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A Mini Review on Components of Flax Seed and Their Effects on Breast Cancer

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ABSTRACT
Breast cancer is recognized as one of the most common cancers worldwide that can lead to death. Alternative treatment options are needed due to drug resistance caused by current treatment methods such as chemotherapy, inclusion of healthy cells in the target, and possible side effects. In this context, there is great interest in natural compounds and their active metabolites. One of these is flaxseed (FS), which is one of the most studied foods to be associated with breast cancer. FS is a functional food with high nutritional value. FS components (fatty acids, fiber, and lignans) and especially the basic lignan structure in FS content, secoisolariciresinol diglucoside (SDG) and its metabolites enterolactone (ENL) and enterodiol (END) have beneficial effects on breast cancer progression. This review aimed to develop a perspective for further research on this type of cancer in the future by giving some general information about FS and its components and evaluating some studies showing potential effects on breast cancer.

Keywords: Chemotherapy, Flaxseed, Lignan, Breast cancer, SDG

1. Introduction

Breast cancer is one of the most frequently diagnosed invasive cancer types, especially in women (Sharma et al. 2010). According to data in 2020, it has been reported that breast cancer with approximately 2.3 million cases is responsible for 11.7% of all cancer cases and 6.9% of cancer-related deaths worldwide (Global Cancer Observatory). According to the 2020 WHO-Turkey cancer profile, it has been reported that breast cancer has a rate of 46.6% in total cancer cases and 12.9% in cancer deaths (Cancer Today. Global Cancer Observatory).

It is estimated that a certain percentage of the occurrence of breast cancers (approximately 5-10%) is due to genetic factors based on mutations of some genes, and the presence of individuals with this disease in the family may cause the person to inherit genetic mutations that create the relevant risk factors (Kabel & Baali 2015; Smolarz et al. 2022). Related hormones (such as estradiol, and progesterone) are also the main determinants of cancer risk in women who do not have a genetic indicator, including gender, poor eating habits, bad lifestyles, alcohol or tobacco consumption, late first pregnancy, long-term hormone treatments, overweight and obesity are factors associated with the incidence of breast cancer (Yue et al. 2013; Britt et al. 2020; Smolarz et al. 2022).

The course of the disease and survival rates in breast cancer can vary greatly depending on the type of cancer, its stage, the types of treatment (such as surgical intervention, radiation, chemotherapy, and hormonal therapy), and even the geographical location of the patient (Sharma et al. 2010; Marghescu et al. 2012; Feng et al. 2018).

Related nuclear receptors for the steroid hormones estrogen (ER) and progesterone (PR) and human epidermal growth factor receptor 2 (HER2) are important hormone receptor markers used in breast cancer (da Luz et al. 2022). Breast tumors are divided into various subtypes based on hormone receptor expression and the amount of the cellular proliferation marker Ki67 (Januškevičienė & Petrikaitė 2019; Moar et al. 2023). These are hormone receptor-positive (HR+), HER2-enriched (HER2+), and triple-negative breast cancers (TNBC) (He et al. 2023). HR+'s are ER+ and PR+'s. They are divided into two subclasses: luminal A (ER+ and/or PR+ and HER2−) and luminal B tumors (ER+ and/or PR+ and HER2+) (or HER2− with high Ki-67) (Tang et al. 2016; da Luz et al. 2022; He et al. 2023; Moar et al. 2023).

Heterogeneity in breast cancer cases can cause difficulties in determining the course of this disease and in pursuing a successful treatment path (Wiggins et al. 2015; Feng et al. 2018). Although tumor cell molecular subtypes are different, the chemotherapy method applied remains the mainstay (Wang et al. 2010; Twelves et al. 2016; Xing et al. 2019). In order to get a stronger effect, chemotherapeutic drug combinations with different mechanisms of action are used, but increased toxicity is observed with this treatment method (Di et al. 2018).

Drug discovery from medicinal plants already plays an important role in cancer treatment. Natural compounds and their active metabolites are used as adjuvant therapy in breast cancer patients to eliminate chemotherapy and radiotherapy-induced side effects and to improve the quality of life of patients (Zhang et al. 2018). Flaxseed (*Linum usitatissimum*) (FS) is a rich functional food known for its high concentration of fiber, lignans, and omega-3 fatty acids (Rubilar et al. 2010; Bernacchia et al. 2014; Goyal et al. 2014). Lignans, from the phytoestrogen group, are diphenolic active natural compounds that exhibit various biological properties of plant origin and are present in many foods in small amounts, while they are found at high levels in FS (Kajla et al. 2015; Nikolić et al. 2017; Rodríguez-García et al. 2019). Studies involving lignans focus on their phytoestrogenic properties and their potential to affect estrogen-sensitive cancers, including breast cancer (Saarinen et al. 2007; Seibold et al. 2014; Chang et al. 2019).

In the review, the main information was presented about lignans and the basic properties of the components of FS, which is an important lignan type, and its connection with breast cancer. It aims to shed light on further studies on breast cancer by mentioning the studies based on its effects on breast cancer, which is a type of estrogen-sensitive cancer.

2. Estrogens and estrogen receptors

The steroid hormones estrogen and progesterone and their respective receptors are regulators of breast functions and are effective in the development of breast cancer (Daniel et al. 2011). In addition to many basic functions (bone homeostasis, modulation of brain functions, cardiovascular systems, and musculoskeletal system, etc.), there are three main forms of estrogens (17β-estradiol (E2), estrone(E1) and 16α-estriol (E3)), which are the primary sex hormones that perform the functions of the female reproductive systems. They are all derived from cholesterol and are known as C18 steroids. The most dominant and active estrogenic hormone among endogenous estrogens is known as E2 (Nazari & Suja 2016). E1 is produced in the ovaries, adrenal cortex, and testicles from androstenedione under the influence of aromatase. It is the main hormone during menopause in women and E1 is converted to E2 by the enzyme 17β-hydroxysteroid dehydrogenase. E2 is mainly secreted by the granulosa cells of the ovarian follicles and the corpus luteum. E3 is an almost completely inactive metabolite of E2 and E1 produced mainly in the liver and is active during pregnancy (Mansur et al. 2012; Samavat & Kurzer 2015; Fuentes & Silveyra 2019; Ceccarelli et al. 2022). While E2 synthesized in the ovaries in premenopausal women is the most important estrogen, endogenous estrogen production decreases in postmenopausal women, and mostly E1 plays a dominant role (Samavat & Kurzer 2015; Das et al. 2022). It is the type of estrogen with the strongest binding affinity for E2 receptors. E2 is known to increase cell proliferation, which is associated with breast cancer development through its receptor-mediated actions (Yue et al. 2013).

Steroid hormones act through receptors on target cells. The hormone binds to its corresponding receptor in the cytosol and the resulting complex acts as a transcription factor by binding to specific response elements or transcription initiation complexes on DNA. It activates or represses transcription and thus regulates cellular activity (Schwartz et al. 2016). Estrogens, a type of steroid hormone, perform their specific actions by binding to estrogen receptors (ERs) and initiate various estrogen-dependent physiological processes by activating transcriptional processes and/or signaling events (Fuentes & Silveyra 2019; Khan et al. 2022). Estradiol in steroid structure plays an active role in the development of breast cancer, binds to its receptor and translocates to the nucleus, and related gene transcriptions are stimulated. Most types of human breast cancer start with estrogen-related receptors expressed, and the expression of the receptors is recognized as important prognostic markers (Roy & Vadlamudi 2012; Hilton et al. 2018).

It has been reported that the most common type of breast cancer is estrogen receptor-positive (ER+) breast cancer, which accounts for a large percentage of all cases (Turner et al. 2017; Almeida et al. 2020). The physiological functions of estrogenic compounds are modulated by the alpha (ERα) and beta (ERβ) subtypes of estrogen receptors encoded by different genes (Mal et al. 2020; Božović et al. 2021). These receptors belong to the family of steroid receptors and bind certain ligands of different tissue distribution with different affinities (Almeida et al. 2020; Mal et al. 2020).

While ERα is found in the mammary gland, fatty tissues, prostate, uterus, male reproductive organs (testes and epididymis), liver, and ovaries, ERβ is mainly found in the bladder, prostate, ovary (granulosa cells), adipose tissue, and colon (Paterni et al. 2014; Khan et al. 2022). ERα appears to be the main arm of estrogen action in the breast. It has been reported that ERα+ has a very high rate (80%) among all breast cancer cases diagnosed in post-menopausal women (Poschner et al. 2019). Although not valid for all studies, it has been reported in general studies that ERα causes a proliferative effect in the breast, and ERβ mostly causes a pro-apoptotic and anti-proliferative effect and inhibits cell proliferation supported by ERα in tissues such as the uterus and breast (Paterni et al. 2014; Hilton et al. 2018).

3. Phytoestrogens and their estrogenic activities

Phytoestrogens are polyphenolic plant-derived compounds structurally similar to the mammalian estrogen 17-β-estradiol, which can exhibit both weak estrogenic and antiestrogenic properties and bind to their receptors (Power et al. 2008; Velentzis et al. 2008). Due to their nature, they can interfere with hormonal signaling by acting as weak estrogenic factors (Torrens-Mas & Roca 2020). Although phytoestrogens have many beneficial effects on health, the main mechanism of their action is their binding to ERs (Gorzkiewicz et al. 2021). Phytoestrogens are characterized by hydroxyl groups in their phenolic rings and these structures match the hydroxyl groups of the aromatic rings of E2 (Basu & Maier 2018; Ceccarelli et al. 2022). The estrogenic activity of phytoestrogens depends on their affinity for specific ERs in the body (Moreira et al. 2014). These compounds, which can bind weakly to both ERα and ERβ, induce estrogenic or antiestrogenic effects, competing with E2 for ligand binding sites of the receptors (Ceccarelli et al. 2022).

Phytoestrogens; classified as isoflavones, coumestans, stilbenes, and lignans, and the isoflavone and lignan family of phytoestrogens are the most frequently studied groups (Basu & Maier 2018; Tanwar et al. 2021). Soybean and soy-derived foods are the most important sources of isoflavone species in acetyl and malonyl glucoside forms (daidzin, glycitin, and genistin) (Helferich et al. 2008). Genistein, daidzein, glycitine, biochanin A, and farmononentin are compounds of the isoflavone group. While genistein and daidzein are the major isoflavones, biochanin A and farmonentin are the precursors that are metabolized to these two isoflavones, respectively (Tanwar et al. 2021).

The most important sources of lignans, a group included in the phytoestrogen family, can be listed as fiber-rich cereal bran, as well as fruits, vegetables, cereals, and seed pods (Velentzis et al. 2008; Touré et al. 2010). Lignans are chemically composed of two phenylpropane units linked by a β-β' bond between the central atoms of their respective side chains; are natural, biologically active compounds (Torrens-Mas & Roca 2020; Chhillar et al. 2021). They are found in small amounts in many foods (whole grains, sesame seeds, vegetables, and fruits) but at significant levels in FS (Di et al. 2018). After ingestion, plant lignans are metabolized by intestinal bacteria to enterolignans, enterodiol (END), and enterolactone (ENL) (Duffy et al. 2007). These metabolites, which are formed following the metabolism of plant lignans in the colon, pass into the circulation and target tissues (Patel et al. 2012).

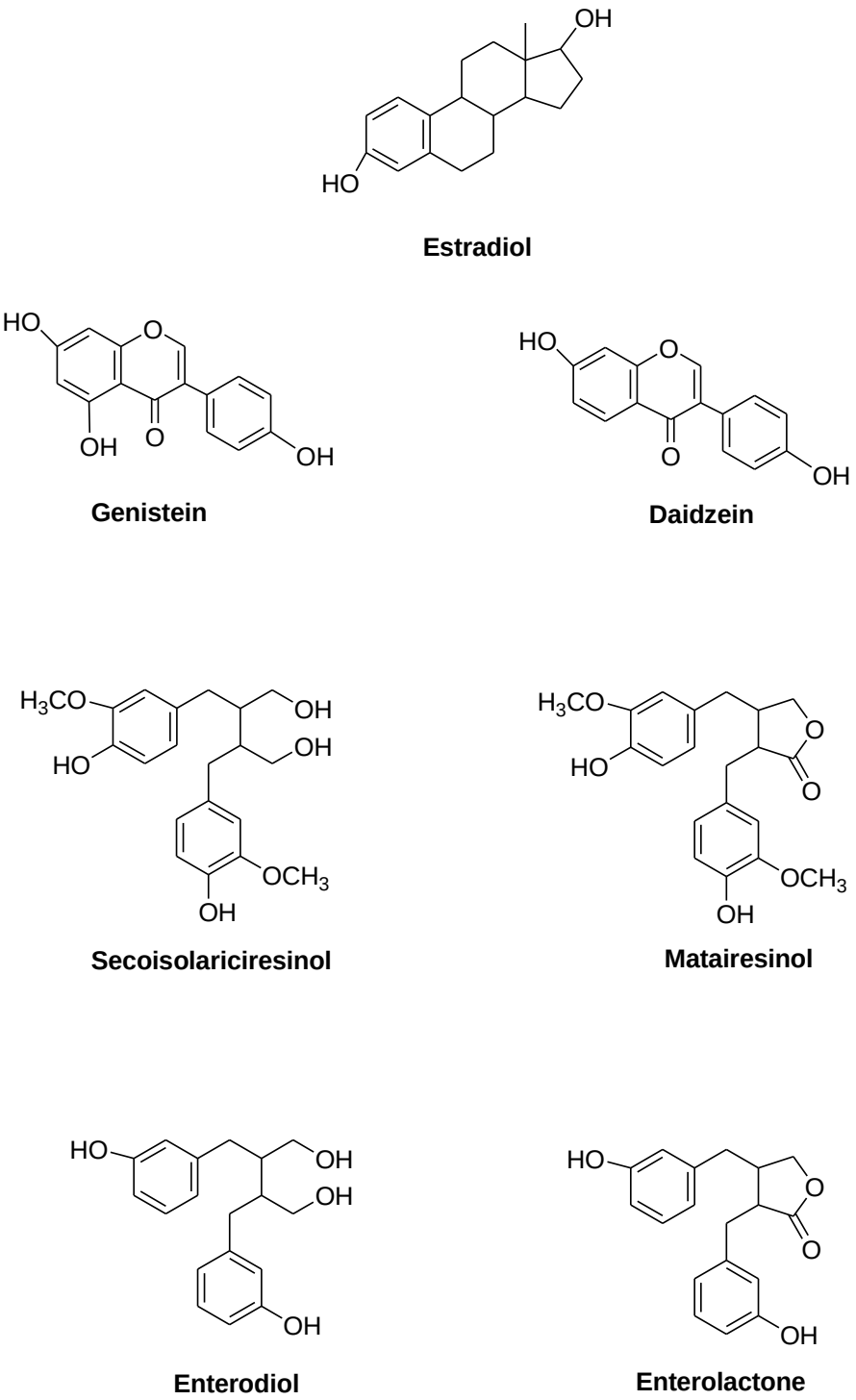

Figure 1- Chemical structures of 17β-estradiol and some isoflavones (Genistein and Daidzein) and lignans (Secoisolariciresinol, Matairesinol, Enterodiol, and Enterolactone)

4. Flaxseed content

Flax (*Linum usitatissimum*) in the form of seed or seed oil is a functional food known for its exceptional nutritional values (Buckner et al. 2019; Hu et al. 2019; Bhimjiyani et al. 2021). FS consists of two types, brown and golden, depending on the climatic conditions in which it grows (Calado et al. 2018). FS contains high levels of dietary fiber, lignans, abundant micronutrients, and omega-3 fatty acids (Khan et al. 2007; Truan et al. 2010; Lee & Cho 2012; Bak et al. 2016). It is unique among oilseeds because of the important fatty acids it contains, such as α-linolenic acid (ALA). It was determined that the concentration of ALA in FS was higher than the concentration of linoleic acid and oleic acid (Kavousi & Chavoshi 2020). It is very important for people to include foods high in ALA in their diet. This is because the human body lacks the desaturation enzymes necessary to produce these fatty acids (Simopoulos 2002). Omega-3 fatty acids are provided in the diet largely through the consumption of seafood. Therefore, both vegetarian and non-fish populations seem to be at a disadvantage in terms

of omega-3 intake (Goyal et al. 2015). FS is a rich vegetarian source thought to meet this need. In addition, FS is rich in dietary fibers, which are known to have many beneficial effects such as modulation of the gut microbiota (Taibi et al. 2019).

5. Flaxseed lignan sources

FS is the richest source of the phytoestrogen secoisolariciresinol diglycoside (SDG), an important plant lignan that can be metabolized by bacteria in the animal or human colon to the mammalian lignans ENL and END (Chen et al. 2002; Chen et al. 2006; Power&Thompson 2007). SDG is a type of polyphenolic lignan found in FS and seeds rich in different oils, whole grains and legumes, and some fruits and vegetables (Dobrowolska&Regulska-Ilow 2021). The predominant lignan in FS is SDG, which makes up 95% of the lignan content of the seed. The remaining 5% consists of lariciresinol, pinoresinol, and matairesinol lignans (Westcott & Muír 2003; Tannous et al. 2020).

After oral ingestion of SDG, it is hydrolyzed to secoisolariciresinol (SECO) and *Peptostreptooccus* and *Eubacterium* bacteria in the colon convert this lignan to the mammalian lignans ENL and END by dehydroxylation and demethylation reactions (Khan et al. 2007; Patel et al. 2012; Bowers et al. 2019) (Figure 2). It is known that SDG and its metabolites enterolignans have preventive and protective effects on various types of cancer due to their antiproliferative, antiestrogenic, antioxidant, or inhibiting some enzymes (Alphonse & Aluko 2015). It has been reported that END and ENL are structurally similar to estrogen and bind to the estrogen receptor (ER), reducing the risk of cancer and exhibiting antiestrogenic effects (Saggar et al. 2010; Calado et al. 2018). It has also been shown that END and ENL can respond to benign prostatic hyperplasia, prostate tissue, and breast cancer by inhibiting 5α-reductase and aromatase-like enzymes (Brooks & Thompson 2005; Zhang et al. 2008).

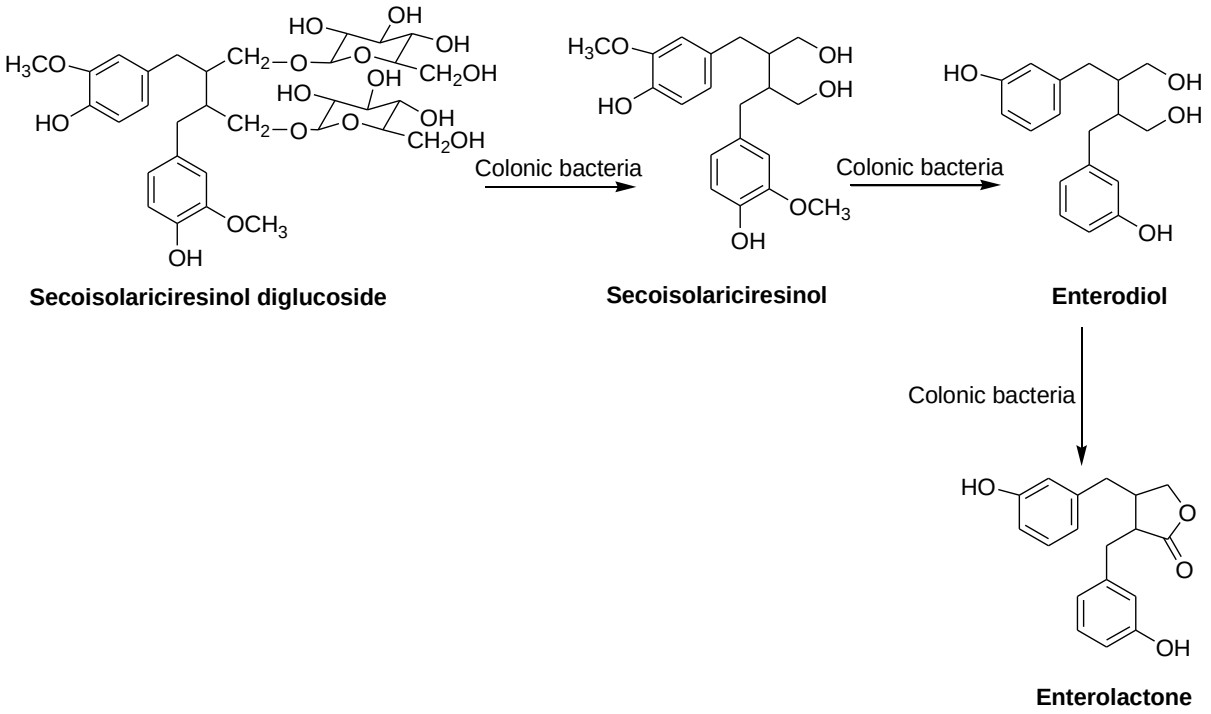

Figure 2- Transformation of SDG to END and ENL

6. Some studies on breast cancer with flaxseed components

Various studies have shown that dietary FS, flaxseed oil (FSO), and FS lignan components have inhibitory effects on the growth and development of breast cancer cells, and FS components combined with chemotherapeutic agents applied to cancer cells have a supportive effect on the cytotoxicity of drugs (Table 1). Chen et al. (2004) investigated the effects of dietary FS and tamoxifen (TAM) alone and in combination on the growth of estrogen-dependent human breast cancer (MCF-7) in athymic mice. It has been reported that FS highly regresses the tumor size before treatment at low E2 level. FS potentiated the tumor inhibitory effect of TAM at both low and high E2 levels. Di et al. (2018) proved in their study that FS lignans significantly increased the cytotoxic effect of classical chemotherapeutic agents (docetaxel, doxorubicin, and carboplatin) in metastatic breast cancer cell lines SKBR3 and MDA-MB-231. It has been observed that the combined treatment of trastuzumab and flaxseed oil, which is the primary treatment method for tumors, resulted in decreased cell proliferation of Akt and MAPK pathways and HER2 signaling, and activation of apoptosis. It has also been indicated that FSO alters the tumor fatty acid profile, which likely contributes to its effect on signaling pathways (Mason et al. 2015).

According to experimental studies, flaxseed has no interaction with drugs used in the treatment of breast cancer and may provide an additional protective effect when consumed with treatment. In animal studies, intake of flaxseed, flaxseed oil, or lignan SDG in combination with TAM has been confirmed to reduce tumor size more than TAM treatment alone (Calado et al. 2018). FS and FSO, a rich source of lignans and ALA, have been found to inhibit growth and metastasis, reduce tumor size, and increase apoptosis of human breast cancer implanted in athymic mouse models (Chen et al. 2002; Chen et al. 2006; Truan et al. 2010). The phenolic extract obtained from FS oil exhibits a strong synergistic effect to reduce proliferation in breast cancer cell lines, especially with chemotherapeutic treatment. It was seen in the study by Guerriero and coworkers that the application of the relevant extract in MCF-7 cells, when applied alone and in combination with the drug, induces apoptosis by increasing the mRNA expression of genes such as p53, Bax, p38, and caspase-3. They found that when combined treatment with DOX, especially in MCF-7 cells, it triggered both extrinsic and intrinsic apoptotic mechanisms. In MDA-MB-231 cells, on the other hand, it was shown that combined treatment induced only the genes related to the extrinsic apoptotic pathway, but both apoptotic pathways were activated when the extract was applied alone (Guerriero et al. 2017). Hu et al. (2019) showed that there was a dose- and time-dependent decrease in cell viability of MCF-7 cells treated with flaxseed extract, increased lipid peroxidation, and triggered apoptosis. In addition, it was determined that there was an increase in the expression of p53, cleaved caspase-3, cleaved-PARP, and cleaved caspase-7 in FS extract-induced apoptosis, and the mitochondrial membrane potential ($\triangle\Psi m$) decreased due to the activation of mitochondrial dysfunction.

Treatment with FSO in different cancer cell lines (cervical cancer, murine melanoma, leukemia, and breast cancer cell lines) has been shown to dose-dependently reduce the growth of malignant cells. In addition, it was determined that MCF-7 breast cancer and B16-BL6 murine melanoma cell lines regulate caspase activation by promoting caspase and PARP cleavage, increasing DNA fragmentation, and inducing apoptosis. The results revealed that cancer cell growth can be specifically inhibited by FSO (Buckner et al. 2019). Tumor size was reduced in mice receiving SDG supplementation. It was determined that phospho-p65 (p-p65), which is the activated form of a subunit of NFκB, was significantly reduced. In addition, *in vitro* ENL administration was found to inhibit viability, survival, and expression of NF-κB target genes in E0771, MDA-MB-231, and MCF-7 breast cancer cell lines (Bowers et al. 2019). Researchers have shown that SDG metabolites reduce proliferation, adhesion, migration, and invasion in estrogen receptor-negative (ER-) human breast cancer MDA-MB-231 cell line and increase the response of these cells to chemotherapy treatment (Mali et al. 2012; Di et al. 2018; Xiong et al. 2015; Bowers et al. 2019).

In a study examining the effect and potential mechanism(s) of TAM alone or in combination with SDG, and FO on the growth of established human estrogen receptor-positive (ER+) breast tumors, it was shown that FS components contribute to the efficacy of TAM by triggering decreased cell proliferation and increased apoptosis by modulation of ER and growth factor-mediated signaling pathways (Saggar et al. 2010). Chen et al. (2009) found that both FS and SDG can significantly reduce the growth of human mammary tumors located in athymic mice and mRNA expressions of some estrogen-sensitive genes, cyclin D1, pS2, ERα and Erβ, and biomarkers in signaling pathways such as epidermal growth factor receptor. SDG and its different derivatives have proven to be promising agents with antiestrogen and pro-apoptotic effects in hormone-dependent breast cancer cells (MCF-7) (Scherbakov et al. 2021).

ENL-induced cellular changes in MDA-MB-231 cells have been investigated and it has been reported that lignan has an antiproliferative effect in these cells and decreases the mRNA levels of Ki67, PCNA, and FoxM1 genes, which are related to cell proliferation (Xiong et al. 2015). It was determined that ENL decreased the viability of MDA-MB-231 and T47D breast cancer cell lines in a concentration- and time-dependent manner, significantly increased the radiosensitivity of the cells by abolishing G2/M blockade, impairing DNA repair, and increasing radiation-induced apoptosis (Bigdeli et al. 2016). It has been reported that the treatment of ER+ breast cancer cells with lignan extracts obtained from flaxseed changes possible estrogen signaling, increases estradiol production depending on the increase in concentration, and down/up-regulates ERα and ERβ expression depending on the concentrations, causing changes in cell development (Richter et al. 2010).

Table 1- Various studies on the effects of FS and its components on breast cancer

Model	***Dosage***	***Outcome***	***Reference***
Ovariectomized mice	10% dietary FS	Reduction in tumor area at both low and high E2 levels	Chen et al. 2004
SKBR3/ MDA-MB-231 cell lines	SECO with 1000μM with serial dilutions ENL (3.12-1000 μM)	Enhancing of FS lignans, especially ENL to the cytotoxic activity of chemotherapeutic drugs	Di et al. 2018
Ovariectomized athymic mice	4% FSO diet (1 or 2.5 mg/kg)	Modulation of combined therapy with reduction of HER2 signaling by AKT and MAPK pathways and decreased cell proliferation and increased apoptosis	Mason et al. 2015
Female athymic nude mice	10% FS diet	Inhibition of breast cancer growth and metastasis	Chen et al. 2002
Female athymic nude mice	SDG (0.2 g/kg) and FO (36.53 g/kg) in the 10% FS diet	Inhibition of tumor metastasis	Chen et al. 2006
Ovariectomized athymic mice	FSO (40 g/kg)	Reduction in tumor size and tumor proliferation, increased apoptosis, decreased expression of EGFR, EGFR2 and Akt	Truan et al. 2010
MCF-7 MDA-MB-231 cell lines	A phenolic extract from FS (3.9-258 μg/mL)	Decreased cell proliferation in both cell lines, induction of apoptosis by increasing mRNA expression of genes such as p53, Bax, p38, and caspase-3 of either cell type-dependent treatment alone or in combination	Guerriero et al. 2017
MCF-7 cell line	FS extract (0-320 μg/mL)	Dose and time-dependent cell growth inhibition, increase in apoptosis and lipid peroxidation; Increased expression of p53, cleaved-caspase 3, cleaved-PARP, and cleaved-caspase-7, decreased mitochondrial transmembrane potential	Hu et al. 2019
MCF-7, MDA-MB-231, and MDA-MB-468 breast cancer cell lines, and other cancer cell lines	0.3%-0.9% (v/v) of flaxseed	Inhibition of cancer cell growth, caspase activation, and induction of apoptosis in some cancer lines (MCF-7 and B16-BL6)	Buckner et al. 2019
C57BL/6 mice, MDA-MB-231, and MCF-7 human cell lines, EO771 mouse mammary tumor cell line	SDG, 100 mg/kg diet ENL (1 μM or 10 μM)	Reducing the expression of p-p65 in mice with SDG administration, reducing cell viability and expression of NF-kB target genes in breast cell lines with ENL application	Bowers et al. 2019
MCF-7, and MDA-MB-231 breast cancer cell lines	ENL (25 or 50 μM)	Inhibition of proliferation and migration of breast cancer cells; downregulation of MMP2, MMP9, and MMP14 gene expressions	Mali et al. 2012
MDA-MB-231 cell line	ENL (0-400 μM)	Accumulation of cells in the S phase and decreased cell proliferation, decrease of mRNA expression levels of Ki67, PCNA, and FoxM1 genes, which are genes associated with cell proliferation and expression of genes associated with the S and G2/M phases of the cell cycle, inhibition of migration and invasion	Xiong et al. 2015
BALB/c athymic mice	F0 (38.5 g/kg diet), SDG (1 g/kg diet) or their combination (10%FS diet)	Decrease of expression of related genes and proteins involved in ER- and growth factor-mediated signaling pathways and cell proliferation	Saggar et al. 2010
Ovariectomized athymic mice	FS (100 g/kg diet) SDG (1 g/kg diet)	Reduction of palpable tumor size, cell proliferation, induction of	Chen et al. 2009

	FH (lignan-rich fraction)(18 g/kg diet)	apoptosis; decrease of expressions of Bcl2, cyclin D1, pS2, ERα, ERβ, EGFR, HER2, and IGF-IR mRNA	
MDA-MB-231 T47D cell lines	ENL (1,10,50,100,200,500 μM)	Decrease of cell viability, elimination of G2/M arrest, DNA repair disruption, and increased radiation-induced apoptosis and radiosensitivity	Bigdeli et al. 2016
MCF-7 cell line	Flax root lignans (10-50-100 μg/mL)	Concentration-dependent increase in estradiol production, ERα and ERβ downregulation at high concentrations	Richter et al. 2010

7. Conclusions

FS is a nutritious functional food containing a high concentration of fiber-based lignans and omega fatty acids. Lignans, which are natural biologically active compounds, are a class of chemicals suitable for drug development. The predominant lignan in FS, SDG, is converted to its metabolites by bacteria in the colon after oral ingestion. Since SDG and its metabolites exhibit phytoestrogenic properties due to their special structures, their potential to affect estrogen-sensitive breast cancer-like cancer types has been focused on. Studies have proven that the nutraceutical application of FS components alone or in combination with drugs can show potent therapeutic efficacy in stopping or reducing breast cancer progression. Understanding how FS interacts with malignant cells offers hope for developing an anticancer drug or drug combination that can cause minimal side effects against cancer cells.

References

Almeida C F, Oliveira A, Ramos M J, Fernandes P A, Teixeira N & Amaral C (2020). Estrogen receptor-positive (ER+) breast cancer treatment: Are multi-target compounds the next promising approach? Biochemical Pharmacology 177: 113989

Alphonse P A S & Aluko R E (2015). Anti-carcinogenic and anti-metastatic effects of flax seed lignan secolariciresinol diglucoside (SDG). Discovery Phytomedicine 2: 12-17

Bak M J, Gupta S D, Wahler J & Suh N (2016). Role of dietary bioactive natural products in estrogen receptor-positive breast cancer. Seminars in Cancer Biology 40-41: 170-191

Basu P & Maier C (2018). Phytoestrogens and breast cancer: In vitro anticancer activities of isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives. Biomedicine&Pharmacoyherapy 107: 1648-1666

Bernacchia R, Preti R & Vinci G (2014). Chemical Composition and Health Benefits of Flaxseed. Austin Journal of Nutrition and Food Sciences 2 (8):1045

Bhimjiyani V H, Borugadda V B, Naik S & Dalai A K (2021). Enrichment of flaxseed (Linum usitatissimum) oil with carotenoids of sea buckthorn pomace via ultrasound-assisted extraction technique: Enrichment of flaxseed oil with sea buckthorn. Current Research in Food Science 4: 478-488

Bigdeli B, Goliaei B, Masoudi-Khoram N, Jooyan N, Nikoofar A, Rouhani M, Haghparast A & Mamashli F (2016). Enterolactone: A novel radiosensitizer for human breast cancer cell lines through impaired DNA repair and increased apoptosis. Toxicology and Applied Pharmacology 313: 18-194

Bowers L W, Lineberger C G, Ford N A, Rossi E L, Punjala A, Camp K K, Kimler B K, Fabian C J & Hursting S D (2019). The flaxseed lignan secoisolariciresinol diglucoside decreases local inflammation, suppresses NFκB signaling, and inhibits mammary tumor growth. Breast Cancer Research and Treatment 173(3): 545-557

Božović A, Mandušić V, Todorović L & Krajnović M (2021) Estrogen receptor beta: the promising biomarker and potential target in metastases. International Journal of Molecular Sciencies 22(4):1656

Britt K L, Cuzick J & Philips K A (2020). Key steps for effective breast cancer prevention. Nature Reviews Cancer 20 (8): 417-436.

Brooks J D & Thompson L U (2005). Mammalian lignans and genistein decrease the activities of aromatase and 17β-hydroxysteroid dehydrogenase in MCF-7 cells. The Journal of Steroid Biochemistry & Molecular Biology 94(5):461-467

Buckner A L, Buckner C A, Montaut S & Lafrenie R M (2019). Treatment with flaxseed oil induces apoptosis in cultured malignant cells. Heliyon 9, 5(8): e02251

Calado A, Neves P M, Santos T & Ravasco P (2018). The Effect of Flaxseed in Breast Cancer: A Literature Review. Frontiers in Nutrition 5: 4

Cancer Today, Global Cancer Observatory. https://gco.iarc.fr/today/data/factsheets/populations/792-turkey-fact–sheets.pdf [accessed November 07, 2023]

Ceccarelli I, Bioletti L, Peparini S, Solomita E, Ricci C, Casini I, Miceli E & Aloisi A M (2022). Estrogens and phytoestrogens in body functions. Nuroscience and Biobehavioral Reviews 132: 648-663

Chang V C, Cotterchio M, Boucher B A, Jenkins D J A, Mirea L, McCann S E & Thompson L U (2019) Effect of Dietary Flaxseed Intake on Circulating Sex Hormone Levels among Postmenopausal Women: A Randomized Controlled Intervention Trial. Nutrition and Cancer 71(3): 385-398

Chen J, Stavro P M & Thompson L U (2002). Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. Nutrition and Cancer 43(2):187-192

Chen J, Hui E, Ip T & Thompson L U (2004). Dietary flaxseed enhances the inhibitory effect of tamoxifen on the growth of estrogen-dependent human breast cancer (mcf-7) in nude mice. Clinical cancer research 10(22): 7703-7711

Chen J, Wang L, Thompson L U (2006). Flaxseed and its components reduce metastasis after surgical excision of solid human breast tumor in nude mice. Cancer Letters 234(2): 168-175

Chen J, Saggar J K, Corey P & Thompson L U (2009). Flaxseed and pure secoisolariciresinol diglucoside, but not flaxseed hull, reduce human breast tumor growth (MCF-7) in athymic mice. The Journal of Nutrition 139(11): 2061-2066

Chhillar H, Chopra P & Ashfaq M A (2021). Lignans from linseed (Linum usitatissimum L.) and its allied species: Retrospect, introspect and prospect. Critical Reviews in Food Science and Nutrition 61(16): 2719-2741

Daniel A R, Hagan C R & Lange C A (2011). Progesterone receptor action: defining a role in breast cancer. Expert Review of Endocrinology &Metabolism 6(3): 359-369

da Luz F A C, Araújo B J & de Araújo R A (2022). The current staging and classification systems of breast cancer and their pitfalls: is it possible to integrate the complexity of this neoplasm into a unified staging system? Critical Reviews in Oncology/Hematology 178: 103781

Das S, Kulkarni S, Singh Y, Kumar P & Thareja S (2022). Selective Estrogen Receptor Modulators (SERMs) for the treatment of ER+ breast cancer: An overview. Journal of Molecular Structure 1270: 133853

Di Y, De Silva F, Krol E S & Alcorn J (2018). Flaxseed Lignans Enhance the Cytotoxicity of Chemotherapeutic Agents against Breast Cancer Cell Lines MDA-MB-231 and SKBR3. Nutrition and Cancer 70(2): 306-315

Dobrowolska K & Regulska-Ilow B (2021). The legitimacy of using dietary supplement diglycoside secoisolariciresinol (SDG) from flaxseed in cancer. Roczniki Panstwowego Zakladu Higieny 72(1): 9-20

Duffy C, Perez K & Partridge A (2007). Implications of phytoestrogen intake for breast cancer. CA: A Cancer Journal for Clinicians 57 (5): 260-277

Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, Ji X, Liu W, Huang B, Luo W, Liu B, Lei Y, Du S, Vuppalapati A, Luu H H, Haydon R C, He T C & Ren G (2018). Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes&Diseases 5(2): 77-106

Fuentes N & Silveyra P (2019). Estrogen receptor signaling mechanisms. Advances in Protein Chemistry and Structural Biology 116: 135-170

Global Cancer Observatory. http://gco.iarc.fr [accessed November 07, 2023]

Gorzkiewicz J, Bartosz G & Sadowska-Bartosz I (2021). The Potential Effects of Phytoestrogens: The Role in Neuroprotection. Molecules 26(10): 2954

Goyal A, Sharma V, Sihag M K, Tomar S K, Arora S, Sabikhi L & Singh A K (2015). Development and physico-chemical characterization of microencapsulated flaxseed oil powder: A functional ingredient for omega-3 fortification. Powder Technology 286: 527-537

Goyal A, Sharma V, Upadhyay N, Gill S & Sihag M (2014). Flax and flaxseed oil: an ancient medicine & modern functional food. Journal of Food Science and Technology 51(9): 1633-1653

Guerriero E, Sorice A, Capone F, Storti G, Colonna G, Ciliberto G & Costantini S (2017). Combining doxorubicin with a phenolic extract from flaxseed oil: Evaluation of the effect on two breast cancer cell lines. International Journal of Oncology 50(2): 468-476

He Q, Hu H, Yang F, Song D, Zhang X & Dai X (2023). Advances in chimeric antigen receptor T cells therapy in the treatment of breast cancer. Biomedicine&Pharmacotherapy 162: 114609

Helferich W G, Andrade J E & Hoagland M S (2008). Phytoestrogens and breast cancer: a complex story. Inflammopharmacology 16(5): 219-226

Hilton H N, Clarke C L, Graham J D (2018). Estrogen and progesterone signalling in the normal breast and its implications for cancer development. Molecular and Cellular Endocrinology 466: 2-14

Hu T, Linghu K, Huang S, Battino M, Georgiev M, Zengin G, Li D, Deng Y, Wang Y T & Cao H (2019). Flaxseed extract induces apoptosis in human breast cancer MCF-7 cells. Food and chemical toxicology 127:188-196

Januškevičienė I & Petrikaité V (2019). Heterogeneity of breast cancer: the importance of interaction between different tumor cell populations. Life Science 239: 117009

Kabel A M & Baali F H (2015). Breast Cancer: Insights into Risk Factors, Pathogenesis, Diagnosis and Management. Journal of Cancer Research and Treatment 3(2): 28-33

Kajla P, Sharma A & Sood D R (2015). Flaxseed—a potential functional food source. Journal of Food Science and Technology 52(4): 1857-1871

Kavousi M, Chavoshi M S (2020). Effect of coated carbon nanotubes with chitosan and cover of flaxseed in the induction of MDA-MB-231 apoptosis by analyzing the expression of Bax and Bcl-2. Meta Gene 26: 100807

Khan G, Penttinen P, Cabanes A, Foxworth A, Chezek A, Mastropole K, Yu B, Smeds A, Halttunen T, Good C, Mäkelä S & Hilakivi-Clarke L (2007). Maternal flaxseed diet during pregnancy or lactation increases female rat offspring's susceptibility to carcinogen-induced mammary tumorigenesis. Reproductive Toxicology 23(3): 397-406

Khan M Z I, Uzair M, Nazli A & Chen J Z (2022). An overview on estrogen receptors signaling and its ligands in breast cancer. European Journal of Medicinal Chemistry 241: 114658

Lee J & Cho K (2012). Flaxseed sprouts induce apoptosis and inhibit growth in MCF-7 and MDA-MB-231 human breast cancer cells. In Vitro Cellular&Developmental Biology Animal 48(4): 244-250

Mal R, Magner A, David J, Datta J, Vallabhaneni M, Kassem M, Manouchehri J, Willingham N, Stover D, Vandeusen J, Sardesai S, Williams N, Wesolowski R, Lustberg M, Ganju R K, Ramaswamy B & Cherian M A (2020). Estrogen Receptor Beta (ERb): A Ligand Activated Tumor Suppressor. Frontiers in Oncology 10: 587386

Mali A V, Wagh U V, Hegde M V, Chandorkar S S, Surve S V & Patole M V (2012). In vitro anti-metastatic activity of enterolactone, a mammalian lignan derived from flax lignan, and down-regulation of matrix metalloproteinases in MCF-7 and MDA MB 231 cell lines. Indian Journal of Cancer 49(1): 181-187

Mansur A, Silva T C B F, Takada J Y, Avakian S D, Strunz C M C, César L A M, Aldrighi J M & Ramires J A F (2012). Long-term prospective study of the influence of estrone levels on events in postmenopausal women with or at high risk for coronary artery disease. The Scientific World Journal 2012: 363595

Marghescu F I, Teodorescu M S & Radu D (2012). The Positive Impact of Flaxseed (Linum Usitatissimum) on Breast Cancer. Journal of Agroalimentary Processes and Technologies 18(2): 161-168

Mason J K, Fu M, Chen J & Thompson L U (2015). Flaxseed oil enhances the effectiveness of trastuzumab in reducing the growth of HER2-overexpressing human breast tumors (BT-474). The Journal of Nutritional Biochemistry 26(1): 16-23

Moar K, Pant A, Saini V, Pandey M, Maurya P K (2023). Potential diagnostic and prognostic biomarkers for breast cancer: A compiled review. Pathology-Research and Practice 251: 154893

Moreira A C, Silva A M, Santos M S, Sardão V A (2014). Phytoestrogens as alternative hormone replacement therapy in menopause: What is real, what is unknown. Journal of Steroid Biochemistry &Molecular Biology 143: 61-71

Nazari E & Suja F (2016). Effects of 17β-estradiol (E2) on aqueous organisms and its treatment problem: a review. Reviews on Enviromental Health 31(4): 465-491

Nikolić I L, Savić-Gajić I M, Tačić A D & Savić I M (2017). Classification and biological activity of phytoestrogens: a review. Advanced Technologies 6(2): 96-106

Patel D, Vaghasiya J, Pancholi S S & Paul A (2012). Therapeutic Potential of Secoisolariciresinol Diglucoside: A Plant Lignan. International Journal of Pharmaceutical Sciences and Drug Research 4(1):15-18

Paterni I, Granchi C, Katzenellenbogen J A & Minutolo F (2014). Estrogen receptors alpha (ERα) and beta (ERβ): Subtype-selective ligands and clinical potential. Steroids 90: 13-29

Poschner S, Maier-Salamon A, Thalhammer T & Jäger W (2019). Resveratrol and other dietary polyphenols are inhibitors of estrogen metabolism in human breast cancer cells. Journal of Steroid Biochemistry and Molecular Biology 190: 11-18

Power K A & Thompson L U (2007). Can the combination of flaxseed and its lignans with soy and its isoflavones reduce the growth stimulatory effect of soy and its isoflavones on established breast cancer? Molecular Nutrition &Food Research 51(7): 845-856

Power K A, Chen J M, Saarinen N M & Thompson L U (2008). Changes in biomarkers of estrogen receptor and growth factor signaling pathways in MCF-7 tumors after short- and long-term treatment with soy and flaxseed. Journal of Steroid Biochemistry & Molecular Biology 112(1-3):13-19

Richter D U, Abarzua S, Chrobak M, Scholz C, Kuhn C, Schulze S, Kupka M S, Friese K, Briese V, Piechulla B & Jeschke U (2010). Effects of phytoestrogen extracts isolated from flax on estradiol production and ER/PR expression in MCF7 breast cancer cells. Anticancer research 30(5):1695-1699

Rodríguez-García C, Sánchez-Quesada C, Toledo E, Delgado-Rodríguez M, Gaforio J J (2019). Naturally Lignan-Rich Foods: A Dietary Tool for Health Promotion? Molecules 24(5): 917

Roy S S & Vadlamudi R K (2012). Role of Estrogen Receptor Signaling in Breast Cancer Metastasis. International Journal of Breast Cancer 2012: 654698

Rubilar M, Gutiérrez C, Verdugo M, Shene C & Sineiro J (2010). Flaxseed as a source of functional ingredients. Journal of soil science and plant nutrition 10(3): 373-377

Saarinen N M, Wärri A, Airio M, Smeds A & Mäkelä S (2007). Role of dietary lignans in the reduction of breast cancer risk. Molecular Nutrition & Food Research 51(7): 857-866

Saggar J K, Chen J, Corey P & Thompson L U (2015). Dietary flaxseed lignan or oil combined with tamoxifen treatment affects MCF-7 tumor growth through estrogen receptor- and growth factor-signaling pathways. Molecular Nutrition &Food Research 54 (3): 415-425.

Samavat H & Kurzer M S (2015). Estrogen Metabolism and Breast Cancer. Cancer Letter 356(200): 231-243

Scherbakov A M, Stasevich O V, Salnikova D I, Andreeva O E & Mikhaevich E I (2021). Antiestrogenic and antiproliferative potency of secoisolariciresinol diglucoside derivatives on MCF-7 breast cancer cells. Natural Product Research 35(24): 6099-6105

Schwartz N, Verma A, Bivens C B, Schwartz Z, Boyan B D (2016). Rapid steroid hormone actions via membrane receptors. Biochimica et Biophysica Acta 1863(9): 2289-2298

Seibold P, Vrielling A, Johnson T S, Buck K, Behrens S, Kaaks R, Linseisen J, Obi N, Heinz J, Flesch-Janys D & Chang-Claude J (2014). Enterolactone concentrations and prognosis after postmenopausal breast cancer: Assessment of effect modification and meta-analysis. International Journal of Cancer 135(4): 923-933

Sharma G N, Dave R, Sanadya J, Sharma P & Sharma K K (2010). Various types and management of breast cancer: an overview. Journal of Advanced Pharmaceutical Technology & Research 1 (2):109-126.

Simopoulos A P (2002). The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomedicine and Pharmacotherapy 56(8): 365-379

Smolarz B, Nowak A N & Romanowicz H (2022). Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). Cancers 14(10): 2569

Taibi A, Lin Z, Tsao R, Thompson LU & Comelli E M (2019). Effects of Flaxseed and Its Components on Mammary Gland MiRNome: Identification of Potential Biomarkers to Prevent Breast Cancer Development. Nutrients 11(11): 2656

Tang Y, Wang Y, Kiani M F & Wang B (2016). Classification, Treatment Strategy, and Associated Drug Resistance in Breast Cancer. Clinical Breast Cancer 16(5): 335-343

Tannous S, Haykal T, Dhaini J, Hodroj M H & Rizk S (2020). The anti-cancer effect of flaxseed lignan derivatives on different acute myeloid leukemia cancer cells. Biomedicine&Pharmacotherapie 132: 110884

Tanwar A K, Dhiman N, Kumar A & Jaitak V (2021). Engagement of phytoestrogens in breast cancer suppression: Structural classification and mechanistic approach. European Journal of Medicinal Chemistry 213: 113037

Torrens-Mas M & Roca P (2020). Phytoestrogens for Cancer Prevention and Treatment. Biology 9(12): 427

Touré A & Xueming X (2010). Flaxseed Lignans: Source, Biosynthesis, Metabolism, Antioxidant Activity, Bio-Active Components, and Health Benefits. Reviews in Food Science and Food Safety 9: 259-328

Truan J S, Chen J M & Thompson L U (2010). Flaxseed oil reduces the growth of human breast tumors (MCF-7) at high levels of circulating estrogen. Molecular Nutrition & Food Research 54(10): 1414-1421

Turner N C, Neven P, Loibl S & Andre F (2017). Advances in the treatment of advanced oestrogen-receptor-positive breast cancer. The Lancet 389(10087): 2403-2414

Twelves C, Jove M, Gombos A & Awada A (2016). Cytotoxic chemotherapy: Still the mainstay of clinical practice for all subtypes metastatic breast cancer. Critical Reviews in Oncology/Hematology 100: 74-87

Velentzis L S, Woodside J V, Cantwell M, Leathem A J & Keshtgar M R (2008). Do phytoestrogens reduce the risk of breast cancer and breast cancer recurrence? What clinicians need to know. European Journal of Cancer 44(13): 1799-1806

Wang Z, Li Y, Ahmad A, Azmi A S, Banerjee S, Kong D & Sarkar F H (2010). Targeting Notch signaling pathway to overcome drug resistance for cancer therapy. Biochimica et Biophysica Acta 1806(2): 258-267

Westcott N D & Muír A D (2003). Flax seed lignan in disease prevention and health promotion. Phytochemistry Reviews 2: 401-417

Wiggins A K A, Mason J K, Thompson L U (2015). Growth and gene expression differ over time in alpha-linolenic acid treated breast cancer cells. Experimental Cell Research 333(1): 147-154

Xiong X Y, Hu X J, Li Y, Liu C M (2015). Inhibitory Effects of Enterolactone on Growth and Metastasis in Human Breast Cancer. Nutrition and Cancer 67(8): 1326-1332

Xing M, Wang J, Yang Q, Wang Y, Li J, Xiong J & Zhou S (2019). FKBP12 is a predictive biomarker for efficacy of anthracycline-based chemotherapy in breast cancer. Cancer Chemotherapy and Pharmacology 84: 861-872

Yue W, Yager J D, Wang J P, Jupe E R & Santen R J (2013). Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. Steroids 78(2): 161-170

Zhang Q Y, Wang F X, Jia K K & Kong L D (2018). Natural Product Interventions for Chemotherapy and Radiotherapy-Induced Side Effects. Frontiers in Pharmacology 9: 1253

Zhang W, Wang X, Liu Y, Tian H, Flickinger B, Empie M W & Sun S Z (2008). Effects of dietary flaxseed lignan extract on symptoms of benign prostatic hyperplasia. Journal of Medicinal Food 11(2): 207–214