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 & Petrikaïtė 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; Twelve 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 ER2 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, glycitein, 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).
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&Regulśka-Iłow 2021). The predominant lignan in FS is SDG, which makes up 95% of the lignan content of the seed. The remaining 5% consists of laariciresinol, pinoresinol, and matairesinol lignans (Westcott & Muir 2003; Tannous et al. 2020).

After oral ingestion of SDG, it is hydrolyzed to secoisolariciresinol (SECO) and Peptostreptococcus 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. 2006).

![Figure 2- Transformation of SDG to END and ENL](image)

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 potentiates 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 (△Ψm) 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 NFkB, 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).
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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.

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