RESEARCH ARTICLE

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Sesamin Suppresses Ovarian Cancer Progression via Modulation of Wnt/β-Catenin and Associated Oncogenic Pathways

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Abstract

Objective: The current research aimed to explore the molecular pathway of sesamin in controlling the Wnt/β-catenin signaling pathway and associated oncogenic regulators in ovarian cancer cells. **Methods:** Molecular docking was conducted to assess sesamin's binding activity toward major signaling proteins (Wnt, β-catenin, GSK3β, TGF-β). Functional confirmation was performed using quantitative PCR (qPCR) to quantify gene expression following a 48-hour treatment of ovarian cancer cells with sesamin. **Result:** Docking simulations revealed strong binding affinities, particularly with Wnt (−9.19 kcal/mol), supported by hydrogen bond interactions. qPCR results showed significant downregulation of Wnt (50%), TGF-β (40%), GSK3β (25%), and β-catenin transcripts compared to the control ($p < 0.001$). **Conclusion:** Sesamin potently inhibits several oncogenic regulators within the Wnt/β-catenin pathway, positioning it as a potential multi-target natural therapeutic for ovarian cancer. These findings support sesamin as a promising candidate for further preclinical and clinical investigation, particularly as an adjuvant therapy to overcome drug resistance and limit tumor progression.

Keywords: Ovarian Cancer- Sesamin- Anticancer Activity

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Introduction

Ovarian cancer is a significant problem worldwide, the most frequent gynecologic cancer cause of death and the fourth most frequent female cancer cause of death in total. Based on the most recent Global Cancer Burden statistics, there were 239,682 new cases and 171,246 deaths among women aged 45 and above in the year 2021, with the illness being responsible for approximately 4.3% of all female cancer mortality. Incident cases are estimated to increase by over 55% to over 500,000 per year by 2050, while deaths per year could rise to 350,000, nearly a 70% increase if trends continue. The increases are fueled by population growth, global aging, and changing demographics, with the greatest burden seen in women aged 55 to 74 years [1]. The clinical management of ovarian cancer is further challenged by the late diagnosis of about 70% of cases, and 5-year survival rates continue to be relatively low sometimes between 30% and 50% worldwide. The disease also has a huge socioeconomic burden, with approximately 900,000 women being affected worldwide over the last five years, and close to one-tenth of a percent of global GDP being caused by its diagnosis and treatment costs. The etiology of ovarian cancer is multifactorial, involving genetic causes, reproductive life, and lifestyle, whereas declining fertility rates and aging of the population can diminish the protective effects of pregnancy and lactation [2]. The Wnt/β-catenin signaling pathway is involved in various processes of ovarian cancer development, such as cell growth, epithelial-to-mesenchymal transition (EMT), metastasis, and acquisition of drug resistance [3]. Stimulation of the Wnt/β-catenin pathway stimulates ovarian cancer cell growth by controlling cell growth and survival genes [4]. The pathway is essential in EMT, a process by which epithelial ovarian cancer cells become deprived of cell junctions and acquire mesenchymal characteristics, increasing their motility and invasiveness [5]. Wnt/β-catenin signaling makes ovarian cancer drug-resistant, especially to platinum-based chemotherapies [6]. Sesamin is a primary natural lignan found predominantly in sesame seeds (*Sesamum indicum* L.), and it is of great scientific interest because of its special structure and

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diverse biological activities [7]. Another characteristic feature of sesamin is its antioxidant action. It possesses strong free radical scavenging properties, suppressing oxidative stress and thus providing protective functions against cell damage [8]. In general, sesamin is a bioactive lignan with potential health promotion and disease prevention applications based on its antioxidant and anti-cancer properties. Literature supports the potent anti-cancer property of sesamin, the natural lignan of sesame seeds, in different cancer models. Anti-Cancer Mechanisms- Experiments have established that sesamin possesses anti-proliferative, pro-apoptotic, anti-metastatic, anti-angiogenic, and pro-autophagic effects in cancer cells in vitro and in vivo. Molecular mechanisms of action of sesamin involve modulation of critical pathways such as *NF-κB, STAT3, JNK, ERK1/2, p38 MAPK, PI3K/AKT, caspase-3,* and *p53* [9]. In leukaemia, sesamin has shown dose- and time-dependent inhibition of leukemic cell growth and induction of apoptosis through caspase-dependent and -independent pathways and with extremely low cytotoxicity to normal cells [10]. Sesamin also exhibits potential chemo preventive activity in breast cancer as well as other solid tumours by inhibiting migration, inducing cell cycle arrest, and inhibiting angiogenesis and metastasis [11]. Systematic reviews note sesamin as a lead compound for adjuvant therapy, which can be combined with standard anticancer drugs to increase cell death and lower therapy resistance. The current research demonstrates the interaction between Wnt signaling and sesamin in ovarian cancer to be novel and important for various crucial reasons. In addition, Wnt activation is generally achieved through secondary mechanisms including microenvironmental signals, epigenetic regulation, and non-coding RNA modulation, which demonstrates the pathway's complex role in tumor biology [12]. Sesamin is a natural lignan that has been reported to possess antioxidant and anti-cancer activity, and it has not yet been widely investigated with regard to Wnt pathway modulation in ovarian cancer. While much of the current literature on sesamin's anti-cancer activities addresses its capacity to modulate apoptosis, inflammation, and cell cycle pathways, its scope to interact with Wnt signaling pathways in ovarian cancer has not yet been clarified [13]. Research into the impact of sesamin on Wnt signaling in ovarian cancer has the potential to identify new mechanisms of action for this natural product and unlock avenues to new treatment approaches that target this essential signaling pathway [14, 15]. The present study aimed to investigate the molecular process of sesamin in controlling the Wnt/β-catenin signaling pathway and related oncogenic regulators (Wnt, β-catenin, GSK3β, and *TGF-β*) in ovarian cancer cells, employing molecular docking and gene expression (qPCR) techniques to assess its prospective applicability as a multi-target natural drug agent. This research is important not only to further molecular insight but also to possibly give a low-toxicity, naturally occurring agent to inhibit ovarian cancer growth, reverse drug resistance, and enhance patient outcomes.

Materials and Methods

SKOV3 cell culture and compound

Human Ovarian Cancer Cells (SKOV3) were received from NCCS, Pune, India, and were grown in a T-75 culture flask in Ham's F-12 medium with 10% FBS. The cells were incubated at 37°C under a humidified atmosphere of 5% CO_2 and 95% air. The cells were trypsinized and sub-cultured for further studies when they were 80% confluent. Based on our previous study, the cytotoxic potential of sesamin was assessed using the MTT assay to determine its IC50 value, which was identified as 75 µM. Dimethyl sulfoxide (DMSO) was used as the solvent, with the final DMSO concentration maintained at 0.1% (v/v). based on these results, subsequent experiments were conducted using SKOV3 cells treated with sesamin at its IC50 concentration (75 µM) for 48 hours [16]. Sesamin (≥98% purity, CAS number: 607-80-7), purchased from Simson pharma limited, was utilized for the following experiments.

Molecular docking

The docking of molecules using Auto Dock Tools is a multi-step process; the AutoGrid procedure forms three-dimensional grid boxes to calculate the binding energies to macromolecule coordinates. AutoGrid is capable of generating grid maps that account for the entire ligand in the target site of the real docking. The whole ligand is inserted into the binding pocket and this is fully encapsulated in cubic grids. And the grid box defined in order to encompass the complete protein structure in such a way as to allow blind docking. Thirty independent docking simulations (n = 30) were performed for each ligand in order to allow for complete conformational space to be explored. The graphical user interface of Auto Dock (version 4.2.6), provided by MGL Tools, is employed to define the AutoDock atom types. In Auto Dock, the Lamarckian genetic algorithm was employed it is among the most successful free docking protocols available. Auto Dock then determines the binding free energy and the optimum fit of a ligand conformation that docks in a macromolecular structure. BIOVIA Discovery Studio was utilized to profile the binding pocket [17].

Quantitative Real-Time PCR analysis

The mRNA expression levels of β-catenin, GSK-3β, *TGF-β*1, and Wnt were analyzed using quantitative real-time polymerase chain reaction (qRT-PCR). Total RNA was isolated from the experimental samples using TAKARA TRIzol reagent (Jayanagar, Bengaluru – 560004, India) according to the manufacturer's instructions. The purity and concentration of RNA were assessed, and 2 µg of total RNA from each sample was reverse-transcribed into complementary DNA (cDNA) using a SuperScript™ III First-Strand cDNA Synthesis Kit (Invitrogen, USA), following the manufacturer's protocol. Real-time PCR amplification was performed using MESA Green qPCR Master Mix (Eurogentec, USA), which contains all necessary PCR components along with SYBR Green dye. The sequences of gene-specific primers and the internal control gene are listed in Table 1. PCR

Tablet 1. List of Primers Used

Target	Forward Primer	Reverse Primer
β-catenin	AAAATGGCAGTGCGTTTAG	TTTGAAGGCAGTCTGTCGTA
GSK-3β	CCGACTAACACCACTGGAAGCT	AGGATGGTAGCCAGAGGTGGAT
TGF-β1	GAGCCCTGGACACCAACTAC	GCTCCAGATGTAGGGACAGG
Wnt	CTTCGGCAAGATCGTCAACC	GCGAAGATGAACGCTGTTTCT
β-actin	AACAAGATGAGATTGGCA	AGTGGGGTGGCTTTTAGGAT

reactions were carried out under the following thermal cycling conditions: an initial pre-activation step at 95 °C for 5 minutes, followed by 40 cycles of denaturation at 95 °C for 5 seconds and combined annealing/extension at primer-specific temperatures ranging from 55 °C to 62.5 °C for 10 seconds. The specificity of each amplification product was confirmed by melting curve analysis for every primer pair. All reactions were performed in triplicate (n=3). Relative gene expression levels were calculated using the comparative Ct (2^{-}ΔΔCt) method as described by Schmittgen and Livak (2008) [18], with data analysis performed using CFX Manager software version 2.1 (Bio-Rad, USA).

Statistical analyses

All the results were statistically analyzed by one-way analysis of variance and Duncan's multiple comparison test using SPSS 7.5 to determine the significance of individual differences among the control and treatment groups. A p value of < 0.05 was considered statistically significant.

Results

Molecular docking

Molecular docking demonstrated significant interactions of sesamin with major Wnt/β-catenin signaling proteins implicated in ovarian cancer. Sesamin had the greatest affinity for Wnt (−9.19 kcal/mol) through MET-87 hydrogen bonding, suggestive of Wnt inhibition. It interacted with GSK3β (−7.21 kcal/mol) by VAL-348, *TGF-β* (−7.33 kcal/mol) by GLY-27, β-catenin (−6.41 kcal/mol) by TYR-482 and GLY-541. These findings imply sesamin is a multi-target modulator that can inhibit ovarian cancer development by simultaneously regulating the activities of Wnt, GSK3β, *TGF-β*, and β-catenin (Table 2, Figure 1).

Gene expression

Expression analysis Of β -Catenin mRNA

Real-time quantitative PCR analysis revealed a dramatic downregulation of β-catenin expression at 48 hours following sesamin treatment ($p < 0.001$). The amplification plot (Figure 2B) verifies effective target

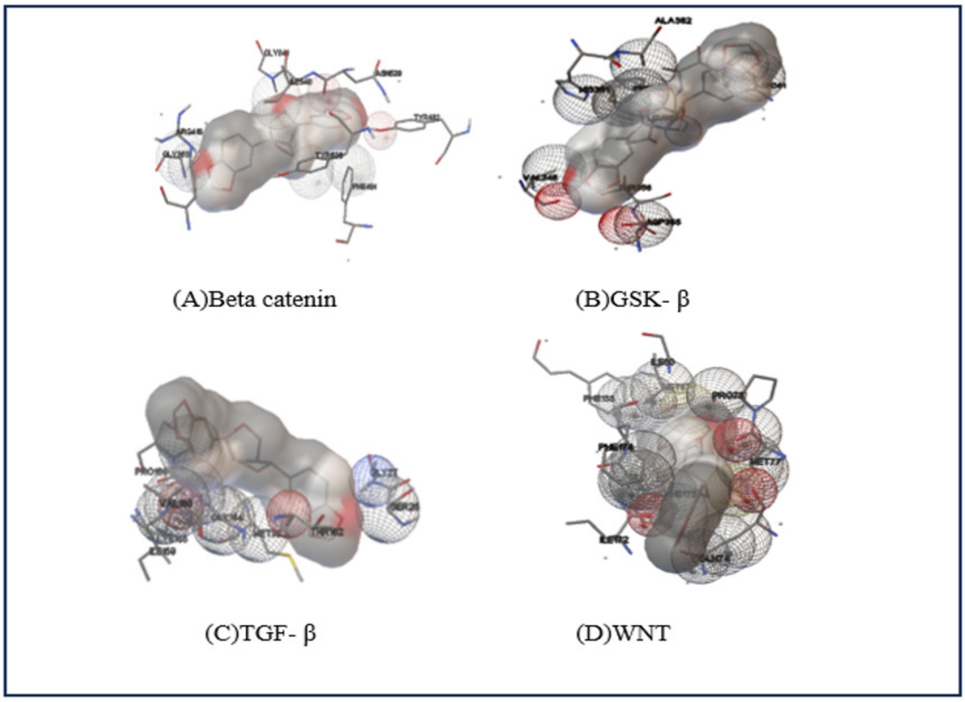

Figure 1. Molecular Docking Study of Sesamin with Major Modulators of the Wnt/β-catenin Signaling Pathway in Ovarian Cancer. Sesamin showed high binding energies with (A)β-catenin (−6.41 kcal/mol), (B)GSK3β (−7.21 kcal/mol), (C)TGF-β (−7.33 kcal/mol), and (D)Wnt (−9.19 kcal/mol). Hydrogen bond interactions were noted at MET-87 (Wnt), VAL-348 (GSK3β), GLY-27 (TGF-β), TYR-482 and GLY-541 (β-catenin) reflecting stable and specific binding. These findings indicate that sesamin could have therapeutic efficacy against ovarian cancer by regulating multiple targets in the Wnt/β-catenin signaling pathway.

Table 2. Molecular Docking of Sesamin with Targeted Molecules

Target Molecules	Compound	Binding Energy	Amino Acid Interacted	Bond Formed
BETA CATENIN	Sesamin	-6.41	GLY-363, ARG-416, TYR-482, PHE-491, TYR-536, ASN-539, ILE-540, GLY-541	2H- TYR-482, GLY-541
GSK3β	Sesamin	-7.21	VAL-348, ASP-355, THR-356, LEU-359, PHE-360, ASN-361, HIS-381, ALA-382	1H- VAL-348
TGF- β	Sesamin	-7.33	PRO166, VAL160, IYS165, ILE159, GLY64, MET92, THR162, GLY27, SER26	1H-GLY-27
Wnt	Sesamin	-9.19	GLN-74, MET-77, PRO-78, ILE-80, MET-87, PHE-138, ILE-172, PHE-173, PHE-174	1H- MET-87

amplification, and the melt curve (Figure 2C) reveals a single sharp peak (~85 °C), confirming primer specificity. These observations establish that sesamin significantly suppresses β-catenin mRNA, which implies Wnt/β-catenin pathway inhibition at the transcriptional level.

Expression analysis of GSK-3β mRNA

qPCR analysis was carried out to assess the expression of GSK3β in treated and control samples. Amplification plot (Figure 3A) indicated increased fluorescence intensity through cycles, confirming successful amplification of target gene. Melt curve analysis (Figure 3B) indicated one sharp peak around 85°C, signifying specificity of amplification in the absence of any nonspecific products or primer-dimer formation. Relative quantification revealed a 20–25% downregulation of GSK3β expression in treated samples compared to control ($p < 0.001$), indicating effective inhibition of the gene and possible modulation of the Wnt/β-catenin pathway (Figure 3C).

Expression analysis of TGF-β mRNA

Quantitative PCR (qPCR) was carried out to analyze the impact of sesamin treatment on *TGF-β* mRNA expression. The amplification plot (Figure 4A) indicated strong amplification of the target gene among experimental samples. The melt curve analysis (Figure 4B) exhibited a single sharp peak at ~77 °C, ensuring the specificity of amplification without any nonspecific products or primer-dimer formation.

Relative quantitation indicated approximately a 40% decrease in *TGF-β* mRNA levels in sesamin-treated cells as opposed to control ($p < 0.001$). The data indicate that sesamin considerably inhibits *TGF-β* expression, which may modulate cancer-related downstream signaling pathways (Figure 4C).

Expression analysis of Wnt mRNA

To analyze the impact of treatment with sesamin on the Wnt signaling pathway, qPCR analysis was performed to measure the expression levels of Wnt mRNA. The amplification plot (Figure 5A) established efficient amplification of the Wnt gene with similar amplification curves in different biological replicates. The melt curve analysis (Figure 5B) showed one clear peak at ~85 °C, verifying amplification specificity and the lack of any nonspecific PCR products or primer-dimers. The relative quantification indicated a nearly 50% decrease in the level of Wnt mRNA following 48 hours of sesamin treatment versus control ($p < 0.001$). These observations reflect that sesamin significantly suppresses the expression of Wnt, indicating its modulating action on the Wnt/β-catenin signaling pathway in ovarian cancer (Figure 5C).

Discussion

The present study is the first to demonstrate that sesamin, a dietary food lignan, is extremely inhibitory to ovarian cancer by suppressing Wnt/β-catenin signaling

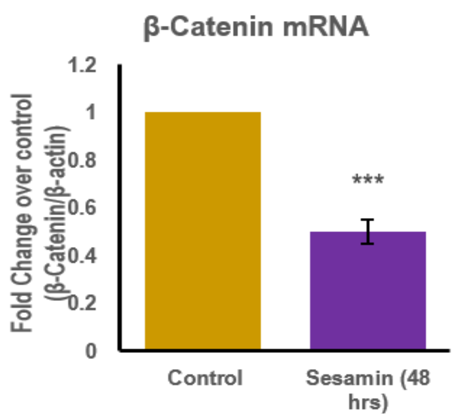

Figure 2. Bar Graph Comparing Relative Fold Change in β-catenin Expression Following 48 hrs of Sesamin Treatment with Control. Data are normalized to β-actin and expressed as mean ± SEM ($p < 0.001$ vs. control).

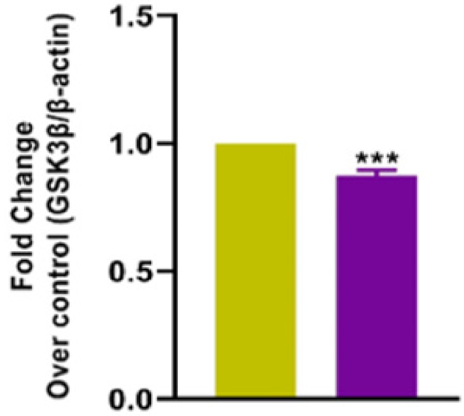

Figure 3. Bar Graph Shows the mean ± SEM of Triplicate Experiments Treatment Decreased the Expression of GSK3β Below Control Levels ($p < 0.001$).

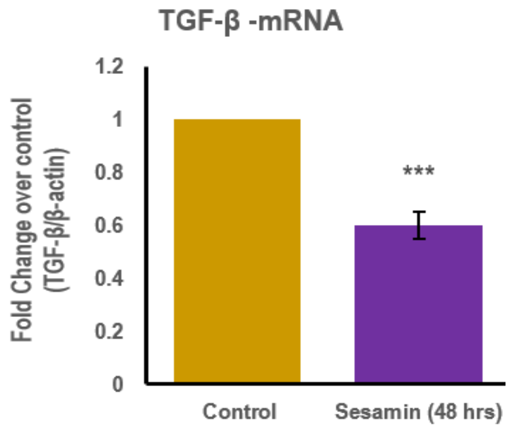

Figure 4. Normalized Fold-Change Expression of TGF-β mRNA Relative to β-actin. Sesamin treatment for 48 hours downregulated TGF-β expression significantly in comparison with control ($p < 0.001$). Data are given as mean ± SEM of triplicate experiments.

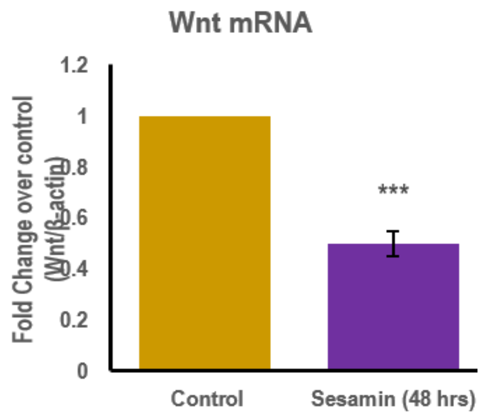

Figure 5. Relative Fold-Change Expression of Wnt mRNA Normalized against β-actin. Sesamin treatment (48 h) inhibited Wnt expression significantly when compared with the control ($p < 0.001$). Data depict mean ± SEM of triplicate experiments.

and its corresponding oncogenic effectors at gene levels. Although molecular docking analysis revealed stable interaction of sesamin with significant regulators like Wnt, GSK3β, β-catenin, and *TGF-β* the functional validation through qPCR provided its capacity to inhibit transcriptional and translational expression of the targets. Quantitative PCR analysis indicated that sesamin reduced mRNA for Wnt, β-catenin, GSK3β, and *TGF-β* considerably. Among them, Wnt transcripts were reduced by nearly 50%, while β-catenin and GSK3β were reduced by ~20–25%, and *TGF-β* by ~40%. Past research has linked dysregulated Wnt signaling to abnormal ovarian cancer cell proliferation and metastasis. For example, [19] noted that hyperactivation of Wnt/β-catenin signaling correlated with unfavourable prognosis and aggressive tumour behaviour in ovarian carcinoma. Likewise, the previous article emphasized the function of Wnt and *TGF-β* crosstalk in inducing EMT and chemoresistance [20]. By inhibiting these transcripts, sesamin can interfere with the transcriptional apparatus necessary for tumor survival and invasion. Remarkably, *TGF-β* plays a double role in cancer, that of tumor suppressor in normal cells but that of pro-metastatic factor in late cancers through its ability to induce EMT [21]. The study's finding of almost a 40% reduction indicates that sesamin is selectively targeting *TGF-β* signaling during the progression of ovarian cancer and restricting metastatic potential [22].

Notably, the altered expression of apoptosis-related genes observed in the present study is likely an indirect consequence of upstream pathway inhibition rather than the result of direct gene targeting. Suppression of Wnt/β-catenin and *TGF-β* signaling is known to attenuate pro-survival cues, thereby indirectly activating the apoptotic cascade. This mode of action is consistent with mechanisms reported for several dietary phytochemicals, including curcumin and resveratrol, which predominantly induce apoptosis through inhibition of oncogenic signaling pathways such as Wnt/β-catenin, PI3K/Akt, and NF-κB, rather than by directly interacting with apoptosis-regulatory genes [23].

In line with this concept, previous studies on sesamin have largely emphasized its antioxidant, anti-inflammatory, and anti-proliferative effects in cancers such as hepatocellular carcinoma, breast cancer, and colorectal cancer [24]. However, its role in ovarian cancer remains relatively underexplored. For example, sesamin has been shown to inhibit proliferation and induce apoptosis in breast cancer via suppression of the PI3K/Akt pathway [25], while in colorectal cancer, it attenuates tumor cell invasion through inhibition of NF-κB signaling [26]. These findings suggest that sesamin exerts its anticancer effects primarily through modulation of key oncogenic pathways rather than single-gene targeting.

Building upon this foundation, the novelty of the present study lies in its dual approach, integrating molecular docking analysis with experimental validation of gene expression in ovarian cancer cells. Our findings demonstrate that sesamin exerts a multi-target inhibitory effect within the Wnt/β-catenin signaling axis, simultaneously modulating Wnt, β-catenin, GSK3β, and *TGF-β*. Such coordinated inhibition is particularly significant, as pathway redundancy is a major obstacle in targeted ovarian cancer therapy. Furthermore, while earlier research has attributed sesamin's anticancer potential to modulation of NF-κB and PI3K/Akt pathways, the present study expands its mechanistic repertoire by identifying its regulatory effects on the Wnt/β-catenin and *TGF-β* pathways—two signaling cascades critically implicated in ovarian tumor initiation, progression, and metastasis [27]. This expanded portfolio of pathway inhibition strengthens the rationale for considering sesamin as a promising emerging therapeutic candidate or adjuvant in the management of ovarian cancer.

Limitations of the study

A limitation of the present study is that the findings are primarily based on mRNA expression analysis, which may not directly correlate with protein expression or functional activity. The key components of the Wnt/β-catenin and *TGF-β* signaling pathways were not validated at the protein level, and therefore, confirmation of these molecular changes at the translational level remains to be explored in future studies.

In conclusion, our research presents strong evidence that sesamin inhibits ovarian cancer development by repressing Wnt, β-catenin, GSK3β, and *TGF-β* at gene levels. Differing from earlier research that identified single targets, our results emphasize sesamin's multi-target inhibition within the Wnt/β-catenin pathway. By interfering simultaneously with transcriptional and translational regulators of proliferation, EMT, and survival, sesamin is a hopeful therapeutic approach for managing ovarian cancer.

Author Contribution Statement

Performed experiments, data collection, and manuscript drafting-Heera Maheswari Jayaveeran; Conceptualization, supervision, and critical revision of the manuscript - Ponnulakshmi Rajagopal; Assisted in experimental design, methodology, and data validation - Manju Parthiban; Conducted bioinformatics, data interpretation, statistical analysis and critical revision of the manuscript- Selvaraj Jayaraman; Contributed to literature review - Krithika C & Sureka Varalakshmi V.

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Conflict of Interest

The author hereby declares that there is no conflict of interest.

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