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Assessment potential mechanism similarity in epigenetic action and functional status between estradiol and phytoestrogenic supplements

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Abstract

Increasing estrogen level beyond the normal limited can be an indicator for a serious health problem which can be the cause of fibrosis or tumor development in the breast tissue. In the current study, we seek to understand the mechanism of estrogen and whether the exposure of estradiol and phytoestrogens together increase the risk of developing breast cancer. Here, we used 32 healthy-adult-female rats. They were randomly divided into four groups. The first group (the control group) and the remaining groups were dosed orally with estradiol (30 micrograms/kg) for twelve weeks and flaxseed oil (0.5 ml) for six weeks. Our study showed a significant increase in the progesterone, estrogen, and their receptors levels within the treated groups. Further, the histological examinations indicate an increase in the number of lobes filled with large numbers of alveoli. On the other hand, the results showed a significant decrease in the DNA methylation pathways of the estrogen receptor alpha gene compared to the control group. Taken together, our data suggested that phytoestrogens have a mechanism of action that mimics the body's internal (endogenous) estrogens, especially in the growth and development of mammary gland tissue. Therefore, adopting a diet rich in plant estrogens for a long period can cause an increase in the level of internal estrogens and disrupt their function.

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Introduction

The association between diet and health has been a vital subject of the scientific inquiry for a long time. In particular, the impact of phytoestrogens, plant-derived compounds with estrogen-like properties, on human physiology. Lignans, phytoestrogens found in flax seeds and oil, have been known for their health benefits in hormonal regulation and cancer prevention. Lignans are found in high concentrations in flax oil, which derived from the seeds of the flax plant *Linum usitatissimum*. It has been known that lignans such as secoisolariciresinol diglucoside (SDG) play a role in metabolic diseases and cancer risk through its antioxidant and anti-inflammatory effects (1). Additionally, numerous studies have been focused on the potential association between phytoestrogens and DNA methylation, suggesting that these compounds may exert their effects through the modulation of epigenetic marks. For instance, lignans have been shown to influence the expression of genes involved in estrogen metabolism, inflammation, and cell cycle regulation, potentially through their impact on DNA methylation patterns. Furthermore, the consumption of flaxseed and flax oil has been linked to improved hormonal balance, reduced risk of hormone-dependent cancers, and

enhanced cardiovascular health, all of which may stem from the interplay between phytoestrogens and epigenetic modifications (2,3). It is also have been shown that the metabolism and the bioactivity of the lignans are critical factors to determine their biological impact. Upon ingestion, lignans undergo conversion by gut microbiota into enterolignans, which can then exert estrogenic effects and influence DNA methylation. However, the variability in gut microbiota composition among individuals may account for the differences in response to lignan-rich diets. Additionally, the timing of exposure to these compounds, particularly during critical developmental periods, may have lasting implications for epigenetic programming and disease risk (4-6).

It is known that high expression of ER with breast tissue leads to carcinogenic tumors, so our study sought to compare the actions of estrogens with phytoestrogen that have the same mechanism in the tumor genesis of breast tissue.

Materials and methods

Ethical approve

This study was conducted in adherence to ethical guidelines, approved by the Thi-Qar Ethical Committee for Animal research (Issue7/54/338. Date 8/3/2024).

Laboratory animals

32 female rats aged 3-4) months with an average weight of 200 grams were used. They were housed in plastic cage in the animal facility at the College of Education Pure Sciences, Thi-Qar University, under standard conditions of temperature (22±25°C) and lighting (12:12-hour light-dark cycle) during the study period. Throughout the study, the rats were provided with ad libitum access to feed and tap water.

Experimental design

The 32 rats were then randomly assigned into four groups; Group A (Negative Control) received 0.5 mL of distilled water for a period of 28 days. Group B1 received 0.5 ml of flaxseed oil orally over a period of six weeks (7). Group D (Positive control) received 30 µg/kg of estradiol over a twelve-week period (8,9). Group F1 received a combined treatment of estradiol (30 micrograms/kg) and flaxseed oil (0.5 ml) for six weeks.

Biochemical analysis

Rat estrogen receptor alpha, estrogen and progesterone hormone levels (ng/ml) were determined using the previously described method (10-12).

Histopathological study

The mammary glands were sectioned transversely and entirely submitted in a labeled histology cassette. Each specimen was cut into a thickness of 5 mm, immediately fixed in 10% formalin solution for 48 hours, processed through water wash, a graded ethanol series, and then embedded in paraffin wax at 70°C. The paraffin-embedded blocks were sectioned to prepare slides and stained with hematoxylin and eosin. All sections were examined for histopathological changes under a light microscope (13-17).

DNA Methylation

The methylation technique for the estrogen receptor alpha gene used in the current study was determined using the previously described method (18-20). In summary: Upon sample collection, samples were directly preserved in DNA stabilizing agents. Samples were then processed for DNA extraction using DNA extraction kit (phenol-chloroform or silica column-based). DNA was then treated with Sodium bisulfite (HSO_3^-) to convert unmethylated cytosines (C) to uracil (U), while methylated cytosines remain unchanged. This step followed by PCR amplification of the ESR1 promoter. Post-treatment DNA shows a sequence difference based on methylation status, which can then be amplified and analyzed. To detect and analyze the methylation profile, samples were run using Gel electrophoresis which showing bands for methylated and/or unmethylated alleles. For the data interpretation, methylation level was Reported as % methylation at specific CpG sites (Figure 1). Methylation status is often inversely correlated with ERα expression (i.e., higher methylation → lower expression).

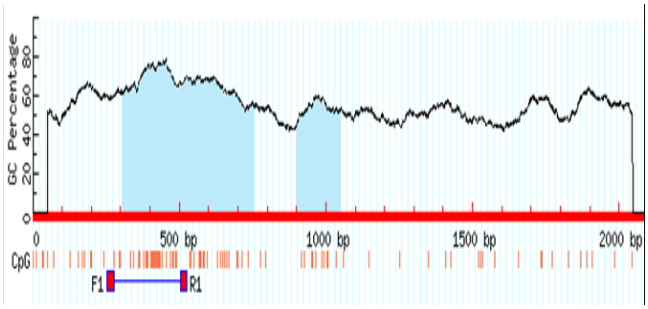

Figure 1: The CpG island in the estrogen receptors region.

Nested PCR

First PCR using extracted and methylated DNA plus these outer primers; ERCha-1F [TAG TAT ATT TTG ATT GTT ATT TTA T]; ERCha-1R [TCT CAA ACC ACT CAA ACT AC]. Second PCR using the outer primers as DNA template plus these inner primers; ERCha-2F [TTT ATT TGT GGT TTA TAG ATA TTT], ERCha-2R [ACA AAA AAA AAA AAA TCAA AAC AC] (20).

Statistical analysis

The study findings underwent evaluation utilizing 0ne-way analysis 0f variance (AN0VA) test. Statistical computations were performed using SPSS V. 21 (SPSS Inc.). Data presentation included mean values ± standard deviation.

Results

Estrogen hormone assessment in all treated groups

The current study demonstrated a significant increase (P≤0.01) in the estrogen hormone concentration in female laboratory rats in the groups (positive control group D, B1 and F1 groups) compared to the negative control group A, at the specified probability level. The study also showed a significant increase (P≤0.01) in the positive control group D compared to groups B1 and a significant decrease in the positive control group D compared to group F1 (Figure 2).

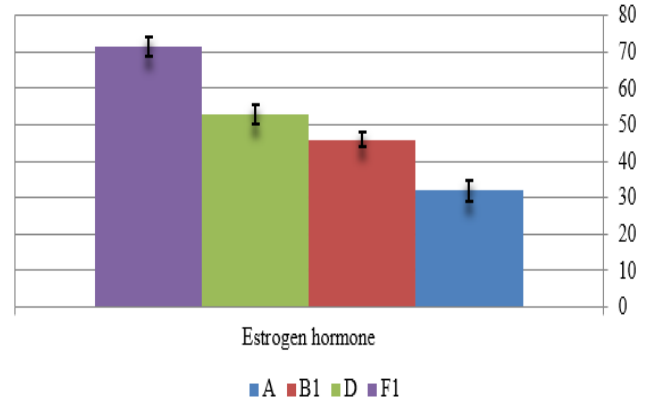

Figure 2: It shows an increase in estrogen hormone in the estradiol group, the flaxseed oil group, and the flaxseed oil and estradiol group together compared to the negative control group.

Estrogen receptor alpha assessment in all treated groups

The current study demonstrated a significant increase (P≤0.01) in the estrogen receptor concentration in female laboratory rats in the groups (positive control group D, B1 and F1 groups) compared to the negative control group A, at the specified probability level . The study also showed a significant increase (P≤0.01) in the positive control group D compared to groups B1 and a significant decrease in the positive control group D compared to groups F1 (Figure 3).

Progesterone hormone assessment in all treated groups

The current study demonstrated a significant increase (P≤0.01) in the progesterone hormone concentration in female laboratory rats in the groups (positive control group D, B1 and F1 groups) compared to the negative control group A, at the specified probability level (Figure 4).

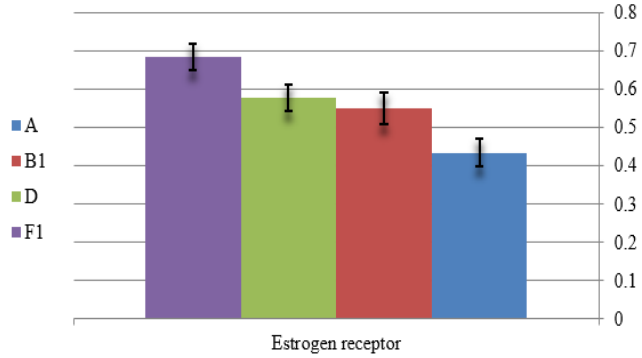

Figure 3: It shows an increase in estrogen receptor in the estradiol group, the flaxseed oil group, and the flaxseed oil and estradiol group together compared to the negative control group.

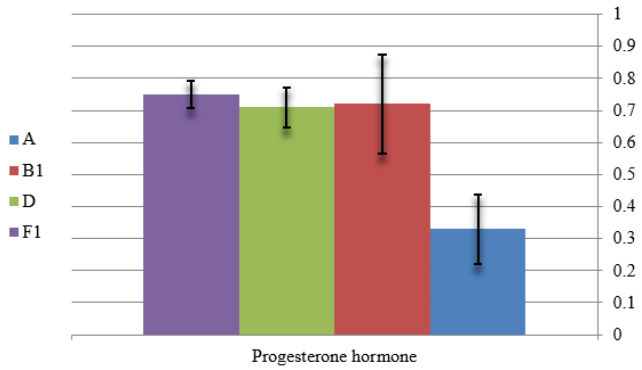

Figure 4: It shows an increase in progesterone hormone in the estradiol group, the flaxseed oil group, and the flaxseed oil and estradiol group together compared to the negative control group.

Hematoxylin eosin sections of the treated exhibited showed an increase in the size of lobules which were packed by alveolar buds and intralobular ducts, these alveoli were more dilated compared with control. Mammary tissue sections from rats treated with flaxseed oil and estradiol + flaxseed oil together showed an increase in branching of alveoli with more flattened luminal epithelium (Figures 5-8) in comparison with control.

Methylation level assessment in all treated groups

The current study demonstrated a significant decrease (P≤0.01) β-factor for total region (T) methylation in study groups (positive control group D, B1 and F1 groups) compared to the negative control group A, at the specified probability level (Figure 9).

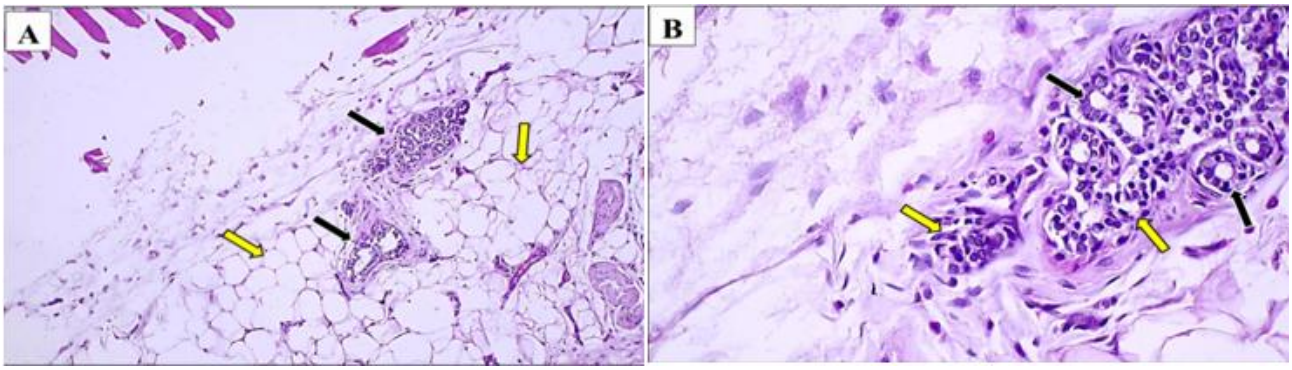

Figure 5: Photomicrograph of mammary glands of control negative rat. A/ Normal histological architectures of mammary glands. Note two lobuloalveolar units (black arrow) embedded within adipose tissue (yellow arrow). B/ The ducts was more prominent than alveolar structure, where ducts (black arrow) showed simple cuboidal epithelial cells and alveolar structures (yellow arrow) showed low cytoplasm to nucleus ratio small epithelial cells. H&E. A: 100x and B: 400x.

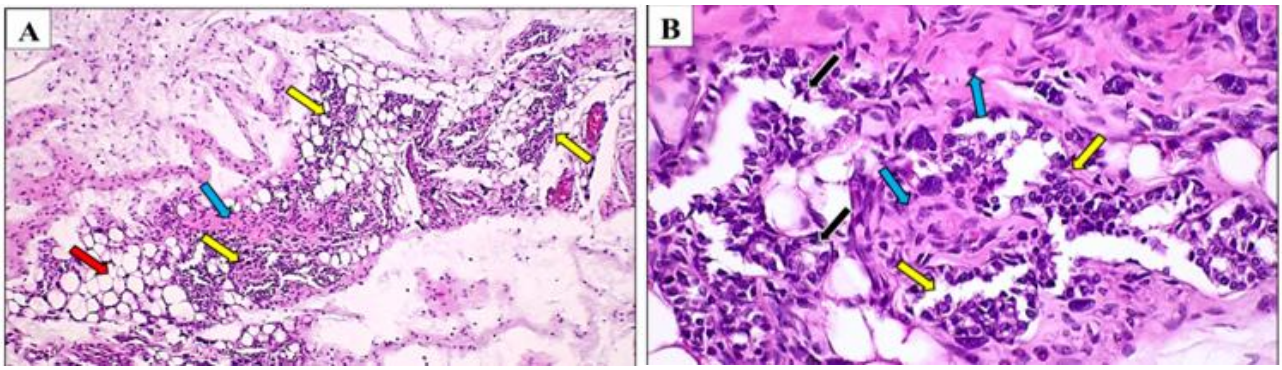

Figure 6: Photomicrograph of mammary glands estradiol only treated rat. A& B/ Note large lobuloalveolar tissue was observed within adipose tissue (red arrow), where the lobuloalveolar tissue was occupied about 80% of total adipose tissue area. Also, the fibrous connective tissue (blue arrow) was observed within the lobuloalveolar tissue. However, the alveolar structures (yellow arrow) were prominent than ducts area (black arrow) in lobuloalveolar tissue. H&E. A: 100x and B: 400x.

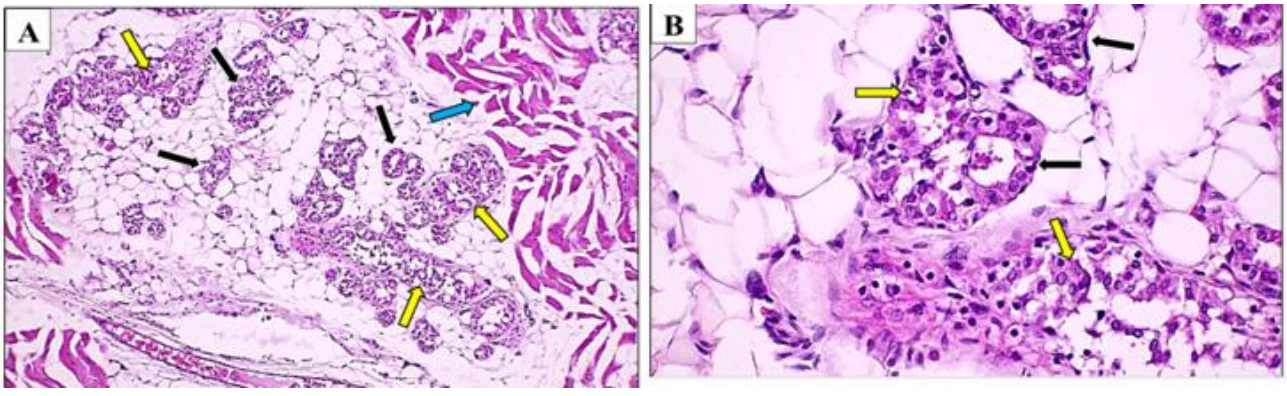

Figure 7: Photomicrograph of mammary glands of flaxseed oil only treated rat. A& B/ Note many lobuloalveolar tissue was observed within adipose tissue and muscular tissue (blue arrow), where the lobuloalveolar tissue was occupied about 40% of total adipose tissue area. However, the ducts (black arrow) were about 50% to alveolar structure area (yellow arrow), There is Zinker necrosis of muscle fibers and oedema between muscle fibers. H&E. A: 100x and B: 400x.

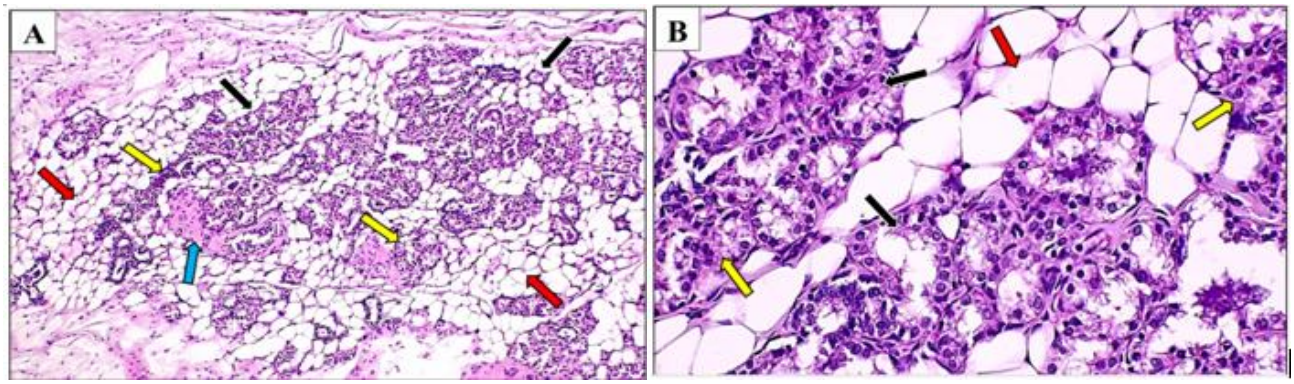

Figure 8: Photomicrograph of mammary glands estradiol and flaxseed oil treated rat. A& B/ Note large lobuloalveolar tissue was observed within adipose tissue (red arrow), where the lobuloalveolar tissue was occupied more than 80% of total adipose tissue area However, ducts area (black arrow) was prominent than the alveolar structures (yellow arrow) in lobuloalveolar tissue. Also, the fibrous connective tissue (blue arrow) was observed within the lobuloalveolar tissue. However, area was less than observed in estradiol and flaxseed oil treated group. Note metaplasia of epithlelial cell. H&E. A: 100x and B: 400x.

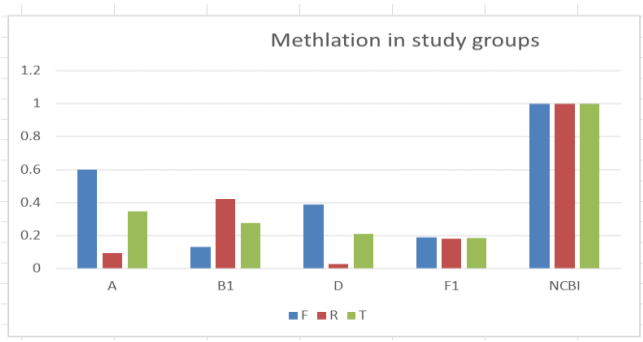

Figure 9: Shows a decrease in the methylation rate in the in the estradiol group, the flaxseed oil group, and the flaxseed oil and estradiol group together compared to the negative control group.

Discussion

The observed increase in estrogen receptor (ER) expression in female rats following exposure to estradiol and phytoestrogens, such as flaxseed oil, highlights the adaptability of the endocrine system and its responsiveness to external estrogenic compounds. Estradiol, a potent natural estrogen, can unregulated its own receptors through feedback mechanisms, enhancing tissue sensitivity to estrogenic signals. Similarly, phytoestrogens, structurally analogous to estradiol, modulate ER expression via direct receptor activation and interactions with signaling pathways, with lignans in flaxseed exhibiting both estrogenic and anti-estrogenic effects depending on hormonal conditions. This regulatory flexibility underscores the need to evaluate the long-term consequences of high phytoestrogen intake, as excessive stimulation of ER pathways may contribute to hormone-dependent tumors, necessitating a careful assessment of dietary phytoestrogen consumption (21-23).

The present study explores the elevation of estrogen levels in female rats, with adult rats exhibiting a greater hormonal response due to a developed hypothalamic-pituitary-gonadal (HPG) axis. Estradiol promotes follicular development, luteinization, and progesterone production through feedback mechanisms involving luteinizing hormone (LH) and progesterone receptors, while phytoestrogens enhance these effects by increasing tissue sensitivity and modulating gonadotropin release, thereby amplifying progesterone synthesis (24-27). Specifically, lignans in flaxseed oil exhibit estrogenic activity by binding to estrogen receptors (ERα and ERβ), mimicking endogenous estrogen, and influencing estrogen metabolism, which subsequently alters the ratio of estrogen metabolites (28-34). Additionally, variations in phytoestrogen intake due to dietary and environmental factors further impact hormonal outcomes, with flaxseed administration in ovariectomized rats shown to elevate estradiol and progesterone levels, potentially via HPG axis activation. These findings underscore the significance of phytoestrogen interactions with endocrine pathways and highlight the need for a balanced approach to their intake to optimize benefits while mitigating potential adverse effects.

The administration of estradiol and phytoestrogens induces significant histological changes in the mammary gland, including increased ductal proliferation, alveolar development, stromal modifications, cellular hyperplasia, and cytoplasmic alterations. Estradiol, a key hormone in mammary gland development, enhances ductal epithelial proliferation, leading to increased ductal complexity, which is essential for efficient milk delivery during lactation (35-38). Concurrently, alveolar structures proliferate in response to estradiol and phytoestrogens, reflecting an adaptive mechanism for enhanced milk production. Stromal changes, notably increased vascularization and edema, facilitate nutrient and oxygen delivery but may also pose risks of

pathological conditions such as hypertrophy and hyperplasia (39-42). The observed cellular hyperplasia, characterized by elevated cell density, suggests a physiological adaptation that could, under prolonged estradiol exposure, raise concerns regarding unregulated growth and malignancy. Additionally, cytoplasmic changes, including nuclear enlargement and increased basophilic staining, indicate heightened metabolic activity associated with protein synthesis, cellular signaling, and stress responses. These findings align with existing literature on estradiol's role in mammary gland development and highlight its potential implications for both normal physiology and pathological transformations (43-45).

The methylation of the estrogen receptor alpha (ERα) gene promoter plays a crucial role in regulating gene expression, particularly in breast tissue, with DNA methylation generally acting as a suppressor of gene transcription. However, estradiol (E2) has been shown to reduce ERα promoter methylation, leading to increased receptor expression and heightened sensitivity to hormonal signals (46-49). This study confirms a significant decrease in ERα promoter methylation following E2 exposure, suggesting that estrogen facilitates transcriptional activation through chromatin remodeling by recruiting co-activators such as histone acetyltransferases (HATs) and ten-eleven translocation (TET) enzymes, which promote an open chromatin structure conducive to gene expression. Similarly, dietary phytoestrogens, such as those found in flaxseed oil, exhibit comparable epigenetic effects on ERα methylation, as demonstrated by a significant reduction in ERα promoter methylation following phytoestrogen administration (50-55).

These compounds, including lignans and isoflavones, are suggested to modulate DNA methyltransferase (DNMT) activity, influence intracellular signaling pathways such as MAPK, and exert antioxidant effects that may alter methylation processes. Beyond breast tissue, phytoestrogens impact metabolic regulation, immune function, and neuroprotection, with potential implications for insulin sensitivity, lipid metabolism, and cognitive function. The hypomethylation-induced re-expression of ERα is particularly relevant in ER-negative breast cancer cells, where it enhances endocrine sensitivity and influences disease progression. However, individual variability in phytoestrogen metabolism, genetic predisposition, and exposure duration may affect their efficacy in modifying gene expression. These findings contribute to the growing body of evidence supporting the role of both endogenous estrogen and phytoestrogens as epigenetic regulators in breast health and disease prevention .

Conclusion

The current study concluded that consuming high levels of phytoestrogens, such as flaxseed oil, without adhering to a balanced diet may lead to increased levels of progesterone, estrogen and their receptors in the blood, which act on a similar mechanism to estrogen, which may affect epigenetic pathways, especially DNA methylation, which is considered a risk factor for breast diseases.

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Conflict of interest

There is no conflict of interest.

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تقييم آليات التشابه المحتملة في التأثير اللاجيني والحالة الوظيفية بين الإستراديول والمكملات النباتية الإستروجينية

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الخلاصة

يمكن أن يشير ارتفاع مستوى الأستروجين عن الحد الطبيعي إلى وجود مشكلة صحية خطيرة، قد تكون سببًا في تطور التليف أو الأورام في نسيج الثدي. في هذه الدراسة، نسعى إلى فهم آلية عمل الأستروجين، وما إذا كان التعرض المتزامن لكل من الإستراديول والفيتوإستروجينات (الاستروجينات النباتية) يزيد من خطر الإصابة بسرطان الثدي. في هذه الدراسة، استخدمنا ٣٢ أنثى جرذ بالغة وسليمة، وتم تقسيمها عشوائيًا إلى أربع مجموعات. المجموعة الأولى (مجموعة السيطرة)، بينما تم إعطاء المجموعات الأخرى جرعات فموية من الإستراديول بتركيز (٣٠ ميكروغرام/كغم) لمدة اثني عشر أسبوعًا وزيت بذور الكتان (٠,٥ مل) لمدة ستة أسابيع. أظهرت نتائج دراستنا زيادة ملحوظة في مستويات كل من البروجسترون والأستروجين ومستقبلاتهما في المجموعات المعالجة. بالإضافة إلى ذلك، أظهرت الفحوصات النسيجية زيادة في عدد الفصوص الممتلئة بعدد كبير من الحويصلات (الأسناخ). ومن ناحية أخرى، أشارت النتائج إلى انخفاض ملحوظ في مسارات مثيلة الحمض النووي لجين الأستروجين ألفا مقارنةً بمجموعة السيطرة. بناءً على ما سبق، تشير بياناتنا إلى أن للفيتوإستروجينات آلية عمل تحاكي الإستروجينات الداخلية (الذاتية) للجسم، لا سيما في نمو وتطور نسيج الغدة الثديية. وعليه، فإن اتباع نظام غذائي غني بالإستروجينات النباتية لفترات طويلة قد يؤدي إلى زيادة مستويات الأستروجين الداخلي واضطراب وظائفه.