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Transcriptomic Effects of Soy-Derived Isoflavone Exposure in Breast Cancer: An Integrative Bioinformatics Analysis

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ABSTRACT

Background: Breast cancer is the leading cause of cancer mortality in women. Studies indicate that soybeans contain powerful compounds that may influence molecular pathways relevant to breast cancer biology. This study aims to identify differentially expressed genes (DEGs) and pathways associated with soy-derived isoflavone exposure using publicly available breast cancer transcriptomic datasets.

Methods: Four microarray datasets were analyzed using GEO2R to identify DEGs ($|\log FC| > 1$, $P < 0.05$). Venn diagrams identified common genes across the studies. Breast cancer-specific genes were further isolated from the DEGs using the Gene Expression Profiling Interactive Analysis (GEPIA) database, with a focus on candidate genes and signaling pathways potentially modulated by soy-derived isoflavone exposure under experimental conditions.

Results: The analysis revealed that isoflavone exposure was associated with upregulation of pathways like cell senescence, actin cytoskeleton regulation, and apoptosis processes often elevated in breast cancer. Conversely, pathways, such as the cell cycle and p53 signaling were downregulated. Notably, the cell cycle pathway, pivotal in breast cancer, exhibited downregulation of key genes (*CDC20*, *CCNB1*, *CDC6*, *MAD2L1*, *CCNA2*, *TTK*, *MCM4*, *CDC25C*, *MCM2*, and *ESPL1*), which are critical for cell cycle progression and checkpoint regulation. Dysregulation of these genes is associated with cancer development. Additionally, enrichment of components related to PI3K/Akt signaling and epithelial-mesenchymal transition was observed, without implying pathway activation or functional benefit.

Conclusion: These findings offer exploratory insights into molecular pathways that may be modulated by isoflavone exposure and warrant further experimental validation.

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies affecting women worldwide, with growing evidence linking its incidence to dietary factors. Several epidemiological studies and meta-analyses have examined associations between soy isoflavone intake and breast cancer outcomes, with some suggesting a modest reduction in overall mortality and recurrence among high consumers of soy isoflavones, particularly in postmenopausal women.[1] Current treatment modalities include local

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interventions (i.e., surgery and radiation therapy) and systemic approaches (i.e., chemotherapy, targeted therapy, hormonal therapy), with therapeutic strategies guided by molecular subtyping.[2]

Phytochemicals from medicinal plants and herbs exhibit multifaceted cancer-related molecular pathways, including enhancement of detoxification pathways, modulation of hormonal and enzymatic activity, attenuation of treatment-related adverse effects, and immunomodulation through cytokine production (interleukins, interferons, tumor necrosis factor-α, colony-stimulating factors).[3]

Among natural compounds, soy-derived phytoestrogens have garnered particular interest for their hypothesized cancer risk-modifying potential. The striking geographical disparity in breast cancer incidence—with significantly lower rates in Asian populations (25–50 mg/day isoflavone intake) compared to Western countries (<2 mg/day)—suggests a potential association between soy consumption and breast cancer outcomes.[4] Clinical evidence from Shu *et al.* demonstrated that breast cancer patients consuming soy isoflavones experienced 29% reduction in mortality risk and 32% decrease in recurrence rates. Beyond oncology, soy isoflavones show therapeutic potential for menopausal symptom management, cardiovascular protection, osteoporosis prevention, and urogenital health maintenance.[5] Human tumor profiling studies have identified gene expression signatures associated with soy supplementation, including modulation of cell cycle-related transcripts, although such results underscore the context specificity of isoflavone effects and do not establish direct clinical benefit.[6]

While epidemiological and clinical data support soy's anticancer effects, the precise molecular mechanisms remain incompletely understood. This study employs integrated bioinformatics approaches to identify differentially expressed genes (DEGs) associated with soy-derived isoflavone exposure in experimental breast cancer, characterize affected signalling pathways, and elucidate potential therapeutic targets.

METHODS

Microarray datasets and analysis

We retrieved 4 breast cancer microarray datasets from GEO: GSE9936, GSE63205, GSE50705, and GSE58792 with the following inclusion criteria: studies examining soy/isoflavone effects on breast cancer, human cell lines or tissue samples, complete experimental and annotation metadata, and comparable experimental designs. The specifications of the datasets are presented in Table 1.

Table 1. Specifications of the Selected Datasets.

Series ID	Source of sample	Platform ID	Number of samples	Platform name	Year
GSE9936	MCF-7 breast cancer cell line	GPL96	105	[HG-U133A] Affymetrix Human Genome U133A Array	2008
GSE63205	Human MCF-7 xenograft tumors	GPL570	12	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	2016
GSE50705	MCF-7 breast cancer cells	GPL570	351	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	2013
GSE58792	Breast cancer tissue	GPL570	51	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	2014

DEGs were identified using *GEO2R* (R *limma* package, v3.50.0) with $|\log FC| > 1$ and $P < 0.05$ (adjusted via Benjamini-Hochberg method). The $|\log FC| > 1$ threshold was selected as a commonly used criterion in exploratory microarray reanalyses to balance biological relevance and false discovery control. The included datasets differ in experimental design, exposure conditions, and sample type (cell lines versus tissue samples). Therefore, the analysis was designed to identify shared transcriptional patterns rather than quantitatively comparable effects across studies. For each dataset, *GEO2R* contrasts were based on original annotations (genistein-exposed vs vehicle for GSE9936/GSE50705; soy flour diet vs purified isoflavone mix vs controls for GSE63205; soy supplementation vs placebo for GSE58792). Due to platform and model heterogeneity, no cross-dataset normalization was applied. The results focused on overlapping genes in ≥3 datasets as an exploratory filter for robustness.

Candidate gene identification

Common DEGs were identified using Venn diagrams, selecting genes shared in at least 3 studies. Gene Expression Profiling Interactive Analysis (GEPIA) was used to contextualize whether the identified genes are commonly dysregulated in breast cancer tissue compared with normal breast tissue, rather than to validate soy-specific effects. GEPIA expression and survival analyses were used exclusively for contextual interpretation of gene relevance in breast cancer and did not imply

therapeutic or prognostic effects of isoflavone exposure.

Pathway and gene ontology analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) (v6.8) was used to analyze biological pathways, processes, cellular components, and molecular functions of DEGs. Survival and expression analyses were conducted using the GEPIA database. Important cancer pathways were identified based on a P value < 0.05.

RESULTS

Differentially expressed genes

Analysis of 4 datasets (GSE9936, GSE63205, GSE50705, and GSE58792) identified 12 359 upregulated and 15 529 downregulated genes associated with isoflavone exposure (Table 1). Venn diagram analysis revealed 66 upregulated and 15 downregulated genes shared across all studies (Figure 1; Supplementary Table A). GEPIA contextual comparison confirmed 1 upregulated and 1 downregulated gene in 4 studies, and 13 upregulated and 97 downregulated genes in 3 studies (Figure S1).

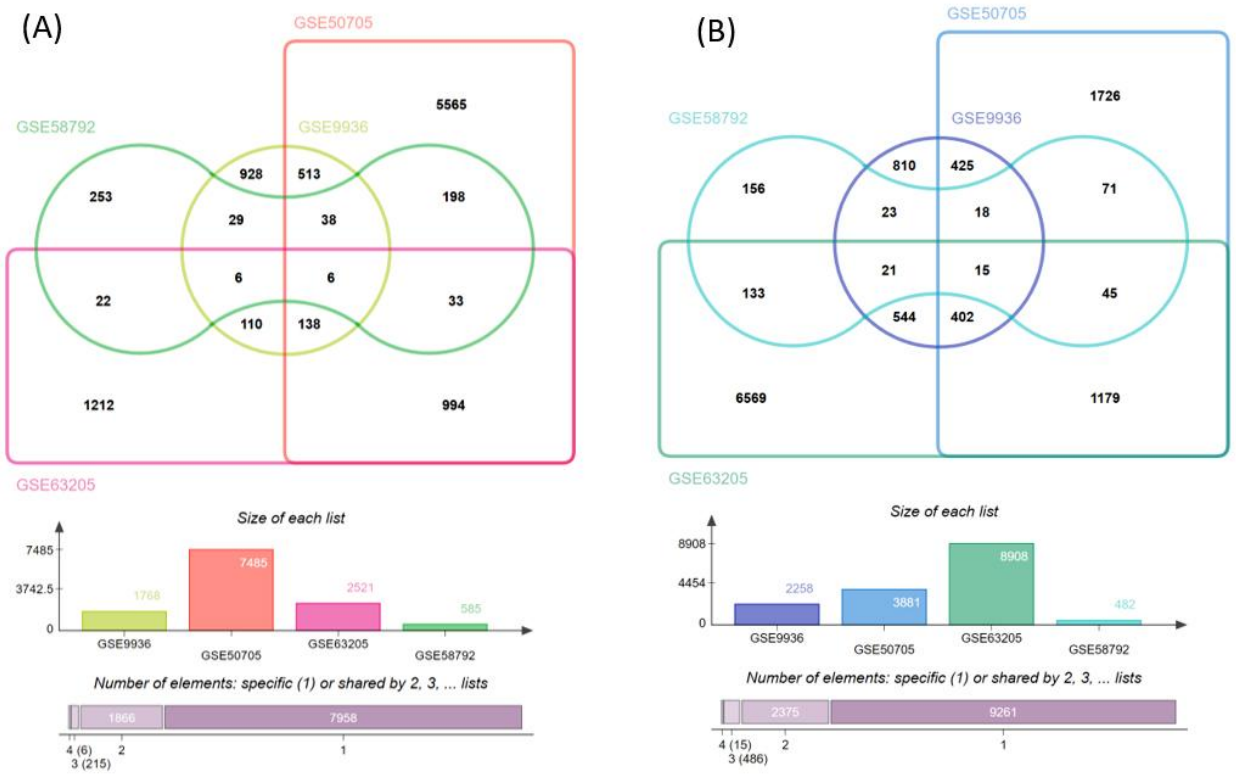

Figure 1. Venn Diagram of Upregulated (A) and Downregulated Genes (B) Across 4 Studies.

Pathway and functional enrichment analysis

Upregulated pathways included apoptosis, cell senescence, and actin cytoskeleton regulation, while downregulated pathways included cell cycle, p53 signaling, and ubiquitin-mediated proteolysis. In terms of biological processes, the upregulated genes were associated with negative regulation of cell proliferation, actin cytoskeleton organization, and negative regulation of cell growth. The downregulated genes were associated with biological processes, such as cell division, mitotic cytokinesis, and cell cycle regulation (Figure 2).

Validation of DEGs and survival analysis

GEPIA box plots were generated to further evaluate the significance of the candidate genes. The results showed that upregulated genes had reduced expression in breast cancer, while downregulated genes were overexpressed, regardless of treatment with soy isoflavones (Figures 3 and 4). Survival analysis confirmed these findings (Figures S2 and S3).

KEGG analysis identified the cell cycle pathway as significantly downregulated (56 genes), including key regulators (*CDC20*, *CCNB1*, *CDC6*, *MAD2L1*, *CCNA2*, *TTK*, *MCM4*, *CDC25C*, *MCM2*, and *ESPL1*), recurrent in 3 studies (Figure 5). These genes are known to participate in DNA biosynthesis, checkpoint regulation, and mitotic progression. Figure 5 provides a schematic illustration of their position within the canonical cell cycle pathway for contextual purposes only and does not demonstrate direct pathway inhibition or mechanistic causality resulting from isoflavone exposure. These findings elucidate potential modulatory effects observed in these models, identifying candidate genes for future mechanistic investigation.

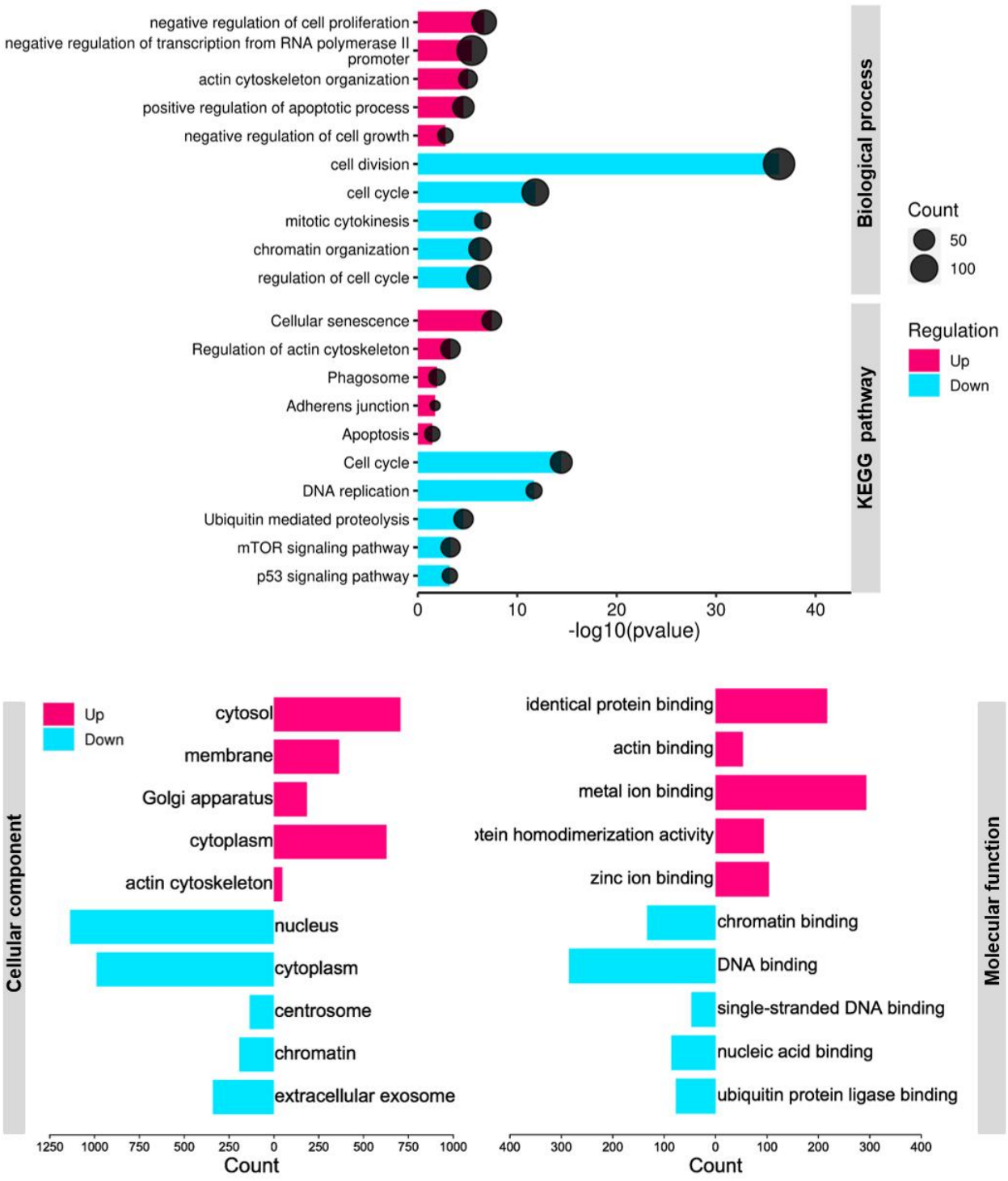

Figure 2. Gene Ontology Analysis of Common Up- and Downregulated Genes in 2 or 3 Studies

DISCUSSION

Breast tissue homeostasis relies on a precise balance between cell proliferation and apoptosis. Tumorigenesis arises not only from uncontrolled proliferation but also from impaired apoptosis, a process targeted by conventional therapies (chemotherapy, radiotherapy, and hormonal treatments).[7] Soy isoflavones such as genistein and daidzein exhibit complex biological effects, acting through estrogen receptor-dependent and -independent pathways that can influence cell proliferation, apoptosis, and epigenetic regulation in a context-dependent manner.[8] Our study elucidates how soy isoflavones modulate key genes and pathways implicated in breast cancer biology under experimental conditions. By integrating data from 4 GEO datasets, we identified DEGs and pathways, revealing transcriptional patterns consistent with modulation of cancer-related pathways under experimental conditions, including enzyme inhibition

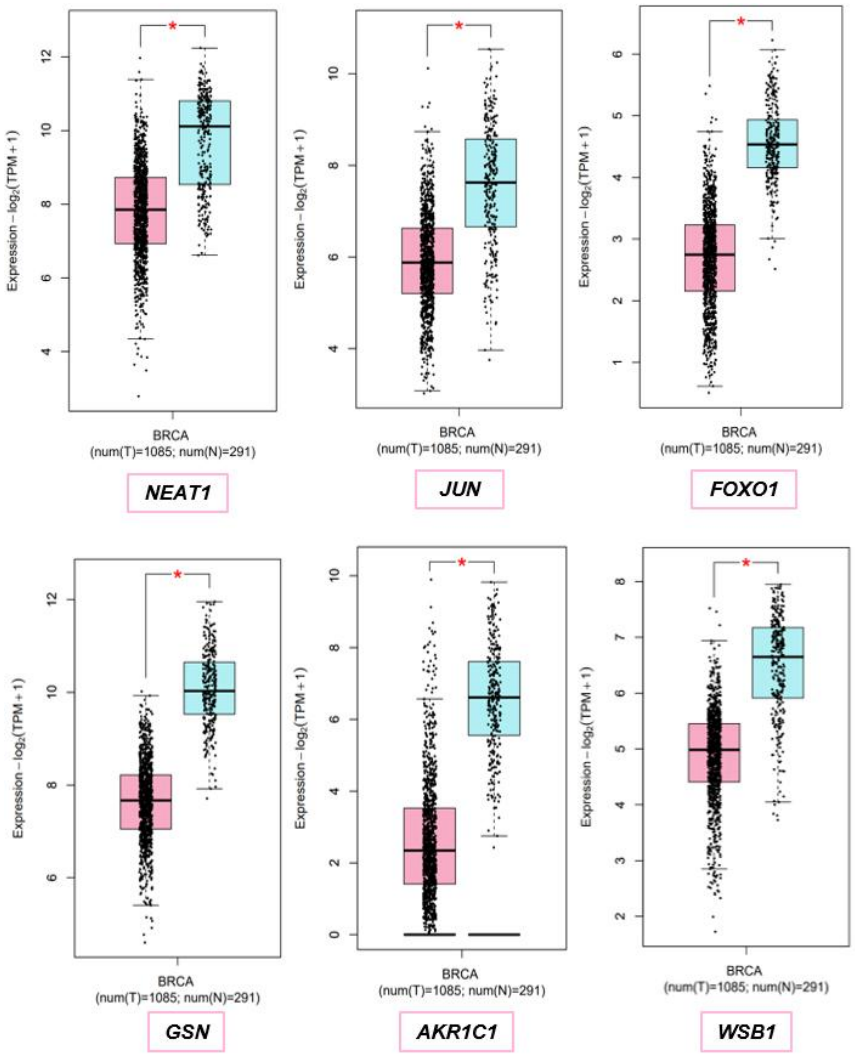

Figure 3. Box Plots of 6 Upregulated Genes Shared in 3 Studies posttreatment

(5α-reductase, cyclin-dependent kinases), downregulation of oncogenic pathways (NF-κB, Akt, MAPK), and proapoptotic effects (*FOXO*, *JUN*, *TFPI2*, *GSN*, *AKR1C1*, *WSB1*, *NEAT1*).

Soy isoflavones modulated the expression of genes linked to PI3K/Akt and EMT pathways (upregulation of *FOXO*, which can oppose Akt signaling in some contexts). However, given the oncogenic roles of these pathways in breast cancer, the net biological implication remains unclear and context-dependent. *FOXO*, a key regulator of PI3K/Akt, counteracts oncogenic signals driven by *PTEN* or *PIK3CA* dysregulation, potentially reducing cell survival and metastasis.[9]

Similarly, *JUN* and *TFPI2*, downregulated in breast cancer but upregulated by soy, modulate EMT, which is critical for invasion and metastasis. JUN is a protein-encoding gene related to breast cancer. Activated C-JUN is often expressed at the invasive front in breast cancer. This gene is related to proliferation and angiogenesis. In human breast cancer cells, GLS protein levels and sensitivity to GLS inhibition are associated with c-Jun levels.[10] Lukey *et al.*[11] argued that JUN's role in metabolic reprogramming may sensitize cancer cells to targeted therapies, suggesting potential biological relevance that warrants further investigation.

GSN, involved in actin cytoskeleton regulation, was also upregulated, potentially limiting cancer cell migration by stabilizing cytoskeletal dynamics. In the research conducted by Biber *et al.,* it was found that perturbations in the regulation of the actin cytoskeleton result in enhanced cancer cell migration, leading to metastatic spread. This paper also explains how the cytoskeleton is a central factor contributing to various hallmarks of cancer. Overall, these findings suggest that GSN may be a promising target for further research into the prevention and treatment of breast cancer.[11] Conversely, soy downregulates protumorigenic genes in the cell cycle pathway, including *CDC20*, *CCNB1*, *CDC6*, *MAD2L1*, *CCNA2*, *TTK*, *MCM4*, *CDC25C*, *MCM2*, and *ESPL1*, shared across 3 studies. These genes, overexpressed in breast cancer, regulate DNA biosynthesis and checkpoints, driving tumor growth.[12]

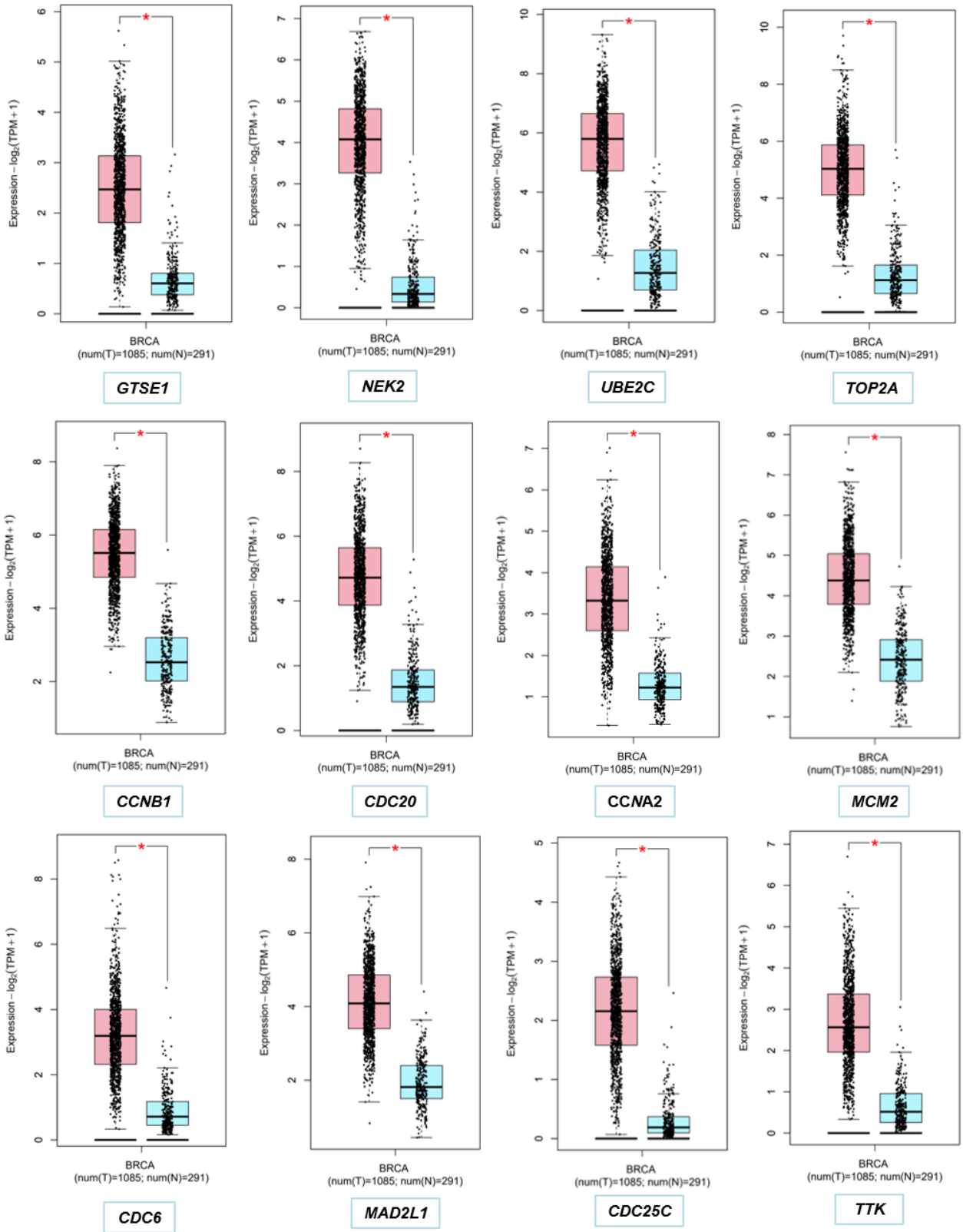

Figure 4. Box Plot of 12 Downregulated Genes Shared in 3 Studies Posttreatment

Their downregulation by soy suggests transcriptional modulation of cell cycle-related genes under experimental conditions, like healthy tissue expression levels. Additionally, soy-derived isoflavone exposure downregulated protumorigenic genes (*NEK2*, *UBE2C*, and *TOP2A*) linked to the G2/M checkpoint and chromosomal instability, which were suppressed, potentially reducing tumor migration and aneuploidy. In various human breast cancer cell lines, *NEK2* knockdown induced aneuploidy and cell cycle arrest that led to cell death.

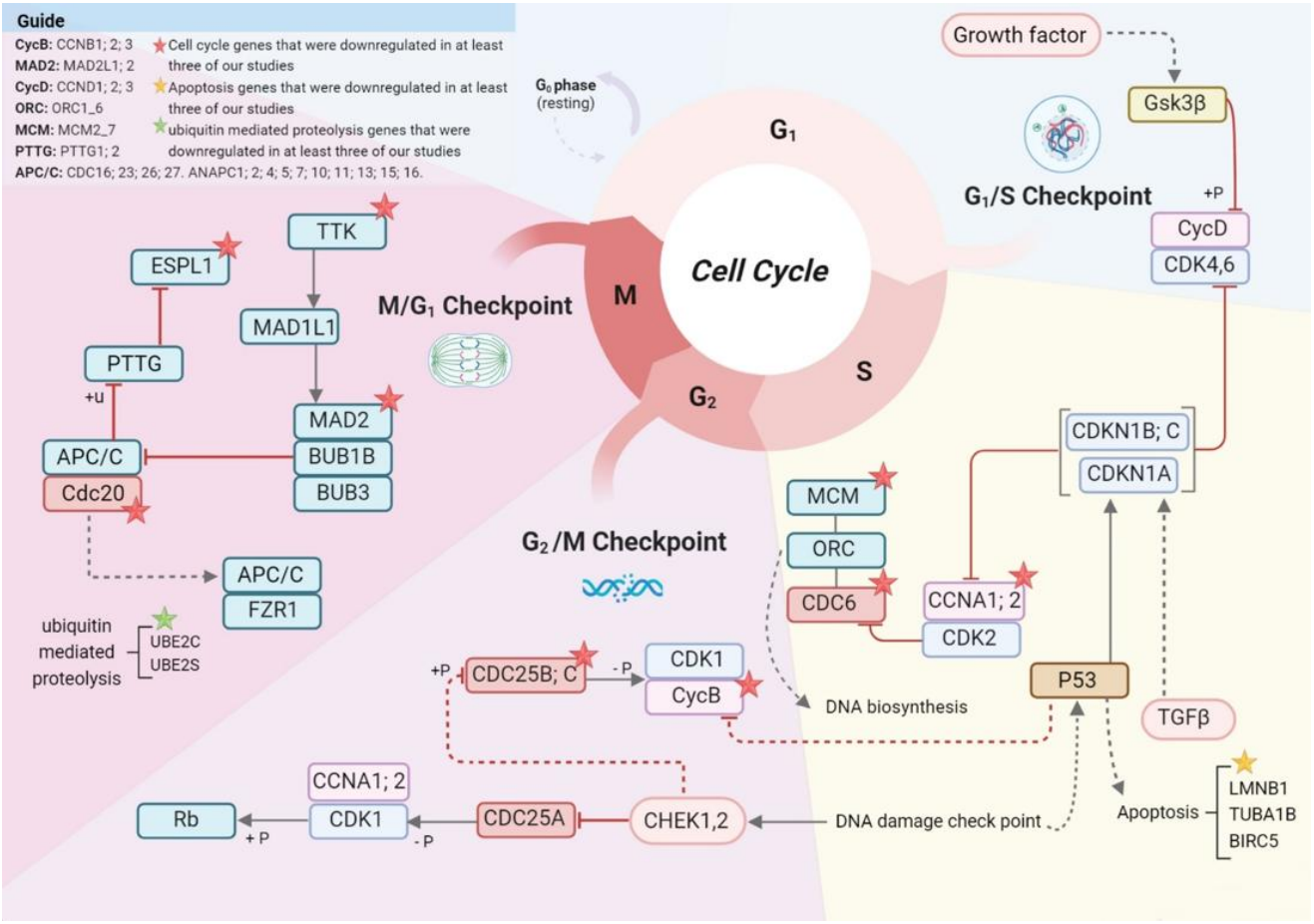

Figure 5. Schematic Representation of the Cell Cycle Pathway Highlighting Genes Identified as Downregulated in the Analyzed Datasets. This illustration is intended to provide pathway context rather than demonstrate direct mechanistic effects of isoflavone exposure**.**

This gene plays a pivotal role in breast cancer growth at primary and secondary sites and may thus be an attractive and novel therapeutic target for this disease.[13] UBE2C is an important part of the ubiquitin-conjugating enzyme complex. In cancers with a high degree of malignancy and tendency to metastasize and poor differentiation, *UBE2C* expression is usually higher, and patient survival is poor. It has been shown that *UBE2C* is highly expressed in BRCA, which confirms the prognostic significance of *UBE2C* in BRCA.[14,15]

GTSE-1 is another gene which is upregulated in breast cancer patients, but is downregulated by soy-derived isoflavones, and is also present in the P53 pathway. GTSE-1 is specifically expressed during the S and G2 phases of the cell cycle. Studies have proven that *GTSE1* can affect the AKT pathway to facilitate the growth of breast cancer cells and can increase the metastasis of breast cancer cells by regulating the EMT pathway.[12] *GTSE1* is associated with increased tumor proliferation and metastasis in breast cancer and contributes to multidrug resistance in breast cancer cells. Considering the function of *GTSE1*, its potential as a new biomarker for assessing breast cancer progression is important.[16]

Soy's impact extends to the immune microenvironment and angiogenesis. The expression of the *AKR1C1* gene increased in experimental breast cancer datasets. Upregulation of *AKR1C1* and *TFPI2* suggests enhanced immune responses and reduced angiogenesis, respectively, consistent with transcriptional changes associated with growth-regulatory processes.[17] *NEAT1* is another gene overexpressed in patients who consume soy. This gene is involved in rhythmic biological processes and immunity, innate immunity, transcription, and regulation of transcription. It has been shown that its regulation is disturbed in various solid cancers. *NEAT1* overexpressed in triple-negative breast cancer, was normalized by soy, potentially improving chemosensitivity.[18] These findings highlight soy isoflavones as a potential molecular target requiring validation in controlled experimental and clinical studies. Soy-induced normalization of *NEAT1* levels could improve therapeutic responses.

Importantly, the present study does not establish causality between dietary soy intake and breast cancer outcomes, but rather highlights transcriptional signatures observed following isoflavone exposure under experimental conditions.

Limitations

This study relies on public GEO datasets, limiting its scope to bioinformatics analysis. Experimental validation of soy's effects on identified genes (*CDC20* and *FOXO*) is needed. Additionally, the specific isoflavones (genistein and daidzein) driving these effects require further investigation. This study is not a formal meta-analysis. No cross-platform normalization was applied, and overlapping genes may partly reflect shared technical or design features.

CONCLUSION

This integrative bioinformatics analysis identifies transcriptional signatures associated with soy-derived isoflavone exposure in breast cancer models. The observed gene expression patterns suggest modulation of pathways related to cell cycle regulation and apoptosis; however, these findings are exploratory and do not establish therapeutic efficacy. Experimental validation is required to determine the biological and clinical relevance of these observations.

ETHICAL CONSIDERATIONS

This study utilized publicly available microarray data from GEO and did not involve human subjects or new data collection, and according to our institutional protocols in medical ethics in the field of research, requiring no ethical approval.

DATA AVAILABILITY

Data are available in GEO at GSE9936 (doi: 10.1210/me.2007-0356), GSE63205 (doi: 10.1002/mnfr.201500028), GSE50705 (doi: 10.1038/oncsis.2015.32), and GSE58792 (doi: 10.1093/jnci/dju189).

CONFLICT OF INTERESTS

The authors declare no competing financial or personal interests.

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AI DISCLOSURE

The authors confirm that no generative artificial intelligence (AI) tools were used in the development of the scientific content of this manuscript. AI-based language editing tools were used only to improve clarity and grammar. All authors are responsible for the content and have approved the final version of the manuscript.

AUTHOR CONTRIBUTION

EB: Data curation, Formal analysis, Investigation, Methodology, Visualization; ZK: Writing – original draft, Formal analysis, Visualization; PH: Supervision, Approval of the final manuscript; ST: Conceptualization, Investigation, Methodology, Writing – review & editing, Supervision.

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