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INVESTIGATION OF THE CYTOTOXIC AND GENOTOXIC EFFECTS OF PAROXETINE ON HUMAN OVARIAN, PROSTATE AND COLON CANCER CELL LINES

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Abstract

Cancer is a major public health problem due to uncontrolled cell proliferation, invasion of surrounding tissues, and its high prevalence and mortality rates. Despite current treatment strategies, the poor prognosis in many cancer types necessitates the exploration of new pharmacological approaches. In this study, we aimed to evaluate the cytotoxic and genotoxic effects of paroxetine, a potent selective serotonin reuptake inhibitor (SSRI), in human ovarian (A2780), prostate (LNCaP), and colon (Caco-2) cancer cell lines in vitro. A2780, LNCaP, and Caco-2 cells were cultured in appropriate media and treated for 24 hours with paroxetine at concentrations of 1, 10, 100, and 1000 µM. Cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-diphenyltetrazolium bromide (MTT) assay, and the inhibitory concentration was calculated using GraphPad Prism 8 software. DNA damage was assessed using the comet assay. Statistical analyses were performed using IBM SPSS Statistics 24.0 (Windows); $p < 0.05$ was considered statistically significant. Paroxetine significantly reduced cell viability in A2780 cells at all concentrations except 1 µM, and in LNCaP and Caco-2 cells at 100 and 1000 µM ($p < 0.05$). Comet assay results demonstrated that paroxetine significantly increased tail length, tail intensity, and olive tail intensity, and decreased head length and head intensity in all cell lines ($p < 0.05$). Our findings indicate that paroxetine exerts both cytotoxic and genotoxic effects on various cancer cell lines in vitro. These results suggest potential roles of SSRIs in cancer biology beyond their established psychiatric applications.

Keywords: Cancer, Cytotoxicity, Genotoxicity, Paroxetine, Selective serotonin reuptake inhibitors.

INTRODUCTION

Cancer encompasses a diverse group of diseases characterized by uncontrolled cell growth, invasion of adjacent tissues, and the ability to metastasize to distant organs, all of which result from disturbances in the normal regulatory mechanisms governing cellular proliferation and division (Golias, Charalabopoulos & Charalabopoulos, 2004; Hanahan & Weinberg, 2011). Because of its widespread occurrence and high mortality, cancer is regarded as a major public health concern (World Health Organization, 2020). Rather than being one uniform disease, cancer comprises a diverse collection of malignancies, each with distinct etiological factors, biological features, and clinical outcomes (Hanahan & Weinberg, 2011). Among these malignancies, ovarian, prostate, and colorectal cancers stand out in terms of morbidity and mortality worldwide (Ferlay et al., 2021; Sung et al., 2021). Genetic predispositions, environmental exposures, hormonal factors, and lifestyle factors play varying roles in the pathogenesis of each (Siegel, Miller, Wagle & Jemal, 2023). Furthermore, the difficulties in early diagnosis of these cancers and the variability in response to treatment necessitate an interdisciplinary approach to managing these diseases (Torre, Siegel, Ward & Jemal, 2016). Therefore, a detailed examination of epidemiological data, risk factors, and current treatment approaches for ovarian, prostate, and colorectal cancers is important for reducing the disease burden.

Selective Serotonin Reuptake Inhibitors (SSRIs) are therapeutic agents that act by blocking the serotonin transporter in presynaptic neurons, thereby elevating serotonin concentrations within the synaptic cleft. The primary clinical use of these agents is in the treatment of depression and various anxiety disorders (Cipriani et al., 2018; Stahl, 1998). In recent years, the potential biological effects of SSRIs beyond psychiatric disorders have also been investigated. It is known that SSRIs, through their inhibition of the serotonin transporter, affect not only the central nervous system but also peripheral serotonin levels (Owens & Nemeroff, 1994). Serotonin has been identified as a neuromodulator that plays a role in fundamental processes of cancer biology, such as cell proliferation, apoptosis, angiogenesis, and immune response (Lesurtel et al., 2006). Preclinical studies have shown that some SSRIs can inhibit tumor cell growth, induce apoptosis, and reduce metastatic potential in vitro and in vivo models (Lee, Kim, Jang, Kim, & Myung, 2010; Stepulak et al., 2008). Additionally, SSRIs have been shown to reduce proinflammatory cytokine release (Takenaka et al., 2022), inhibit DNA synthesis in Burkitt lymphoma cells, cause cell cycle arrest in the G0/G1 phase, and induce apoptosis (Serafeim et al., 2003). Paroxetine is a potent SSRI characterized by high-affinity binding to the serotonin transporter, conferring greater selectivity (Cool, Leibach, & Ganapathy, 1990). Studies have reported that paroxetine exhibits anti-inflammatory activity by modulating the inflammatory response (Durairaj, Steury & Parameswaran, 2015; Kabiri et al., 2020). Few studies have investigated whether paroxetine has anticancer activity. A study by Cho and colleagues showed that paroxetine reduces cell viability by inducing apoptosis in human breast cancer MCF-7 cells (Cho et al., 2019). Another study indicated that it reduced cell proliferation by increasing apoptotic activity in human colorectal cancer HCT116 and HT-29 cells (Jang, Jung, Vo & Jeong, 2019).

Existing studies are limited yet promising with respect to the antitumor effect of paroxetine; however, they contain gaps that require further investigation. The present work aimed to examine the effects of paroxetine on cell viability using three different human cancer cell lines: A2780 (ovarian), LNCaP (prostate) and Caco-2 (colon).

MATERIAL AND METHOD

Cell Culture

This study was performed in the laboratories of the Physiology Department, Faculty of Medicine, Inonu University, using A2780, LNCaP, and Caco-2 human cancer cell lines. The cells were inoculated into 75-cm^2 culture flasks and maintained under conditions appropriate for each cell line. A2780 and LNCaP cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 5 mL of non-essential amino acids. Caco-2 cells were grown in Dulbecco's Modified Eagle Medium F-12 (DMEM/F-12) supplemented with 10% FBS, 100 U/mL penicillin, and 1 mL of insulin. The media were refreshed biweekly, and all cultures were incubated at 37 °C in a humidified incubator with 5% CO_2.

MTT Assay

The cytotoxic effect of paroxetine on the viability of A2780, LNCaP, and Caco-2 cells over 24 hours was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The MTT assay is a widely employed enzymatic method for determining cytotoxicity. In this assay, MTT is taken up by metabolically active cells and reduced to an insoluble blue-violet formazan by mitochondrial succinate dehydrogenase. As this conversion occurs exclusively in the mitochondria of viable cells, it serves as a reliable indicator of cell survival. The intensity of the resulting color is quantified spectrophotometrically, and the absorbance values are directly correlated with the number of viable cells (Denizot & Lang, 1986). All experiments were conducted with 10 independent replicates, with 8 technical replicates (n = 8) performed for each experimental group within each replicate (Beytur et al., 2022; Küçükbay, Mumcu, Tekin, & Sandal, 2019).

Seeding and Incubation of Cells in Microplates

Confluent cells were detached from flasks using trypsin-ethylenediaminetetraacetic acid and stained with trypan blue (0.4%). Cells with a viability rate above 90% were counted. The number of cells to be seeded was calculated as 10^3 cells per well in a 96-well microplate. The cells seeded into the microplates were incubated under culture conditions for 24 hours (Koran et al., 2023).

Treatment of Cells with Paroxetine

At the end of the 24-hour incubation period, the media adhering to the bottoms of the wells were removed, leaving only the cells. Paroxetine was prepared at concentrations of 1, 10, 100, and 1000 µM (Cho et al., 2019) in dimethyl sulfoxide (DMSO), and 100 µL of each solution was added to each well to treat the cells. Additionally, control groups contained only cell medium, whereas solvent groups contained cell medium with 1% DMSO. The additions were performed in eight replicates, and after all additions were completed, the cells were again incubated for 24 hours (Karataş, Tekin, Alici, & Sandal, 2019).

Determination of Cell Viability

An MTT solution was freshly prepared at 0.5 mg/mL in sterile phosphate buffer. After aspiration of the culture medium and removal of paroxetine, 50 µL of the resulting solution was added to each well of the microplate, and the cells were incubated for three hours. Subsequently, the MTT reagent was removed, and 100 µL of DMSO was added to solubilize the resulting formazan crystals. Optical density was measured at 550 nm using a Thermo MultiskanGo ELISA microplate reader (USA). Average absorbance values were computed using wells containing only culture media as the control, which is indicative of 100% cell viability. Cell viability after treatment with DMSO (solvent control) and paroxetine was expressed as a percentage relative to the control group (Koran et al., 2017).

Calculation of Inhibition Concentration 50 Values

The inhibitory concentration 50 (IC50), also known as the half-maximal inhibitory concentration, denotes the concentration of a compound that produces 50% inhibition of a specific biological reaction (Bag & Ghorai, 2016). In our study, the IC50 represented the inhibitory concentration of paroxetine that reduced cell viability by 50%. Based on the MTT assay results obtained, the IC50 values for paroxetine were calculated for each cell line. This calculation was performed using the GraphPad 8 program, available at the Molecular Research Laboratory, Department of Physiology, Faculty of Medicine, Inonu University.

Comet Assay

The comet assay is widely used to detect DNA damage. In this study, the Comet Assay was performed with minor modifications to the method described by Devlin et al (Devlin et al., 2008).

Pre-Electrophoresis Steps

Initially, a 0.65% high-melting agarose (HMA) solution was prepared in phosphate-buffered saline and applied to pre-chilled slides, which were then dried in the dark for 24 hours. For each cell line, the IC_{50} of paroxetine was determined, and the cells were exposed to this concentration for 1 hour. Following incubation, paroxetine was removed, and the cells were then encapsulated in low-melting agarose and deposited onto HMA-precoated slides. Coverslips were positioned on the slides and then stored at +4°C in the dark for 15–20 minutes to allow the agarose to solidify. After the agarose solidified, coverslips were removed, and the slides were submerged in cold lysis solution and incubated at 4°C in the dark for one hour. The lysis buffer was freshly prepared by adding 1% Triton X-100 and 1% DMSO to the stock solution (Oz, Sekerci, Yuksel, & Tekin, 2023; Ozkaya, Keskin, Tekin, Tekin, & Beytur, 2023).

Electrophoresis and Neutralization

Following the lysis step, the slides were transferred into a horizontal electrophoresis unit (Bio-Rad, USA) filled with pre-chilled neutral electrophoresis buffer. Electrophoresis was carried out under constant conditions of 25 V and 300 mA for 20 minutes, during which negatively charged DNA fragments migrated toward the positive electrode. At the end of electrophoresis, the slides were neutralized by washing three times with 0.4 M Tris buffer (pH 7.5) at 4°C for 5 minutes each, effectively halting further DNA migration (Oz et al., 2023; Ozkaya et al., 2023).

Imaging and Damage Scoring

50 µL of ethidium bromide was used to stain the slides, which were then incubated in the dark for 20–30 minutes at +4°C. Fluorescence images were captured using a Leica microscope, and DNA damage scoring was performed with the Comet IV software. For each slide, at least 100 cells were randomly selected and evaluated to determine the effects on Tail Length (TL), Tail Intensity (TI), Olive Tail Intensity (OTI), Head Length (HL), and Head Intensity (HI) (Çalışkan et al., 2023). Variations in these parameters were used to assess both the occurrence and the extent of DNA damage. All analyses were independently repeated 10 times on separate days (Oz et al., 2023; Ozkaya et al., 2023). The experimental flow diagram is shown in Figure 1.

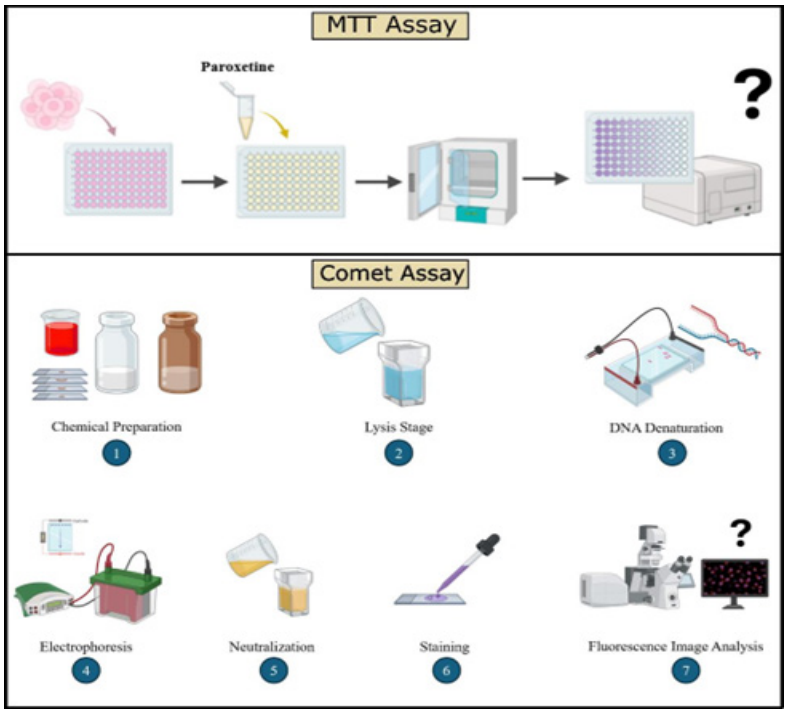

Figure 1. Summary of the experimental process.

Statistical Analysis of Data

Statistical analyses were conducted using IBM SPSS Statistics version 24.0 (Windows). Normality was assessed using the Shapiro-Wilk test. To compare quantitative variables among groups, the Kruskal–Wallis H test was used. When notable differences were observed, post hoc analyses were performed using paired Mann–Whitney U tests with Bonferroni correction. A p-value below 0.05 was considered statistically significant. The IC50 and log IC50 values for paroxetine were calculated using GraphPad Prism 8 software, based on MTT results obtained from the experiments. The figures were created using BioRender (biorender.com). The graphs were created using SigmaPlot 12 and GraphPad 8 software.

RESULT

Effect of Paroxetine on Cell Viability

The effect of paroxetine concentrations on the viability of A2780, LNCaP, and Caco-2 cells is shown in Figure 2. At all application doses except for a 1 µM concentration of with paroxetine, the viability of A2780 cells decreased significantly (Figure 2A, $p<0.05$). The viability of LNCaP (Figure 2B) and Caco-2 (Figure 2C) cells decreased significantly at paroxetine concentrations of 100 and 1000 µM ($p < 0.05$). The IC50 (µM) and LogIC50 values, calculated after incubating all cells with paroxetine for 24 hours, are shown in Table 1.

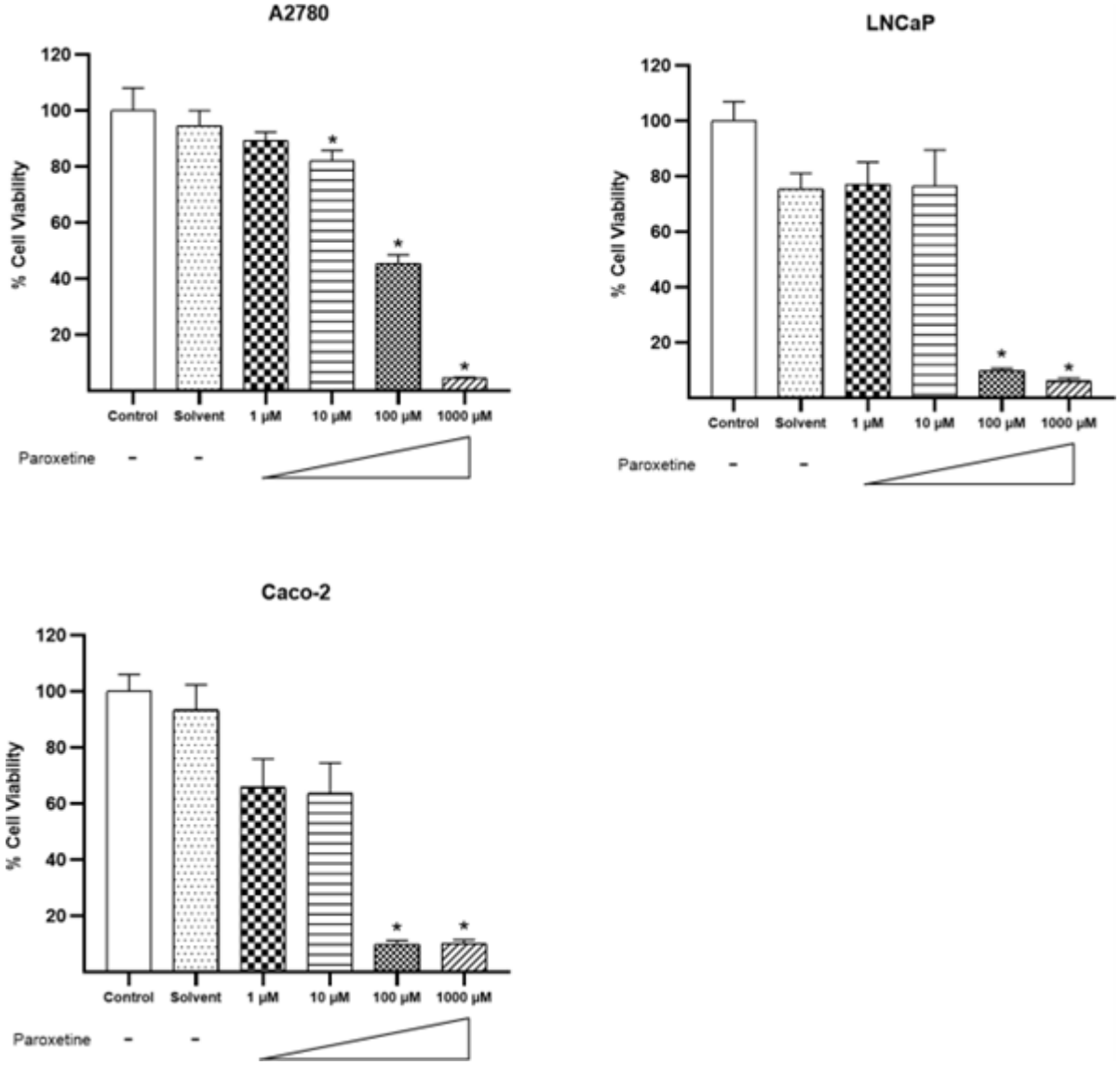

Figure 2. Effect of paroxetine concentrations on A2780, LNCaP, and Caco-2 cell viability: (A) Effect of paroxetine on A2780 cell viability; (B) Effect of paroxetine on LNCaP cell viability; (C) Effect of paroxetine on Caco-2 cell viability. Experiments were conducted in 10 independent replicates, each including eight technical replicates (n = 8) per group; bars represent mean ± SD (*p < 0.05 vs. solvent).

Table 1. IC_{50} values and $LogIC_{50}$ values of paroxetine for A2780, LNCaP and Caco-2 cells.

Cell Lines	IC_{50} Values of Paroxetin (µM)	$LogIC_{50}$ Values of Paroxetine
A2780	138.9	2.143
LNCaP	46.59	1.668
Caco-2	11.53	1.062

Genotoxic Effect of Paroxetine

Figure 3 shows the genotoxic effect of paroxetine on A2780, LNCaP, and Caco-2 cells. Figure 4 shows the effect of paroxetine administration on TL, TI, OTI, HL, and HI in each cell line. Paroxetine administration increased TL, TI, and OTI levels ($p < 0.05$) and decreased HL and HI levels ($p < 0.05$) in all cells; the concentrations used in the Comet assay corresponded to the IC_{50} values determined for each cell line.

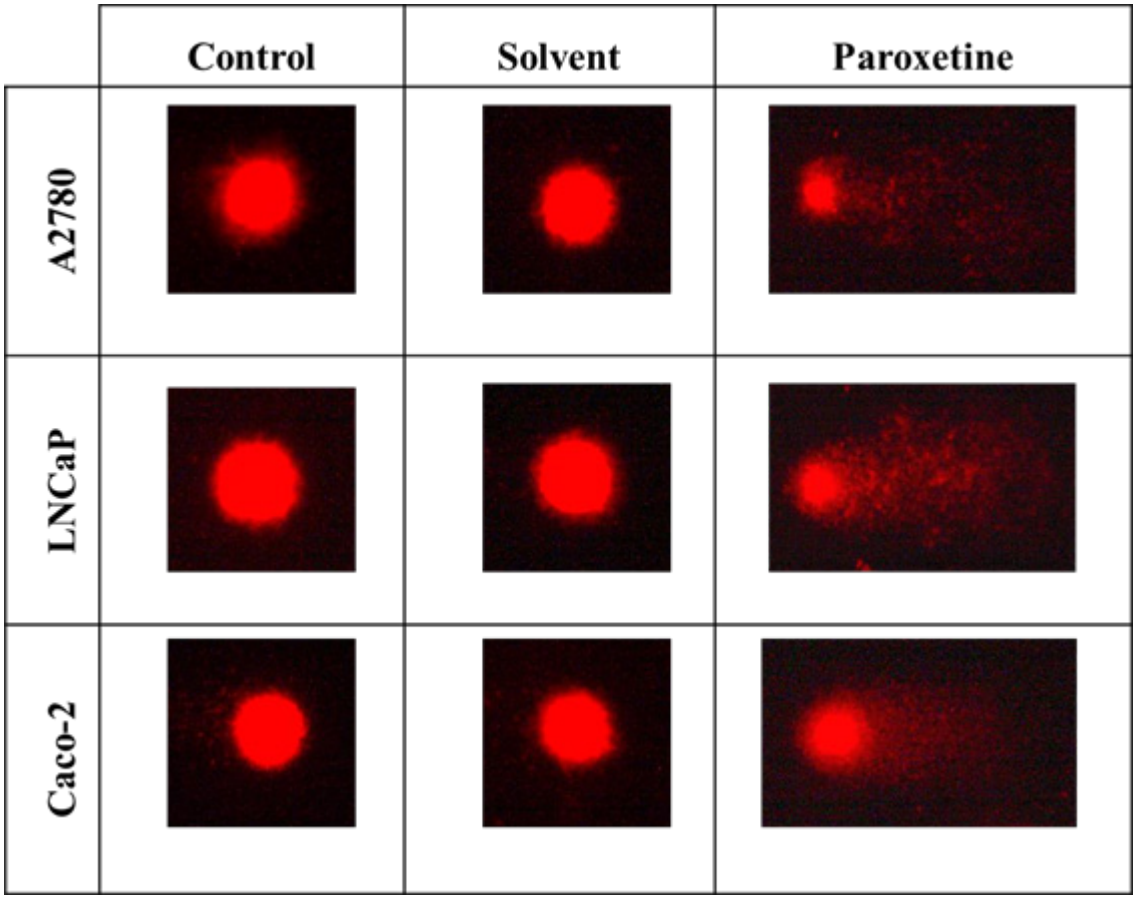

Figure 3. Representative Comet assay images obtained by fluorescence microscopy showing DNA damage in A2780, LNCaP, and Caco-2 cells following paroxetine treatment at IC_{50} values. At least 100 cells were evaluated for each slide.

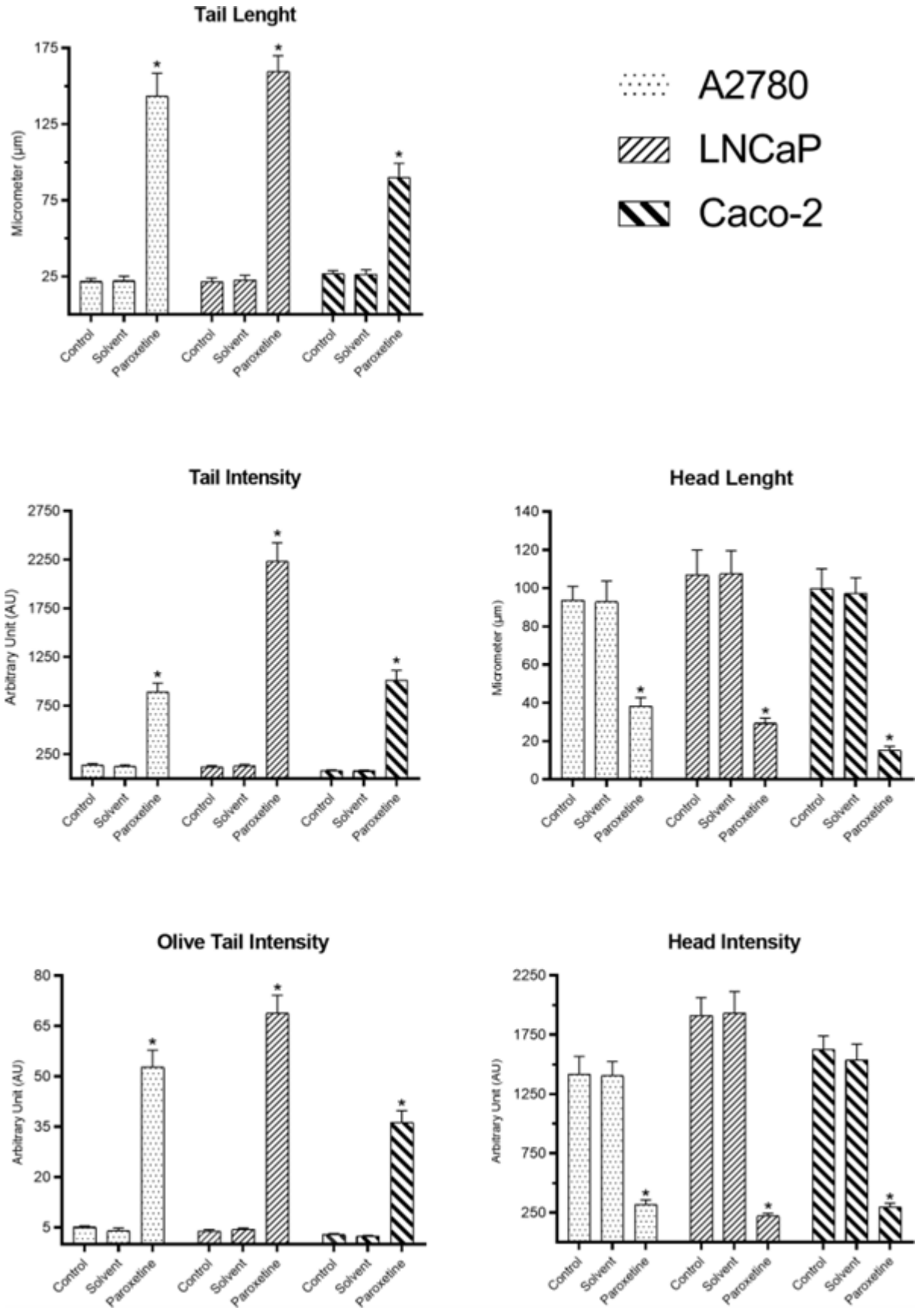

Figure 4. Effect of paroxetine (IC_{50} concentrations) on Comet assay parameters on A2780, LNCaP and Caco-2 cells. Experiments were conducted in 10 independent replicates. Bars represent mean ± SD (*$p < 0.05$ vs. solvent).

DISCUSSION

Uncontrolled proliferation of abnormal cells is the hallmark of cancer. Given its increasing prevalence and high mortality, it remains a significant public health concern (Nwosu, 2024; Hassanpour & Dehghani, 2017). Despite improvements in existing diagnostic tools and treatment options, the development of novel and more efficient strategies remains essential. The literature reports that some pharmacological agents known to have anti-inflammatory activity may exhibit anticancer effects. Indeed, various studies have demonstrated that compounds belonging to the SSRI group reduce proinflammatory cytokine levels in different cell types, such as human epidermal keratinocytes, macrophages, and lymphocytes (Takenaka et al., 2022; Tóth et al., 2024). Paroxetine, a potent selective serotonin reuptake inhibitor, has been shown to affect inflammatory response pathways (Durairaj et al., 2015; Kabiri et al., 2020). In light of this information, we hypothesized that paroxetine might exert a cytotoxic effect on certain cell lines.

Cho et al. (2019) reported that paroxetine exhibited cytotoxic effects on breast cancer cell lines. Jang et al. also reported that administering paroxetine to human colorectal cancer cell lines reduced cell viability (Jang et al., 2019). Research indicated that paroxetine reduces the viability of non-small-cell lung cancer cells (Wang et al., 2020). Motafeghi and his team investigated the effects of paroxetine, an SSRI, both in combination with and separately from another SSRI, amitriptyline, on HT29 and A549 cancer cell lines. The study showed that both agents inhibited cell growth when administered alone, and their combined administration enhanced this inhibitory effect (Motafeghi, Shahsavari, Mortazavi, & Shokrzadeh, 2023).

The study revealed that exposure to paroxetine reduced survival across all examined cancer cell lines. In A2780, all doses except the lowest concentration reduced viability to a statistically significant degree. In LNCaP and Caco-2 cell lines, this reduction occurred at the two highest tested concentrations of paroxetine. Our findings are consistent with studies reporting cytotoxic effects of paroxetine in certain cancer cell lines. Furthermore, paroxetine treatment increased TL, TI, and OTI levels and decreased HL and HI levels in A2780, LNCaP, and Caco-2 cells. The DNA damage observed with the comet assay in our study suggests that paroxetine can disrupt cellular DNA integrity. These data suggest that paroxetine may exert both cytotoxic and genotoxic effects on various cancer cell lines in vitro. However, these findings cannot be directly linked to therapeutic or anticancer mechanisms. The cytotoxic and genotoxic effects observed in this study are consistent with those reported in the literature previous findings such as Cho et al.'s study in breast cancer cells, Jang et al.'s study in colorectal cancer, and Wang et al.'s study in non-small cell lung cancer. Paroxetine's similar effects across different cell types suggest that this drug may have biological activity in certain cancer cells, but the validity of its repositioning as an anticancer agent has not yet been confirmed. However, our study is limited to in vitro conditions; more comprehensive research using in vivo experimental models and investigating mechanistic aspects is needed to determine whether the data obtained are clinically meaningful. In particular, elucidating the cellular signaling pathways through which paroxetine exerts cytotoxic and genotoxic effects could guide drug repurposing strategies for this compound. To use the potential anticancer effects of paroxetine in clinical applications, its dose-dependent toxicity profile, selectivity for healthy cells, and potential synergistic or antagonistic interactions with other chemotherapeutic agents need to be investigated. The potential roles of commonly used antidepressants, such as paroxetine, in cancer biology are important for reducing treatment costs and for providing a new perspective on existing pharmacological options. Future comprehensive studies of molecular mechanisms and preclinical investigations will clarify the possible biological effects of paroxetine.

CONCLUSION

When considered alongside previous studies, the findings of this study indicate that paroxetine may exhibit cytotoxic effects on some cancer cells in vitro. However, these data are not sufficient to draw direct conclusions about the drug's chemotherapeutic potential. Preclinical data should be supported by in vivo studies to more clearly demonstrate the potential biological effects. Investigating the potential synergistic effects of paroxetine with other agents could inform future chemotherapeutic strategies.

Ethics Committee Approval

This study was conducted on established human cancer cell lines and did not involve human participants or animals; therefore, ethics committee approval was not required.

Informed Consent: This study did not involve human participants; therefore, informed consent was not required

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that they received no financial support for this research.

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