RESEARCH ARTICLE

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Sesamin Mitigates Gastric Carcinogenesis via Modulation of the *PI3K/AKT/mTOR* Signaling Pathway in AGS Cells and MNNG-Induced Rats

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Abstract

Background: Gastric cancer (GC) is a leading cause of cancer-related death worldwide, frequently associated with dysregulated *PI3K/AKT/mTOR* signaling and defective apoptosis. Sesamin, a lignan from sesame seeds, is rich in antioxidant and anticancer activities, yet it has not been well investigated for its therapeutic potential in GC. **Objective:** This study aims to investigate the anticancer potential of sesamin against gastric cancer by targeting the *PI3K/AKT/mTOR* signaling pathway in AGS cells and MNNG-induced rats, evaluating its effects on apoptosis, oxidative stress, and tumor biomarkers to elucidate its molecular mechanism of action. **Methods:** *In vitro*, molecular changes in AGS gastric cancer (GC) cells were determined by RT-PCR (*p53, caspase-3, MDM2, PTEN, AKT, mTOR, NF-κB*). *In vivo*, N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) was used to induce gastric cancer in Wistar rats. The intervention of sesamin was studied by histopathological analysis, and ELISA was used for the measurement of tumor markers (CEA and CA 19-9) and oxidative stress markers. Gene expression was analyzed by RT-PCR (*p53*, *caspase-3*, *AKT*, *NF-κB*, *mTOR*). **Results:** Sesamin treatment in AGS cells upregulated *PTEN, p53*, and *caspase-3*, while downregulating MDM2, *AKT*, *mTOR*, and *NF-κB* at the mRNA level in the in vitro study. In the in vivo mRNA expression analysis, sesamin treatment confirmed enhanced *p53* and *caspase-3* with reduced *AKT* expression and slightly increased *mTOR* expression. In MNNG-induced rats, sesamin improved gastric histology, decreased tumor markers (CEA, CA 19-9), suppressed IL-1β, and elevated GSH. RT-PCR analysis further validated the induction of pro-apoptotic genes and suppression of oncogenic PI3K/*AKT*/*mTOR*/*NF-κB* signaling, consistent with in vitro findings. **Conclusion:** Sesamin has demonstrated effective anti-gastric cancer activity by inducing *p53*/*caspase-3*-mediated apoptosis and inhibiting the PI3K/*AKT*/*mTOR*/*NF-κB* signaling pathway. These findings illustrate the therapeutic potential of sesamin against gastric cancer and reveal molecular clues for its use as a natural chemopreventive agent.

Keywords: Sesamin- Gastric cancer- AGS cell line- MNNG- induced rat model

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Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality, with more than 1.09 million new cases and approximately 770,000 deaths in 2020. The highest incidence is among people above 65 years, with the risk being higher among men, and it has the highest mortality and incidence in Eastern Asia, which accounts for approximately 75% of the global incidence and mortality [1]. Major risk factors are chronic Helicobacter pylori infection, smoking, excessive consumption of salted or processed foods, low fruit and vegetable intake, obesity, advanced age, male gender, family history, and exposure to specific chemicals or dust [2]. Lifestyle changes like smoking abstinence, lesser alcohol consumption, and a healthy diet can decrease GC risk [3].

PTEN, phosphatase and tensin homolog, is a tumor suppressor that acts by dephosphorylating PIP3, thereby blocking the *PI3K/AKT/mTOR* pathway, keeping cellular homeostasis and inhibiting tumor growth. *PTEN* loss or inactivation in GC results in hyperactivation of *AKT* and *mTOR*, inducing proliferation, angiogenesis, and resistance to apoptosis [4]. The *PI3K*/*AKT*/*mTOR* pathway

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controls cell growth, survival, metabolism, angiogenesis, and metastasis and is associated with poor prognosis when hyperactivated. Its suppression promotes apoptosis by upregulation of tumor suppressors such as *p53*, activation of *caspase-3*, and suppression of anti-apoptotic proteins [5].

p53 mediates DNA damage response, apoptosis, and cell cycle arrest, whereas *MDM2* inhibits *p53* through ubiquitination, which contributes to GC progression. *Caspase-3* is one of the most important executors of apoptosis, and *NF-κB*, *PI3K/AKT*-activated *NF-κB*, enhances survival and inflammatory gene expression. Collectively, this network inhibits apoptosis, induces proliferation, and favors tumor development; hence, disrupting it has a potential therapeutic effect in GC [6–8].

Sesamin, a lignan from Sesamum indicum, has anticancer, anti-inflammatory, and antioxidant activities in various cancers such as gastric, breast, colorectal, leukemia, and bladder cancers [9]. Sesamin suppresses proliferation, invasion, migration, angiogenesis, and inflammation while inducing autophagy and apoptosis. Mechanistically, it acts on *NF-κB, STAT3, PI3K/AKT*, *caspase-3*, and *p53*. *NF-κB* inhibition decreases survival signals, whereas *caspase-3* activation and *p53* modification induce apoptosis. It also inhibits VEGF and STAT3-induced MMP2 expression, preventing angiogenesis, invasion, and metastasis [10, 11].

Despite its broad anticancer effects, sesamin's impact on the *PI3K*/*AKT*/*mTOR* pathway in GC remains unclear. Most studies focus on other mechanisms, leaving a gap in understanding its role in regulating tumor growth, survival, and chemoresistance via this pathway. This research aims to evaluate sesamin's inhibitory effect on GC progression and clarify its molecular targeting of *PI3K*/*AKT*/*mTOR* using AGS cells and MNNG-induced rat models, supporting its potential as a natural therapeutic agent against gastric cancer.

Materials and Methods

Cell Culture and Chemicals

Ham's F-12 media containing 10% FBS was used to cultivate the AGS human GC cell line, which was purchased from NCCS, Pune, India, in a T-75 culture flask. The cells were kept at 37°C in a 95% air and 5% CO_2 humidified environment. When the cells accomplished 80% confluence, they were trypsinized and subcultured for further research. Based on our pervious study, MMT cytotoxicity was performed to determine the IC_{50} value of sesamin and it was found to be 43 µM [12]. Dimethyl sulfoxide (DMSO) was used as solvent. The final concentration of DMSO was maintained at ≤0.1% (v/v). Accordingly, further experiment was carried out using AGS cells treated with sesamin 43µM for 48 hrs. Sesamin (≥98% purity, CAS number: 607-80-7), MNNG (99% extra pure, Cat No: 70-25-7), and 5-Fluorouracil (99% extra pure, Cat No: 51-21-8) were purchased from simson pharma limited was used for the following experiments.

Animal Studies

The Wistar rats were acquired from Mass Biotech Pvt. Ltd,s and were kept in special clean rooms to prevent infection. The animal study was approved by the IAEC of Meenakshi Medical College Hospital and Research Institute. The study followed the guidelines set by the IAEC [permit number: IAEC/003/October 2023]. All 40 Male Wistar rats were kept in a controlled, clean environment. The animals were divided into 5 groups, with six animals per group [13]. Except for Group I, which was the control group, the other rats were given MNNG at a dose of 400mg per kilogram of body weight for 10 days to induce cancer. Once cancer was confirmed, the rats were split into five groups. Group II was the group with induced cancer. Group III received 50mg of sesamin per kilogram of body weight for 45 days. Group IV got 100mg of sesamin per kilogram of body weight for 45 days. Group V was given 200mg of 5-Fluorouracil per kilogram of body weight for 45 days (Figure 1). All the rats were anesthetized using xylazine and ketamine, then they were humanely euthanized by cervical dislocation and then examined.

Hematoxylin and Eosin (H&E) Staining

Gastric tissue sections that are 4 to 5 micrometers thick were treated with xylene to remove the paraffin. They were then gradually rehydrated using ethanol at different strengths until they reached distilled water. The slides were stained with hematoxylin for 5 minutes, then rinsed under running tap water. They were next treated with 1% acid alcohol to make the cells clear and then blued using ammonia water. After that, the sections were counterstained with eosin for 1 to 2 minutes. The slides were then dehydrated again using ethanol at different strengths, cleared with xylene, and finally covered with DPX mounting medium. The stained tissue sections were examined under a light microscope to assess any histopathological changes.

Estimation of serum CEA, CA19.9, IL-1β and GSH using ELISA

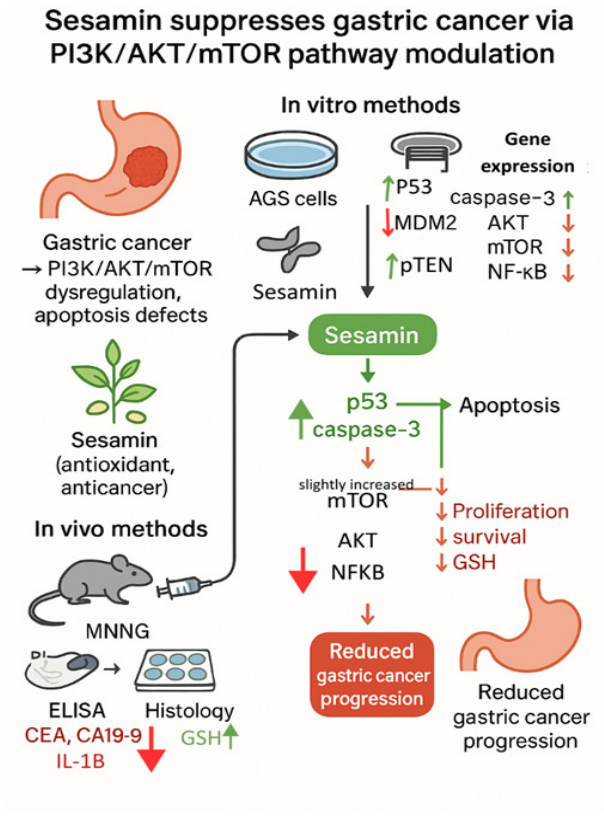
Serum concentrations of CEA, CA19-9, IL-1β, and GSH were determined with commercial ELISA kits (Fine test and Krishgen Biosystems kits) following the manufacturer's guidelines. In brief, standards and serum samples were pipetted into antibody-coated wells, incubated with enzyme conjugate, and color developed with TMB substrate. Absorbance was read at 450 nm using a microplate reader and concentrations derived from standard curves. Values were given as mean ± SD (n = 6), and statistical significance was assessed by one-way ANOVA followed by Student's–Newman–Keul's test ($p < 0.05$).

Gene expression analysis by Real-Time PCR

Total RNA was isolated from 100 mg of tissue with the Invitrogen TRIR kit. Samples were homogenized in TRIR, chloroform-treated, centrifuged, and RNA precipitated using isopropanol. Pellets were washed in 75% ethanol and spectrophotometrically quantitated. For qRT-PCR, a 45 µL reaction mixture with 2× SYBR Green master mix, primers (Table 1), and cDNA was made. Each tube was added 5 µL of template, positive, or negative control. For

Table 1. RT-PCR Primer List

Target	Forward primer	Reverse primer	Accession number
p53	5′-GCTGATGGCCATCATCAAGT-3′	5′-CAGGGTGATGATGAAGATGTG-3′	NM_001126112.3
mTOR	5′-CCTCGACAGCAGCATCAAAC-3′	5′-TAGGTGCGAACTTGGTGATG-3	NM_004958.4
Caspase-3	5′-GGTATTGAGACAGACAGTGG-3′	5′-CATGGGATCTGTTTCTTTGC-3′	NM_004346.6
Akt-1	5′-AGCTGCTTCTAGACCCTGGA-3′	5′-TTCTTGTCCCGTTGATGAGG-3′	NM_005163.2
NF-κB	5′-CAGGAGGAGCATGGACTTGT-3’	5’-GGCAGGTTTCTGCTTCTGAG-3’	NM_021975.4
MDM-2	5′-TGC ATC GAC TCC TTT TCC AGA-3′	5′-CTG ATC CTC CTC TTC TTC CTT C-3′	NM_002392.6
β-actin	5′-AGAGCTACGAGCTGCCTGAC-3′	5′-AGCACTGTGTTGGCGTACAG-3′	NM_001101.5



Graphical Abstract. Sesamin Suppresses GC Progression via Targeting the *PI3K/ AKT/ mTOR* Pathway in AGS Cells and MNNG-Induced Rat Model

PCR, 40 cycles (95°C 5 min; 95°C 5 s, 60°C 20 s, 72°C 40 s) were used. Relative gene expression was determined by the $2^{-\Delta\Delta Ct}$ method with β-actin as a reference.

Statistical analyses

Values were presented as the means ± SEM of three independent invitro experiments (n=3), each of which was done in triplicate, and *in vivo* experiments with six animals for each group (n=6). Statistical analysis was performed with one-way ANOVA, $P < 0.05$ being taken as the criterion of statistical significance.

Results

Gene expression analysis of AGS cells treated with sesamin.

PTEN mRNA Expression

PTEN mRNA expression was considerably upregulated in sesamin-treated AGS cells compared to controls ($p < 0.05$), as validated by qRT-PCR. Amplification and melt curve analyses ensured specificity, and bar graphs revealed higher *PTEN* transcript levels following 48 h of treatment (Figure 2A).

AKT1 mRNA Expression

*AKT*1 mRNA expression was significantly suppressed in sesamin-treated AGS cells versus controls ($p < 0.05$), as revealed by qRT-PCR. Amplification and melt curve analysis validated assay specificity, while bar graphs reflected decreased *AKT*1 transcript levels following treatment for 48 h (Figure 2B).

mTOR Expression

mTOR mRNA expression was profoundly suppressed in sesamin-treated AGS cells in comparison to controls ($p < 0.05$) based on qRT-PCR. Amplification and melt curve analysis affirmed specific and efficient amplification with

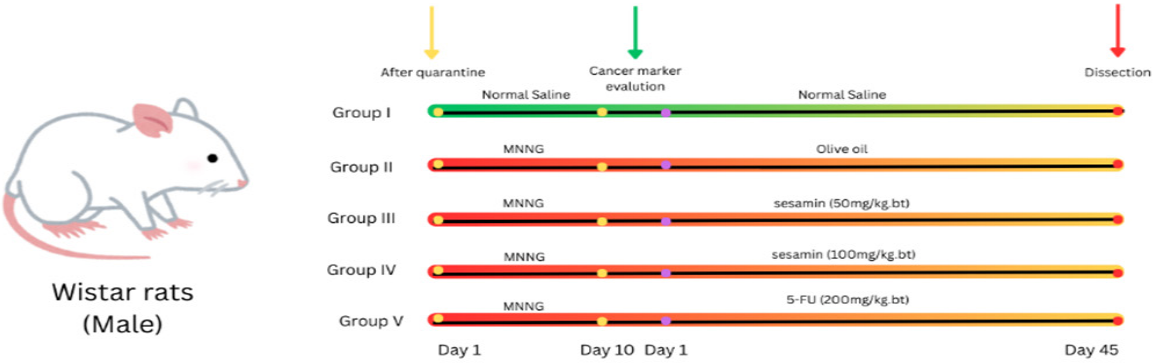


Figure 1. Experimental Procedure for the Animal Study

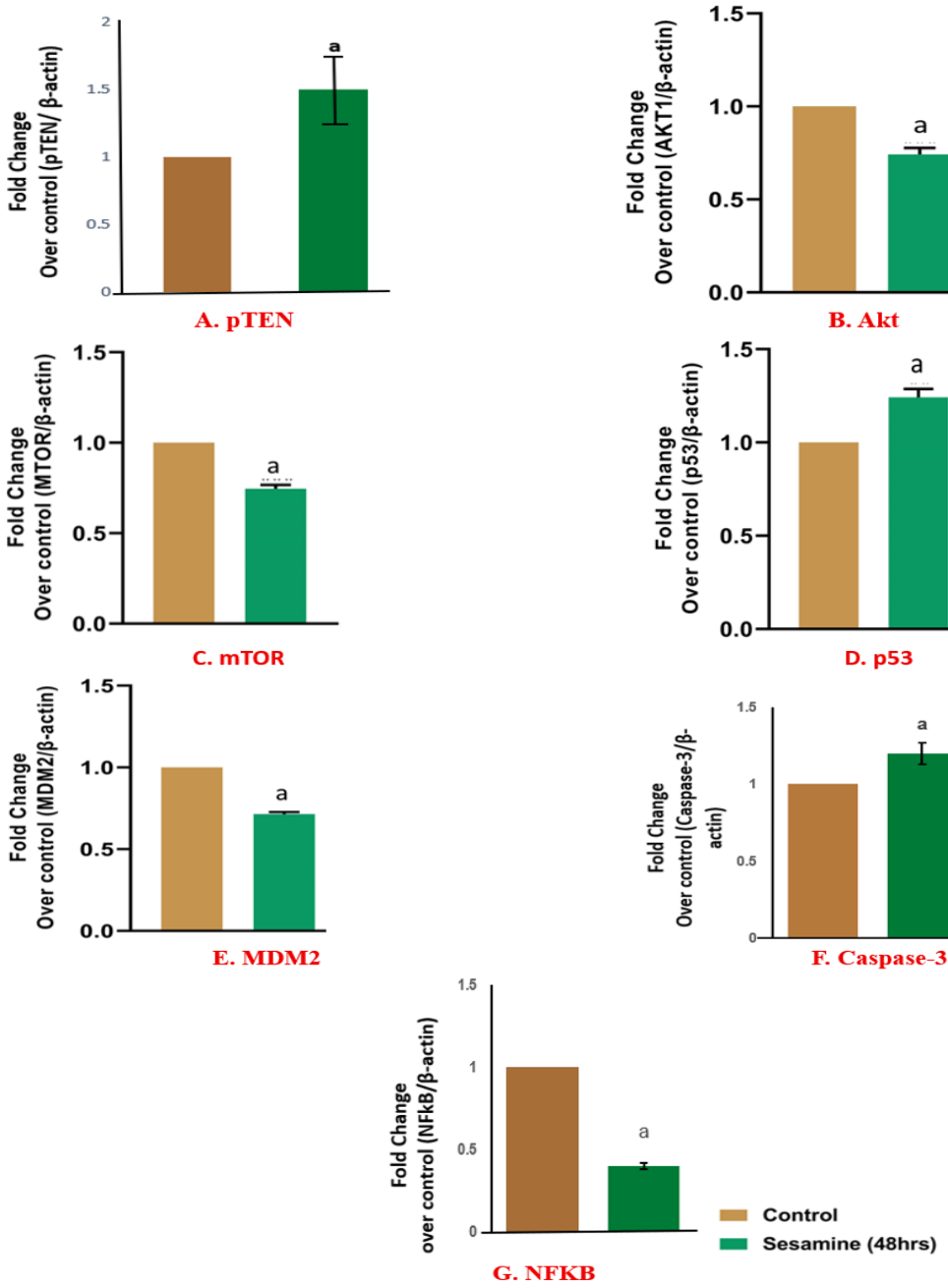


Figure 2. Effect of Sesamin on the mRNA Expression of *PTEN* (A), *Akt* (B), *mTOR* (C), *p53* (D), *MDM2* (E), *Caspase-3* (F) and *NFKB* (G) in human AGS cells. Left: PTEN mRNA fold change vs. control (mean ± SD, n=3; a $p < 0.05$).

one peak, a measure of assay credibility. Following 48 h of sesamin treatment, *mTOR* expression was lowered by about 30–40% compared to controls (Figure 2C).

P53 Expression

The qRT-PCR analysis demonstrated a strong induction of *p53* expression in sesamin-treated AGS cells after 48 h over untreated controls (1.3-fold increase; $p < 0.05$). These findings support the activation of the *p53* tumor suppressor pathway, leading to cell cycle arrest and apoptosis as previously reported for *p53*-mediated anticancer responses (Figure 2D).

MDM2 Expression

qRT-PCR analysis revealed that the treatment of sesamin downregulated *MDM2* expression by nearly 0.6-fold in AGS GC cells as compared to control groups ($p < 0.05$). This decrease in relative mRNA levels following treatment for 48 hours is illustrated in Figure 2E, which shows significant sesamin-mediated impact on *MDM2* transcription.

Caspase-3 Expression

qRT-PCR analysis revealed that sesamin treatment for 48 hours upregulated *Caspase-3* by about 1.2-fold in AGS GC cells versus controls ($p < 0.05$), relative to β-actin (Figure 2F). This illustrates substantial upregulation of *Caspase-3* after exposure to sesamin.

NF-κB Expression

qRT-PCR analysis proved that sesamin treatment for 48 hours remarkably suppressed *NF-κB* expression in

AGS GC cells to about 0.4-fold from controls ($p < 0.05$), against β-actin. These data suggest a drastic decrease in *NF-κB* transcript levels upon sesamin treatment, as shown in Figure 2G.

Histology Analysis of Wistar Rats Gastric Tissue

H&E staining of control rats showed normal gastric architecture, intact columnar epithelium, well-organized muscularis and lamina propria layers (Figure 3). MNNG-induced GC resulted in extreme histopathological changes, which were epithelial dysplasia, nuclear pleomorphism, glandular vacuolation, inflammation infiltration, and muscular disorganization. Low-dose sesamin (50 mg/kg B.Wt) also restored tissue architecture partially, decreasing vacuolation, inflammation, and muscular damage. High-dose sesamin (100 mg/kg B.Wt) significantly improved the histology, such as well-packed nuclei, less dysplasia, fewer inflammatory cells, and intact muscular structure, similar to 5-fluorouracil treatment. 5-FU Treated groups showed improvement in tissue architecture but with visible signs of toxicity. These findings suggest that sesamin, especially at high doses, can protect against MNNG-induced gastric carcinogenesis efficiently.

Effect of Sesamin on Serum tumor markers (CEA & CA 19.9) Levels in MNNG-Induced GC Rats

MNNG-induced GC rats had much higher levels of serum CEA (14 ± 2 ng/mL) and CA 19-9 (15 ± 3 ng/mL) than controls. Treatment with sesamin decreased these tumor markers in a dose-dependent fashion, with 100 mg/kg decreasing CEA to 7 ± 2 ng/mL and CA 19-9 to 8 ± 2 ng/mL, which is similar to 5-FU treatment. These results confirm that sesamin potently inhibits tumor-associated antigen levels, indicative of its protective and therapeutic values for gastric cancer (Figures 4A, B).

Effect of Sesamin on Serum IL-1β Levels in MNNG-Induced GC Rats

MNNG-induced GC rats had their serum IL-1β levels markedly increased compared to controls, reflecting

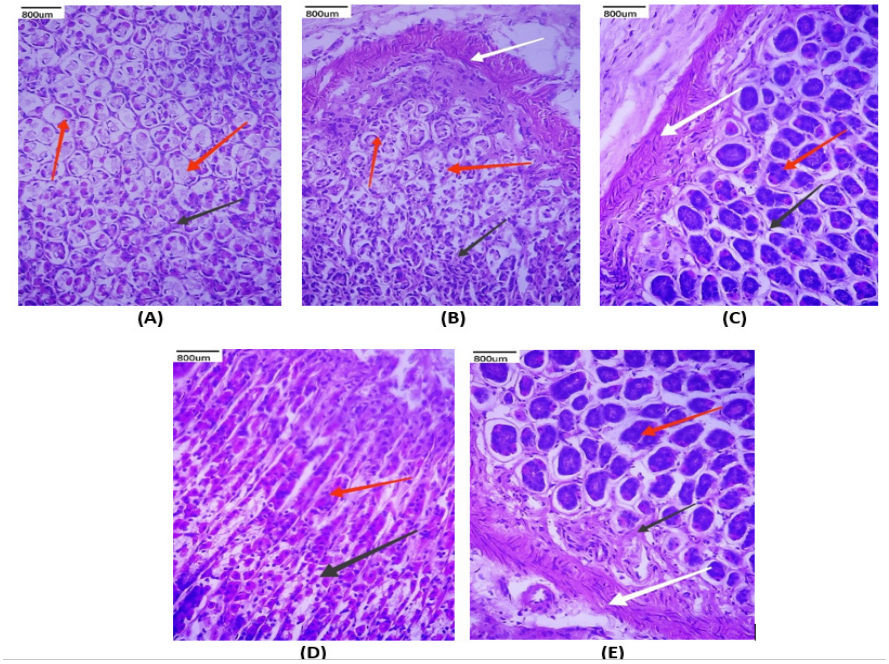


Figure 3. Histopathology Result of Stomach Tissue: Control (A), MNNG (B), MNNG + Sesamin 50 mg/kg (C), MNNG + Sesamin 100 mg/kg (D), and MNNG + 5-FU 200 mg/kg (E). 100× magnification.

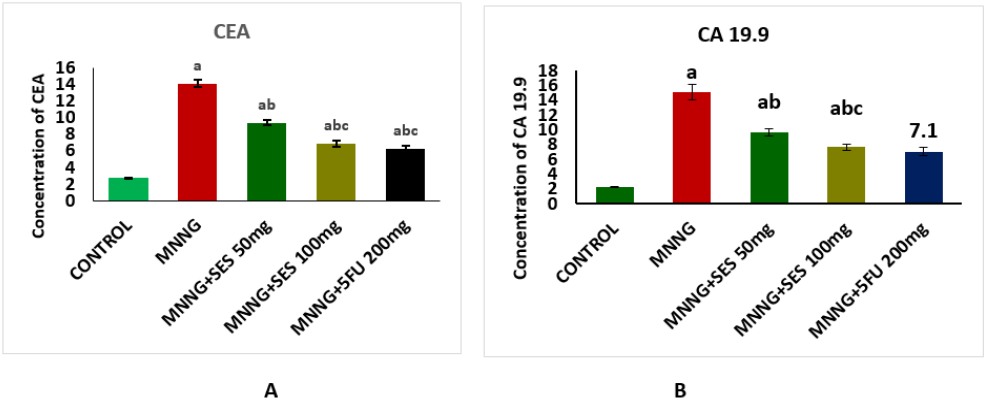


Figure 4. Serum CEA (A) and CA 19.9 (B) levels in Control, MNNG, MNNG + Sesamin (50 mg/kg), MNNG + Sesamin (100 mg/kg), and MNNG + 5-FU (200 mg/kg) groups. Data are mean ± SD (n = 6). Different superscript letters indicate significant differences ($p < 0.05$, one-way ANOVA followed by SNK test).

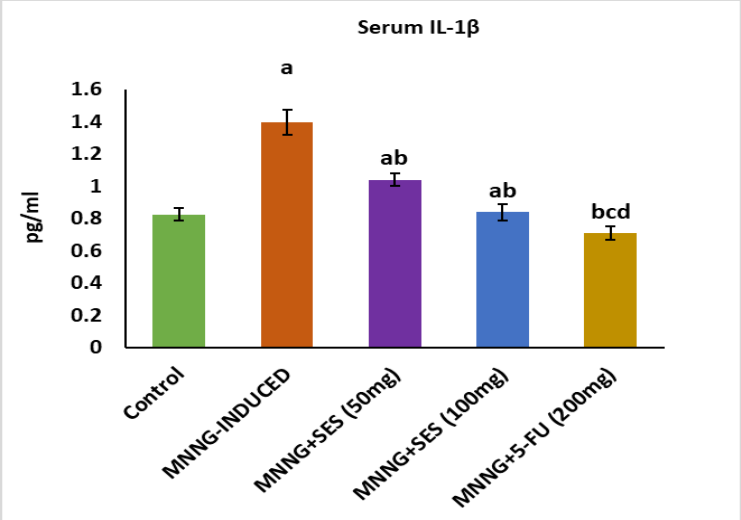


Figure 5. Serum IL-1β Levels in Control, MNNG, MNNG + Sesamin (50 mg/kg), MNNG + Sesamin (100 mg/kg), and MNNG + 5-FU (200 mg/kg) groups. Data are mean ± SD (n = 6). Different superscript letters indicate significant differences ($p < 0.05$, one-way ANOVA followed by SNK test).

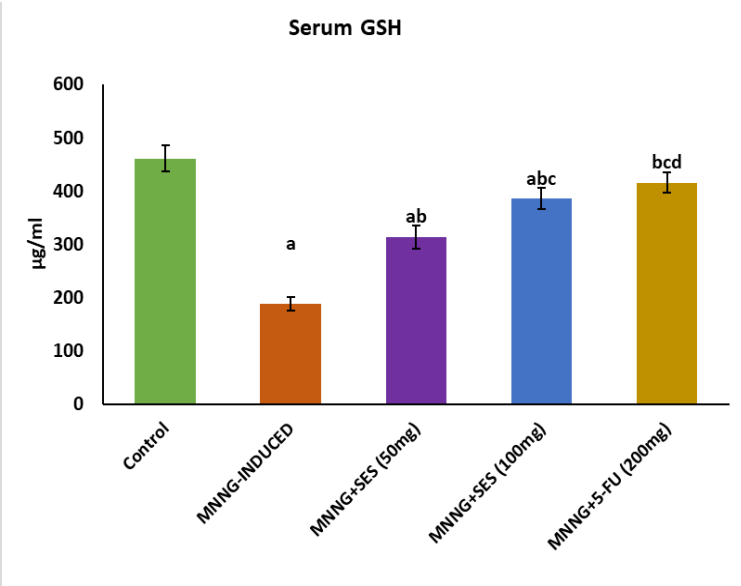


Figure 6. Serum GSH Levels in Control, MNNG, MNNG + Sesamin (50 mg/kg), MNNG + Sesamin (100 mg/kg), and MNNG + 5-FU (200 mg/kg) Groups. Data are mean ± SD (n = 6). Different superscript letters indicate significant differences ($p < 0.05$, one-way ANOVA followed by SNK test).

increased systemic inflammation. IL-1β was decreased with sesamin treatment in a dose-dependent fashion, with 100 mg/kg restoring normal levels close to the basal values. 5-fluorouracil decreased IL-1β to levels slightly more than sesamin. These findings demonstrate the strong anti-inflammatory activity of sesamin in GC-bearing rats (Figure 5).

Effect of Sesamin on Serum Glutathione Levels in MNNG-Induced GC Rats

MNNG-treated GC rats had significantly lower serum GSH content than controls, showing oxidative stress. Sesamin treatment elevated GSH in a dose-dependent fashion, with 100 mg/kg levels close to normal. 5-fluorouracil also elevated GSH slightly more than sesamin. The data clearly show that sesamin significantly enhances antioxidant defense in GC-bearing rats (Figure 6).

Effect of Sesamin on gene Expression in MNNG-Induced GC Rats

Akt mRNA Expression

qRT-PCR analysis demonstrated that MNNG significantly enhanced Akt mRNA expression to 2.3-fold in the control group (1.0-fold). Sesamin decreased Akt expression dose-dependently to 2.0-fold (50 mg/kg) and 1.6-fold (100 mg/kg), whereas 5-FU decreased it to 1.2-fold, reaching near-control levels (Figure 7A).

mTOR mRNA Expression

qRT-PCR analysis indicated baseline *mTOR* expression in control and MNNG-only groups (1.0-fold). Sesamin

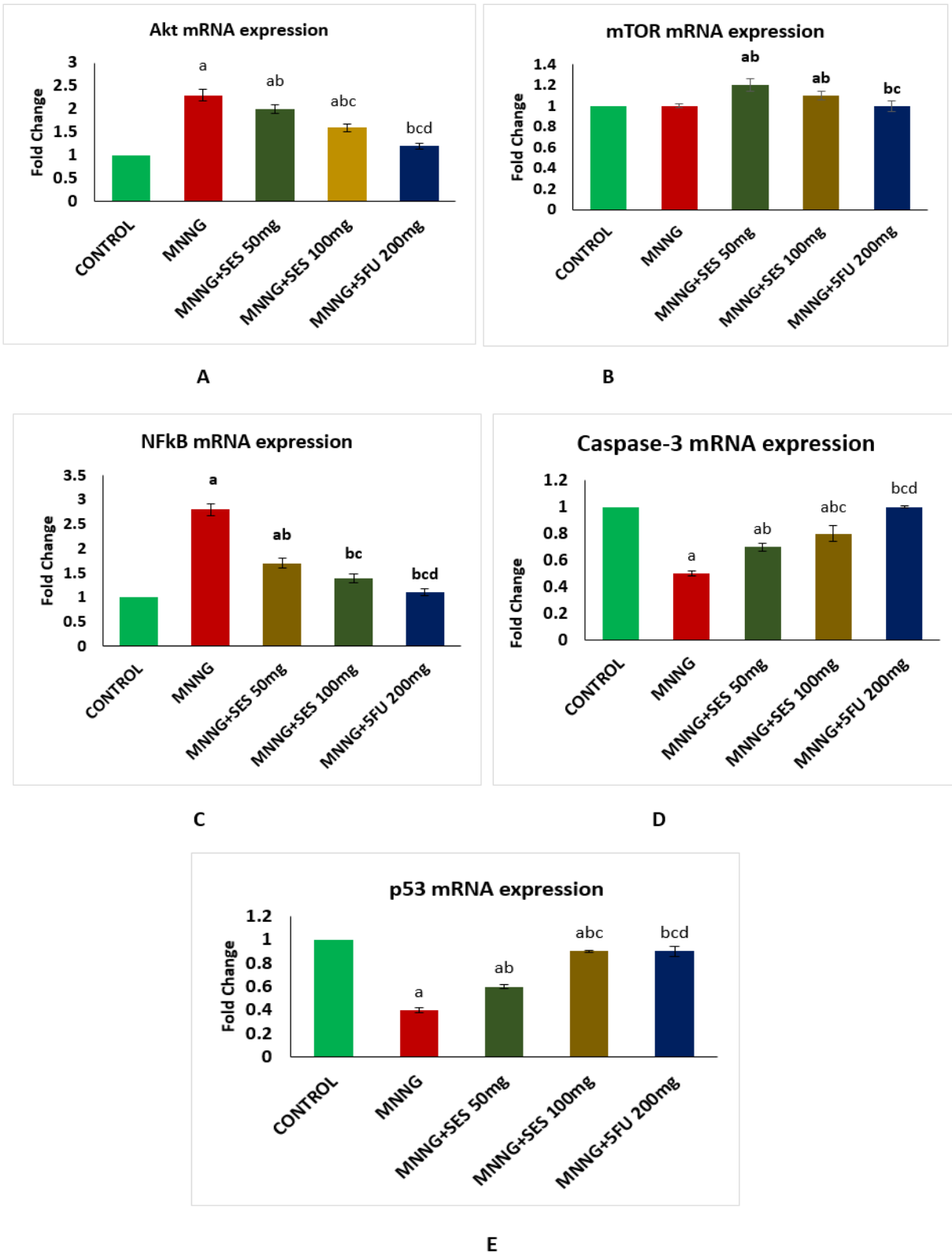


Figure 7. Effect of Sesamin on *Akt* (A), *mTOR* (B), *p53* (C), *Caspase-3* (D) and *NFKB* (E) mRNA Expression in MNNG-induced Wistar Rat Tissues. qRT-PCR analysis normalized to β-actin. Amplification (left) and melt curve (right) confirm specificity. Data are mean ± SD (n=6); different superscript letters indicate $p<0.05$ (one-way ANOVA, SNK test).

treatment increased *mTOR* expression marginally to 1.2-fold (50 mg/kg, $p < 0.05$) and 1.1-fold (100 mg/kg, not significant), whereas 5-FU was at baseline levels (1.0-fold), reflecting minimal impact of sesamin on *mTOR* relative to Akt (Figure 7B).

p53 Expression

In vivo qRT-PCR analysis revealed significant *p53*

downregulation in MNNG-induced GC rats (0.42-fold) compared to controls (1.0-fold). Sesamin treatment dose-dependently increased *p53* to 0.61-fold (50 mg/kg) and 0.91-fold (100 mg/kg), while 5-FU almost normalized expression (0.93-fold), demonstrating restoration of tumor suppressor function (Figure 7C).

Caspase-3 Expression

In vivo qRT-PCR exhibited pronounced repression of *Caspase-3* in MNNG-induced GC rats (0.52-fold) versus controls (1.0-fold). Sesamin administration restored expression dose-dependently at 0.71-fold (50 mg/kg) and 0.82-fold (100 mg/kg), while 5-FU approached normalization at 0.98-fold, suggesting sesamin efficiently restores apoptotic signaling (Figure 7D).

NF-κB Expression

qRT-PCR analysis showed *NF-κB* expression to be remarkably increased in MNNG-treated GC rats (2.8-fold) versus controls (1.0-fold). Sesamin inhibited *NF-κB* expression dose-dependently to 1.7-fold (50 mg/kg) and 1.4-fold (100 mg/kg), whereas 5-FU almost normalized it to 1.1-fold, which suggests efficient inhibition of pro-inflammatory signaling like the conventional drug (Figure 7E).

Discussion

The present *in vivo* and *in vitro* study elucidates the modulatory role of sesamin on key molecular targets involved in gastric carcinogenesis. Both AGS cells and MNNG-induced gastric cancer rats exhibited marked upregulation of *NF-κB* and *AKT*, accompanied by suppression of *p53* and *caspase-3*, consistent with chronic inflammation, impaired apoptosis, and activation of survival signaling during tumorigenesis [14]. Sesamin treatment, particularly at 100 mg/kg, significantly suppressed *NF-κB* expression, reflecting its anti-inflammatory action likely mediated through stabilization of IκB and inhibition of *NF-κB* nuclear translocation [15].

Gene expression analysis demonstrated significant upregulation of *p53* and *caspase-3* mRNA in sesamin-treated AGS cells and MNNG-induced rats, indicating activation of mitochondria-mediated apoptotic pathways. These findings are consistent with previous reports on natural compounds such as berberine, oleanolic acid, curcumin, and resveratrol, which induce *p53*-dependent, caspase-mediated apoptosis in cancer models [16–18]. The involvement of *NF-κB* and *p53* cross-regulation in gastric tumorigenesis has been increasingly recognized, supporting our interpretation of the coordinated regulation of inflammatory and apoptotic gene expression observed in the present study [19, 20]. Reduced *MDM2* expression further supports restoration of *p53* function through modulation of the *MDM2–p53* axis, reinforcing sesamin's pro-apoptotic potential in gastric cancer cells [21, 22]. Collectively, these molecular changes support sesamin as a promising anticancer agent, corroborated by prior in silico docking studies demonstrating interactions with *PI3K*/*AKT*/*mTOR* pathway components [12].

Histopathological examination revealed severe epithelial disruption, inflammatory infiltration, and mucosal degeneration in MNNG-induced gastric cancer, consistent with earlier reports [23, 24]. Sesamin treatment, especially at 100 mg/kg, markedly restored gastric architecture, reduced inflammatory cell infiltration, and preserved lamina propria and muscular layers, reflecting its antioxidant and anti-inflammatory properties [25, 26]. In contrast, 5-fluorouracil partially restored tissue integrity but was associated with cytotoxic changes, highlighting the cytoprotective advantage of sesamin [27].

Regarding *PI3K/AKT/mTOR* signaling, *in vitro* AGS cells exhibited clear downregulation of *AKT* and *mTOR* mRNA following sesamin treatment, indicating direct suppression of proliferative signaling under controlled conditions. In vivo, while *AKT* expression was significantly reduced, *mTOR* mRNA showed a marginal, non–dose-dependent elevation at lower sesamin doses, with normalization at the higher dose. This differential response likely reflects compensatory feedback regulation and the complex tumor microenvironment *in vivo*, where *mTOR* activity is predominantly governed by post-translational modifications rather than transcriptional control. Importantly, the overall functional outcome—enhanced apoptosis, reduced tumor biomarkers, improved histopathology, and suppression of inflammatory signaling supports effective attenuation of *PI3K*/*AKT*-driven oncogenic signaling despite modest transcriptional variability in *mTOR* [28-30].

Cumulatively, these findings demonstrate that sesamin exerts anti-gastric cancer activity through dual modulation of oncogenic and apoptotic pathways, characterized by inhibition of *NF-κB*/*PI3K*/*AKT* signaling and reactivation of *p53*-dependent apoptosis. This coordinated molecular regulation suppresses cell survival, proliferation, and inflammation while promoting apoptotic cell death, consistent with reports that dietary lignans can modulate cancer-related signaling networks [31]. Sesamin therefore represents a promising natural therapeutic candidate for gastric cancer, warranting further investigation, particularly at the protein and phosphorylation levels, both as a monotherapy and in combination with standard chemotherapeutic agents such as 5-fluorouracil.

Limitations of the current study

The anti-gastric cancer effects of sesamin in this study are primarily based on mRNA expression and biochemical analyses, which represents a key limitation. mRNA levels do not always correlate with protein expression or functional activity, and protein-level validation of *PI3K*/*AKT*/*mTOR* signaling components was not performed. Specifically, phosphorylation status of *AKT* and *mTOR*, as well as proteins such as *PTEN*, *p53*, *NF-κB*, and cleaved *caspase-3*, were not assessed by Western blotting or immunohistochemistry. Future studies incorporating protein and phospho-protein analyses are necessary to strengthen mechanistic and translational relevance.

In conclusion, this study provides compelling evidence that sesamin effectively attenuates gastric cancer progression by modulating the *PI3K*/*AKT*/*mTOR*/*NF-κB* signaling axis and inducing apoptosis through activation of *p53* and *caspase-3*, along with restoration

of the tumor suppressor *PTEN*. Both *in vitro* and *in vivo* findings consistently demonstrate sesamin's ability to suppress oncogenic signaling, reduce tumor biomarkers, and restore gastric tissue architecture, underscoring its potential as a natural anticancer agent. Although these findings are promising, further investigations are required to address pharmacokinetic and bioavailability limitations associated with sesamin. Notably, sesamin exhibits low oral bioavailability due to poor aqueous solubility, rapid metabolism, and first-pass hepatic clearance; however, emerging strategies such as nanoformulations, lipid-based delivery systems, and structural optimization may enhance its therapeutic efficacy and support future clinical translation.

Author Contribution Statement

Performed experiments, data collection, and manuscript drafting- Manju Parthiban; Conceptualization, supervision, and critical revision of the manuscript - Ponnulakshmi Rajagopal; Assisted in experimental design, methodology, and data validation - Heera Maheswari Jayaveeran; 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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Ethical Declaration

The animal study was approved by the IAEC of Meenakshi Medical College Hospital and Research Institute. The study followed the guidelines set by the IAEC [permit number: IAEC/003/October 2023].

Conflict of Interest

There is no conflict of interest, the author hereby certifies.

References

1. Lin JL, Lin JX, Lin GT, Huang CM, Zheng CH, Xie JW, et al. Global incidence and mortality trends of gastric cancer and predicted mortality of gastric cancer by 2035. BMC Public Health. 2024;24(1):1763. https://doi.org/10.1186/s12889-024-19104-6.
2. Ko KP. Risk factors of gastric cancer and lifestyle modification for prevention. J Gastric Cancer. 2024;24(1):99-107. https://doi.org/10.5230/jgc.2024.24.e10.
3. Man J, Ni Y, Yang X, Zhang T, Yuan Z, Chen H, et al. Healthy lifestyle factors, cancer family history, and gastric cancer risk: A population-based case-control study in china. Front Nutr. 2021;8:774530. https://doi.org/10.3389/fnut.2021.774530.
4. He T, Zhang X, Hao J, Ding S. Phosphatase and tensin homolog in non-neoplastic digestive disease: More than just tumor suppressor. Front Physiol. 2021;12:684529. https://doi.org/10.3389/fphys.2021.684529.
5. Matsuoka T, Yashiro M. The role of pi3k/akt/mtor signaling in gastric carcinoma. Cancers (Basel). 2014;6(3):1441-63. https://doi.org/10.3390/cancers6031441.
6. Sane S, Rezvani K. Essential roles of e3 ubiquitin ligases in *p53* regulation. Int J Mol Sci. 2017;18(2). https://doi.org/10.3390/ijms18020442.
7. Lei ZN, Teng QX, Tian Q, Chen W, Xie Y, Wu K, et al. Signaling pathways and therapeutic interventions in gastric cancer. Signal Transduct Target Ther. 2022;7(1):358. https://doi.org/10.1038/s41392-022-01190-w.
8. Morgos DT, Stefani C, Miricescu D, Greabu M, Stanciu S, Nica S, et al. Targeting pi3k/akt/mtor and mapk signaling pathways in gastric cancer. Int J Mol Sci. 2024;25(3). https://doi.org/10.3390/ijms25031848.
9. Majdalawieh AF, Massri M, Nasrallah GK. A comprehensive review on the anti-cancer properties and mechanisms of action of sesamin, a lignan in sesame seeds (sesamum indicum). Eur J Pharmacol. 2017;815:512-21. https://doi.org/10.1016/j.ejphar.2017.10.020.
10. Eskandari E, Eaves CJ. Paradoxical roles of *caspase-3* in regulating cell survival, proliferation, and tumorigenesis. J Cell Biol. 2022;221(6). https://doi.org/10.1083/jcb.202201159.
11. Wu MS, Aquino LBB, Barbaza MYU, Hsieh CL, Castro-Cruz KA, Yang LL, et al. Anti-inflammatory and anticancer properties of bioactive compounds from sesamum indicum l.-a review. Molecules. 2019;24(24). https://doi.org/10.3390/molecules24244426.
12. Parthiban M, Rajagopal P, Maheswari Jayaveeran H, Krithika C, Jayaraman S, Varalakshmi VS. Targeting pi3k/akt/mtor pathway: Cytotoxicity, flow cytometry, and molecular docking in ags cells by sesamin. J Nat Remedies. 2025;25(10):2411-31. https://doi.org/10.18311/jnr/2025/51079.
13. Altyar AE, Albadrani GM, Farouk SM, Alamoudi MK, Sayed AA, Mohammedsaleh ZM, et al. The antioxidant, anti-inflammatory, and anti-apoptotic effects of sesamin against cisplatin-induced renal and testicular toxicity in rats. Ren Fail. 2024;46(2):2378212. https://doi.org/10.1080/0886022x.2024.2378212.
14. Cao L, Zhu S, Lu H, Soutto M, Bhat N, Chen Z, et al. Helicobacter pylori-induced rasal2 through activation of nuclear factor-κb promotes gastric tumorigenesis via β-catenin signaling axis. Gastroenterology. 2022;162(6):1716-31.e17. https://doi.org/10.1053/j.gastro.2022.01.046.
15. Radzka J, Łapińska Z, Szwedowicz U, Gajewska-Naryniecka A, Gizak A, Kulbacka J. Alternations of nf-κb signaling by natural compounds in muscle-derived cancers. Int J Mol Sci. 2023;24(15). https://doi.org/10.3390/ijms241511900.
16. Zhao M, Yang Y, Nian Q, Shen C, Xiao X, Liao W, et al. Phytochemicals and mitochondria: Therapeutic allies against gastric cancer. Phytomedicine. 2023;110:154608. https://doi.org/10.1016/j.phymed.2022.154608.
17. Razali NSC, Lam KW, Rajab NF, Jamal ARA, Kamaludin NF, Chan KM. Curcumin piperidone derivatives induce caspase-dependent apoptosis and suppress mirna-21 expression in ln-18 human glioblastoma cells. Genes Environ. 2024;46(1):4. https://doi.org/10.1186/s41021-023-00297-y.
18. Brockmueller A, Buhrmann C, Shayan P, Shakibaei M. Resveratrol induces apoptosis by modulating the reciprocal crosstalk between *p53* and sirt-1 in the crc tumor microenvironment. Front Immunol. 2023;14:1225530. https://doi.org/10.3389/fimmu.2023.1225530.

19. Carrà G, Lingua MF, Maffeo B, Taulli R, Morotti A. P53 vs nf-κb: The role of nuclear factor-kappa b in the regulation of *p53* activity and vice versa. Cell Mol Life Sci. 2020;77(22):4449-58. https://doi.org/10.1007/s00018-020-03524-9.
20. Chaithongyot S, Jantaree P, Sokolova O, Naumann M. Nf-κb in gastric cancer development and therapy. Biomedicines. 2021;9(8). https://doi.org/10.3390/biomedicines9080870.
21. Hu J, Cao J, Topatana W, Juengpanich S, Li S, Zhang B, et al. Targeting mutant *p53* for cancer therapy: Direct and indirect strategies. J Hematol Oncol. 2021;14(1):157. https://doi.org/10.1186/s13045-021-01169-0.
22. Yu DH, Xu ZY, Mo S, Yuan L, Cheng XD, Qin JJ. Targeting mdmx for cancer therapy: Rationale, strategies, and challenges. Front Oncol. 2020;10:1389. https://doi.org/10.3389/fonc.2020.01389.
23. Wani AK, Akhtar N, Mir TUG, Singh R, Jha PK, Mallik SK, et al. Targeting apoptotic pathway of cancer cells with phytochemicals and plant-based nanomaterials. Biomolecules. 2023;13(2). https://doi.org/10.3390/biom13020194.
24. Elmore S. Apoptosis: A review of programmed cell death. Toxicol Pathol. 2007;35(4):495-516. https://doi.org/10.1080/01926230701320337.
25. 25. Majdalawieh AF, Dalibalta S, Yousef SM. Effects of sesamin on health and disease: A review of preclinical and clinical studies. Nutrients. 2020;12(4):1042.
26. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: Mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330-8. https://doi.org/10.1038/nrc1074.
27. Ghoncheh m, mohammadian-hafshejani a, salehiniya h. The protective role of dietary lignans, including sesamin, in cancer prevention: Evidence from *in vivo* and *in vitro* studies. Nutr cancer. 2017;69(3):365–76.
28. Xu L, Peng L, Cao T, Zhang L, Li M, Liu Y. Apigenin inhibits the proliferation and aerobic glycolysis of endometrial cancer cells by regulating the pi3k/akt signaling pathway. European Journal of Gynaecological Oncology. 2024;45(5):125-31. https://doi.org/10.22514/ejgo.2024.100.
29. Ali Mohamod Wasaf H, Md S, Md M, Md. Shawon M, Mohammed Burhan U, Emon M, et al. Quercetin promises anticancer activity through pi3k-akt-mtor pathway: A literature review. Pharmacological Research - Natural Products. 2025;7:100206. https://doi.org/https://doi.org/10.1016/j.prenap.2025.100206.
30. Ghafouri-Fard S, Bahroudi Z, Shoorei H, Hussen BM, Talebi SF, Baig SG, et al. Disease-associated regulation of gene expression by resveratrol: Special focus on the pi3k/akt signaling pathway. Cancer Cell Int. 2022;22(1):298. https://doi.org/10.1186/s12935-022-02719-3.
31. Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, et al. Pi3k/akt/mtor signaling transduction pathway and targeted therapies in cancer. Mol Cancer. 2023;22(1):138. https://doi.org/10.1186/s12943-023-01827-6.