the therapeutic implications of phytoestrogens are still being debated, particularly in hormone-sensitive breast cancer subtypes, existing evidence suggests that, when ingested carefully, these chemicals may complement conventional therapies and improve patient outcomes. Furthermore, their natural origin, minimal toxicity, and extra health advantages make them ideal candidates for inclusion in comprehensive cancer care regimens. This study emphasizes the importance of dietary choices in modifying cancer risk and progression, with phytoestrogens serving as crucial components of preventive nutritional oncology. As we move toward personalized medicine, future research should focus on defining dose-response relationships, identifying biomarkers for responsiveness, and conducting large-scale, longitudinal studies to offer clear guidelines for the safe and effective use of phytoestrogens in varied populations.

**Using Artificial Intelligence (AI):**

No artificial intelligence (AI)-assisted technologies were used in the production of the submitted work.

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