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Phenelzine-paclitaxel Co-treatment Promotes Non-apoptotic Cytotoxicity Linked to Increased BCL-2, iNOS, and COX-2 Levels in Hep-G2 Cells

Saeed Mahdianipur[1], Homa Davoodi[2], Hadi Esmaeili Gouvarchin Ghaleh[1], and Majid Mirzaei Nodoushan[1]

[1] *Applied Virology Research Center, Biomedicine Technologies Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[2] *Cancer Research Center, Golestan University of Medical Sciences, Gorgan, Iran*

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ABSTRACT

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death and frequently co-occurs with depression, with both conditions linked to heightened inflammatory activity. Emerging evidence suggests the serotonergic system may bridge neuroinflammation and cancer progression. Although serotonin-modulating agents such as phenelzine show anticancer potential, their efficacy and mechanistic effects in HCC, especially in combination with standard chemotherapeutics like paclitaxel, remain unexplored.

We examined the cytotoxic effects of phenelzine and paclitaxel co-treatment in human hepatocellular carcinoma (Hep-G2) cells, assessing cell viability alongside molecular markers of apoptosis and inflammation.

Viability assays demonstrated that co-treatment produced significantly greater cytotoxicity than either agent alone. However, molecular analyses revealed downregulation of classical apoptotic signaling, evidenced by a decreased *BAX*/*BCL-2* ratio driven primarily by *BCL-2* upregulation. Concurrently, phenelzine co-treatment markedly elevated pro-inflammatory markers, including nuclear factor-κB (*NF-κB*), cyclooxygenase-2 (*COX-2*), and inducible nitric oxide synthase (*iNOS*).

Given the established role of *NF-κB* in activating anti-apoptotic pathways, these findings suggest that phenelzine co-administration shifts the mechanism of paclitaxel-induced cell death away from classical apoptosis toward inflammation-mediated cytotoxicity. This work underscores the complex neuroimmune-oncological crosstalk underlying HCC and highlights the need for careful evaluation of the distinct inflammatory consequences of neuromodulatory drugs in oncologic settings.

Keywords: Apoptosis; Carcinoma; Hepatocellular; Inflammation; Paclitaxel; Phenelzine

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major global health burden and the third leading cause of cancer-related mortality worldwide.[1] Serotonin (5-

Corresponding Author: Hadi Esmaeili Gouvarchin Ghaleh, PhD; Applied Virology Research Center, Biomedicine Technologies Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran. Tel: (+98 914) 507 5438, Email: h.smaili1369@gmail.com

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hydroxytryptamine [5-HT]), a multifunctional monoamine neurotransmitter, has recently gained attention for its role in regulating physiological processes and may link neuropsychiatric disorders, neuroimmune inflammation, and tumor biology. Serotonin functions as a critical signaling molecule in the nervous, endocrine, and immune systems,[2,3] and cancer cells are known to exploit neurotransmitter-initiated signaling pathways such as the serotonergic system to fuel their proliferation and dissemination.[4]

Although serotonin-modulating agents were originally developed for the management of neurological and psychiatric conditions, accumulating evidence suggests that they may also have therapeutic potential in HCC.[5] Initially introduced in the 1950s, monoamine oxidase inhibitors (MAOIs, eg, phenelzine) remain efficacious in treating several forms of depression. Their clinical utility also extends to other neuropsychiatric indications, notably social phobia, panic disorder, and atypical depressive states.[6] Patients with depression and those with hepatocellular carcinoma both demonstrate upregulation of inflammatory pathways, processes that are crucial for HCC development and tumor cell proliferation.[7,8] Inflammation is considered a significant risk factor for cancer development.[9–11] Additionally, inflammation has been implicated in the pathogenesis of depression, particularly in vulnerable individuals, through the depletion of plasma tryptophan and the consequent reduction in central serotonin signaling,[12] a condition that approximately 1 out of 4 of total HCC patients experiences.[13] Paclitaxel, a microtubule-stabilizing agent, is widely used as a chemotherapy drug for various solid tumors, including HCC.[14,15]

Chemotherapy agents have been shown to increase cyclooxygenase 2 (*COX-2*) expression and promote inflammation.[16] Critically, phenelzine may compound this inflammation, as it has been shown to activate nuclear factor-κB (NF-κB) signaling and increase pro-inflammatory cytokines and oxidative stress.[17,18] While phenelzine demonstrates promising anticancer potential in prostate and breast cancer clinical trials,[19] direct evidence for its anticancer effects in hepatocellular carcinoma (HCC) is lacking. HCC presents a distinct context: evidence shows that MAO enzyme is downregulated in HCC, and reversible MAO inhibition has failed to reduce cell viability.[20] This study therefore examines phenelzine in combination with paclitaxel, a standard chemotherapeutic reference agent, widely used in solid tumors such as HCC,[14,21] in human hepatocellular carcinoma (Hep-G2) cells as a model for hepatocellular carcinoma, measuring inflammatory markers (*NF-κB*, inducible nitric oxide synthase [*iNOS*], *COX-2*) and apoptosis regulators (BAX, BCL-2).

MATERIALS AND METHODS

Cell Culture and Treatment

Hep-G2 cells (Iranian Biological Resource Center, Iran) were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Bioidea, Iran) supplemented with 5% (v/v) fetal bovine serum (FBS; Bioidea, Iran), 100 IU/mL penicillin, and 100 µg/mL streptomycin (Bioidea, Iran). Cells were cultured at 37°C in a humidified incubator containing 5% CO_2.

The cytotoxic effects of all experimental treatments were initially evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay across a range of concentrations. Treatment concentrations were selected based on preliminary optimization experiments (data not shown). Cells were seeded at a density of 1×10^6 cells/mL and divided into experimental groups. Control cells received the highest concentration of solvent used in the study (0.08% water). Treatment groups consisted of paclitaxel (1 µM or 3 µM; Sobhan Darou, Iran), phenelzine (1 µM; Sigma Chemical Company, St. Louis, MO, USA), and combinations of phenelzine with each paclitaxel concentration. All treatments were administered for 48 hours. Three independent biological replicates were employed to ensure statistical validity.

MTT Assay

A stock solution of MTT (5 mg/mL; 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was prepared, sterilized by filtration, and protected from light. The second column of each microplate was designated as the control group. Following treatment, the culture medium was removed and replaced with 100 µL of fresh medium and 20 µL of MTT solution per well. After incubation, the generated formazan crystals were dissolved in 100 µL of dimethyl sulfoxide (DMSO). Absorbance values were measured using an ELISA microplate reader at 570 nm with a reference wavelength of 630 nm.

Cell viability (%) = 100 × (a / b)

a=Optical Density (OD) of the test sample minus the blank's OD

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b=OD of the control minus the blank's OD

RNA Extraction and Real-Time Quantitative PCR (RT-qPCR)

Total RNA was extracted from approximately 1×10^6 cells using a commercial RNA extraction kit (Sinaclon, Iran) in accordance with the manufacturer's protocol. The quantity and purity of the isolated RNA were measured using a NanoDrop spectrophotometer (DeNovix DS-11, USA). The RNA concentration was then adjusted to 1000 ng/µL, and the samples were stored at −80°C for subsequent analyses. After DNase I treatment (Sinaclon, Iran), 1 µg of purified RNA was converted into complementary DNA (cDNA) using a cDNA synthesis kit from the same manufacturer, following the provided instructions. Gene expression was subsequently assessed on an Applied Biosystems StepOnePlus Real-Time PCR System (Thermo Fisher Scientific, USA). The transcriptional levels of *BAX*, *BCL2*, *NF-κB*, *COX2*, and *iNOS* were measured using Sina Green HS-qPCR Mix (Sinaclon, Iran), and specificity of the amplified products was verified through melting-curve analysis.

Primers were synthesized by Gene Fanavaran (Tehran, Iran). Primer sequences and corresponding references are listed in Supplementary Table 1.

The *COX2* primer pair was designed using AlleleID software (PREMIER Biosoft), whereas the remaining primers were adopted from previously published studies. *GAPDH* was used as the endogenous reference gene for normalization. Relative gene expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

Results from three independent experiments are expressed as median (interquartile range [IQR]). Data were normalized to solvent-treated controls. Normality was assessed using the Shapiro–Wilk test, and non-parametric analyses were applied due to non-normal distribution. Group comparisons were performed using the Kruskal–Wallis test followed by Dunn's post-hoc analysis. Drug interactions were evaluated using the Bliss independence model, with synergy defined as effects exceeding expected additive responses (p<0.05).

RESULTS

MTT Assay

Treatment of Hep-G2 cells with phenelzine at 0.5 µM and 1 µM concentrations, as well as paclitaxel at 1 µM, did not result in significant reduction of viability; however, the combination of 1 µM phenelzine and 1 µM paclitaxel reduced the Hep-G2 cell viability to 78% (p=0.002). Paclitaxel at 3 µM concentration reduced viability to 72% (p<0.001), Co-treatment of paclitaxel at 3 µM concentration with phenelzine at concentrations of 0.5 µM and 1 µM reduced the viability to 69% and 45%, respectively (p<0.001) (Figure 1). Notably, Bliss independence analysis revealed that the combination of 3 µM paclitaxel and 1 µM phenelzine was highly synergistic, as the observed reduction in viability significantly exceeded the predicted additive effect (p=0.002).

Modulation of Expression of Apoptosis-related Genes by Paclitaxel and Phenelzine

Treatment of Hep-G2 cells with 3 µM concentration of paclitaxel increased *BAX* expression by 2-fold (p=0.006). Similarly, co-treatment with phenelzine (1 µM) and paclitaxel at both concentrations (1 µM and 3 µM) significantly elevated *BAX* expression by 2-fold (p<0.001) relative to control. Concurrently, co-treatment with phenelzine significantly upregulated *BCL2* expression in cells treated with paclitaxel. In cells treated with 1 µM paclitaxel, phenelzine (1 µM) induced a 5-fold increase in *BCL2* expression relative to paclitaxel alone (p=0.002) and control (p<0.001). At 3 µM paclitaxel, phenelzine co-treatment increased *BCL2* expression to 10-fold above paclitaxel-only and control groups (p<0.001). The *BAX*/*BCL2* expression ratio was increased 2-fold in cells treated with 3 µM paclitaxel compared with the control group (p=0.019), we observed a significant reduction in the *BAX*/*BCL2* ratio with phenelzine co-treatment, by 3-fold (p=0.003) at 1 µM paclitaxel. This reduction was 7-fold (p<0.001) at 3 µM paclitaxel relative to the respective paclitaxel-only groups. Additionally, there was a significant 4-fold (p=0.008) decrease in *BAX*/*BCL2* expression ratio in cells treated with 3 µM concentration of paclitaxel and 1 µM phenelzine compared with the control group (Figure 2).

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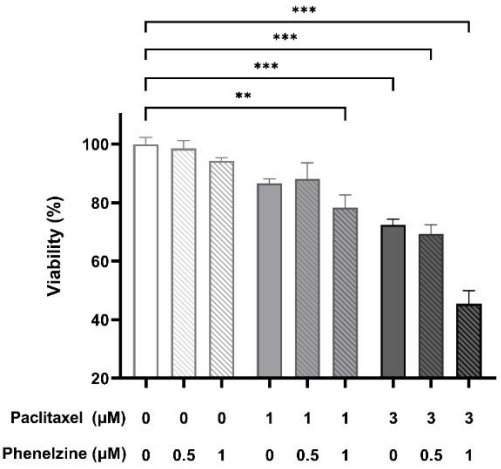

Figure 1. Viability of Hep-G2 cells. Data are presented as median values with interquartile ranges (IQR). Bars represent the median cell viability of each treatment group after 48 hours of exposure, and error bars indicate the IQR. Treatment groups included phenelzine, two concentrations of paclitaxel, their combinations, and the control group. The concentrations administered to each group are indicated below the x-axis. A dash ("−") denotes the absence of the corresponding treatment. Statistical significance is indicated as follows: *p<0.05, **p<0.01, and ***p<0.001.

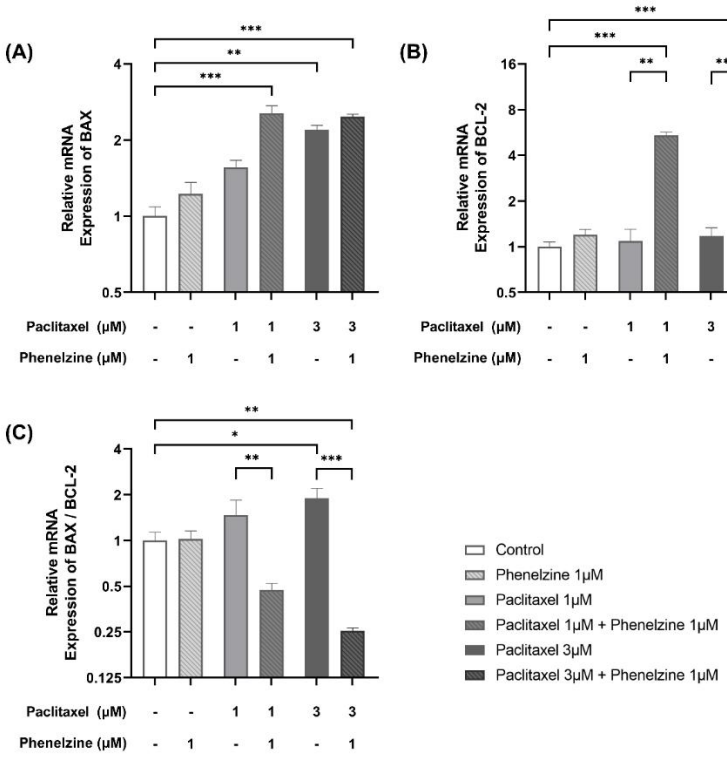

Figure 2. Relative mRNA expression of apoptosis-related genes in Hep-G2 cells. Data are presented as median values with interquartile ranges (IQR). Bars represent the median relative mRNA expression level for each treatment group, and error bars indicate the IQR. Treatment groups included phenelzine, two concentrations of paclitaxel, their combinations, and the control group. The concentrations administered to each group are indicated below the x-axis. A dash ("−") denotes the absence of the corresponding treatment. A. Relative mRNA expression of *BAX*. B. Relative mRNA expression of *BCL2*. C. Relative *BAX*/*BCL2* expression ratio. Statistical significance is indicated as follows: *p<0.05, **p<0.01, and ***p<0.001.

Modulation of Expression of Inflammation-Related Genes by Paclitaxel and Phenelzine

In Hep-G2 cells, co-treatment with 1 µM phenelzine and 1 µM paclitaxel significantly increased the relative mRNA expression of *NF-κB*, *COX2*, and *iNOS* by approximately 3-fold (p=0.003), 3.5-fold (p=0.005), and 2-fold (p=0.001), respectively, compared to paclitaxel alone. Similarly, in cells treated with 3 µM paclitaxel, phenelzine treatment elevated gene expression of *NF-κB* by 5-fold (p<0.001) and both *COX2* and *iNOS* by 4-fold (p=0.004, p=0.006, respectively) relative to paclitaxel alone. Compared with control levels, phenelzine (1 µM) significantly upregulated *COX2* expression by 4.5-fold (p<0.001). Additionally, the co-administration of phenelzine with 1 µM paclitaxel resulted in a 3-fold increase in *NF-κB* (p=0.037), a 5-fold increase in *COX2* (p=0.001), and a 2-fold increase in *iNOS* (p=0.001). Moreover, co-treatment with phenelzine and 3 µM paclitaxel increased *NF-κB* expression by 4-fold (p=0.009), *COX2* by 7-fold (p<0.001), and *iNOS* by 6-fold (p<0.001) relative to the control group (Figure 3).

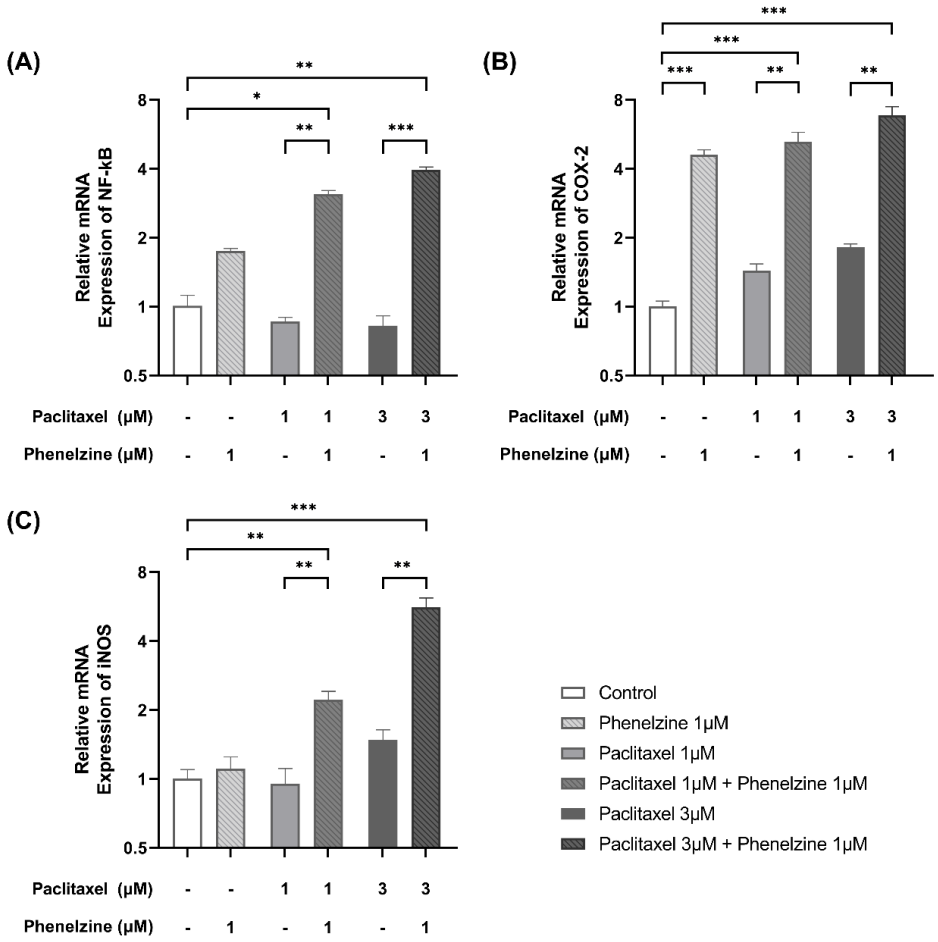

Figure 3. Relative mRNA expression of inflammation-related genes in Hep-G2 cells. Data are presented as median values with interquartile ranges (IQR). Bars represent the median relative mRNA expression level for each treatment group, and error bars indicate the IQR. Treatment groups included phenelzine, two concentrations of paclitaxel, their combinations, and the control group. The concentrations administered to each group are indicated below the x-axis. A dash ("–") denotes the absence of the corresponding treatment. A. Relative mRNA expression of *NF-κB*. B. Relative mRNA expression of *COX2*. C. Relative mRNA expression of *iNOS*. Statistical significance is indicated as follows: **p*<0.05, ***p*<0.01, and ****p*<0.001.

DISCUSSION

Considering the shared inflammatory pathways between HCC and depression, this study aimed to evaluate the combined effects of the MAOI phenelzine and paclitaxel on Hep-G2 cells. We observed a reduction in cell viability following combined phenelzine and paclitaxel treatment in the MTT assay. Despite significant cytotoxic effects, our data revealed a decreased *BAX*/*BCL2* ratio, which was mostly driven by BCL-2 without proportional BAX changes in groups treated with both phenelzine and paclitaxel. Concurrently, phenelzine co-treatment markedly elevated the expression of pro-inflammatory markers *NF-κB*, *COX-2*, and *iNOS*, with a more pronounced increase observed at the 3 μM paclitaxel concentration compared with the 1 μM concentration, suggesting activation of inflammatory pathways alongside the observed anti-apoptotic shift. These findings suggest a shift from classical apoptotic to inflammation-driven cytotoxicity.

Evidence supports that *BCL-2* upregulation can occur through NF-κB-mediated inflammatory signaling rather than classical apoptotic regulation.[27] While *NF-κB* induces survival genes like BCL-2, its chronic activation drives sustained inflammation that can culminate in cell death through non-apoptotic pathways, notably by upregulation of *iNOS* and *COX2* genes and nitrosative/oxidative stress that overwhelms survival capacity. This mechanistic interplay provides an explanation for the seemingly paradoxical coexistence of *BCL-2* upregulation and reduced cell viability observed in our combination treatment groups. Sustained *NF-κB* activation in cancer cells drives malignant progression through the coordinate upregulation of target genes that enhance proliferation, survival, genomic instability, and metastatic capacity. Specifically, *NF-κB* promotes a number of apoptosis inhibitors, such as BCL-2, conferring apoptosis resistance and chemoresistance. Simultaneously, *NF-κB*-driven expression of *iNOS* contributes to genomic destabilization through the generation of reactive nitrogen intermediates (RNIs), in concert with COX-2 induction.[27]

This pattern is consistent with reports that *COX-2* upregulation decreases cancer cell response to chemotherapy, reducing apoptotic susceptibility in hepatocellular and colon cancer.[28–30] However, elevated *COX-2* simultaneously drives non-apoptotic death pathways, through inflammation, oxidative stress, and membrane damage.[31–33] Similarly, increased *iNOS* expression is consistently associated with reduced cell viability and impaired mitochondrial dehydrogenase activity, as measured by MTT assays.[34,35] This relationship occurs across multiple cell types, including synovial cells, hepatocytes, and insulin-producing cells, with *iNOS*-derived NO implicated in mitochondrial dysfunction through oxidative stress mechanisms.[36–38]

Our results demonstrate that phenelzine significantly elevates *COX-2* expression, while paclitaxel alone produces a more modest, non-significant increase. The combination of both paclitaxel and phenelzine results in *COX-2* expression that surpasses the effect of either drug alone. Notably, paclitaxel alone did not increase *NF-κB* expression. However, the combination treatment markedly enhanced *NF-κB* levels. Although *NF-κB* classically induces COX-2 expression, tumor-derived PGE_2 can promote nuclear p50 NF-κB accumulation in monocytic myeloid-derived suppressor cells (M-MDSCs) via prostaglandin E_2 (PGE_2) receptor signaling.[39] This pattern can also suggest that the observed *NF-κB* upregulation may be a consequence of sufficiently high levels of COX-2-derived prostaglandins (PGE_2) triggering NF-κB signaling in this setting. This aligns with evidence that chemotherapy drugs such as paclitaxel can acutely upregulate COX-2 expression and prostaglandin E_2 (PGE_2) production in cancer cells.[16] Interestingly, this upregulation of COX-2 was still pronounced in the absence of NF-κB signaling.[16]

This study has several limitations, as follows. The Hep-G2 model cannot capture tumor microenvironment complexities, particularly immune-nervous-cancer cell interactions; the absence of immune cells prevents determining whether elevated inflammatory markers trigger antitumor immunity or promote malignancy; and unmeasured serotonin levels leave it unclear whether phenelzine's effects stem from MAO inhibition or off-target mechanisms.

Cell viability was assessed solely by the MTT assay, which may be susceptible to phenelzine-related mitochondrial metabolic interference; *NF-κB* was measured at the expression level only, without phosphorylation or nuclear translocation data; reactive oxygen species and endoplasmic reticulum stress markers were not evaluated; and further time-course measurements to fully characterize the temporal dynamics of the observed inflammatory responses could

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not be obtained within the scope of the present experimental framework.

This study provides the first characterization of phenelzine-paclitaxel co-treatment in HCC, identifying a mechanistic shift from classical apoptosis to inflammation-mediated cytotoxicity as a distinct neuroimmune-oncological interaction. In light of the established role of NF-κB in activating anti-apoptotic pathways, including BCL-2 upregulation, our findings raise the possibility that phenelzine co-administration could shift the cell death mechanism from classical apoptosis to inflammation-mediated cytotoxicity. While inflammation-mediated cell death may enhance cytotoxicity in certain contexts, sustained upregulation of *COX-2* and *NF-κB* could paradoxically promote tumor survival, angiogenesis, and metastasis. Given the potential impact of inflammatory signaling on cancer prognosis, rigorous patient stratification is essential when considering neuromodulatory agents in oncological settings. Notably, psychotropic medications commonly prescribed to cancer patients for comorbid depression or anxiety may inadvertently modulate tumor biology through inflammatory pathways, warranting systematic evaluation of such pharmacological interactions in the oncology context.

STATEMENT OF ETHICS

All experimental procedures involving animals were conducted in accordance with the guidelines of the Research Ethics Committees of Baqiyatallah University of Medical Sciences (Approval Code: IR.BMSU.BLC.1404.003).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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