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The Effects of Ferulic Acid on Proliferation and Apoptosis in Ishikawa Cells

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ABSTRACT

Purpose: This study investigated the impact of applying ferulic acid on cellular responses linked to cell proliferation and apoptosis in Ishikawa endometrial cancer cells.

Methods: The effects of ferulic acid on the viability of Ishikawa cells were evaluated using an MTT assay. The application dose was determined based on preliminary experiments conducted over a wide dose range. Cellular morphological changes were examined using an inverted microscope. Cell proliferation was assessed using Ki-67 immunocytochemical staining, while the apoptotic response was analysed through Bax and Bcl-2 immunoreactivity and the Bax/Bcl-2 ratio.

Results: MTT analysis revealed that ferulic acid exhibited dose-dependent effects on cell viability, with a dose of 800 µM most effectively reducing viability to approximately 50%. Morphologically, ferulic acid -treated cells exhibited decreased cell density and disrupted monolayer integrity. Immunocytochemical analysis revealed decreased Ki-67 immunoreactivity and increased Bax and decreased Bcl-2 immunoreactivity, resulting in a significant increase in the Bax/Bcl-2 ratio.

Conclusion: These findings demonstrate that ferulic acid exhibits cytotoxic effects in Ishikawa endometrial cancer cells by suppressing proliferative activity and increasing apoptosis. These characteristics suggest that ferulic acid could be a candidate for supportive combination approaches to current endometrial cancer treatments. However, further experimental and clinical studies are required to evaluate this potential.

Keywords: Apoptosis, Cell proliferation, Ferulic acid, Ishikawa cells, Ki-67, Bax, Bcl-2

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Introduction

Uterine cancer is the fourth most common and sixth deadliest cancer in women, after breast, lung and colorectal cancers. It is also the second most common malignancy in individuals over 50 with a uterus (1). Data show that early-stage endometrial cancer (EC) accounts for around 67% of EC cases, with an 81% five-year survival rate. By contrast, the five-year survival rate drops to 16% in metastatic cases, and the risk of recurrence increases significantly (2). The high proportion of endometrial cancers diagnosed at an early stage highlights the importance of understanding the disease's biological characteristics and cellular behaviours at this stage. To this end, in vitro models representing early-stage, hormone-dependent endometrial cancer are commonly employed in experimental studies. One such model is the Ishikawa cell line, which is considered suitable for evaluating cell proliferation, hormone responses, apoptotic mechanisms and cellular responses to treatment (3). In particular, its high proliferative activity and ability to monitor cell cycle-related markers make this cell line valuable for investigating the effects of antiproliferative and proapoptotic agents. Because of these characteristics, Ishikawa cells are widely used in experimental and pharmacological studies of endometrial cancer.

Ferulic acid (FA) is a naturally occurring phenolic compound commonly found in plants. It is known for its strong antioxidant, anti-inflammatory and cytoprotective properties. FA is a phenolic phytochemical found in plant seeds and leaves, both in its free form and covalently bound to polysaccharides, glycoproteins, polyamines, lignin and hydroxy fatty acids in the cell wall (4). FA is a widely used compound, primarily in the cosmetic, pharmaceutical, and food industries, and it exhibits a protective effect against oxidative stress-related cellular damage thanks to its strong antioxidant capacity, which is due to core and side-chain conjugation (5). Due to these properties, FA has been reported to contribute to maintaining cellular integrity in normal cells and to play a protective role against oxidative damage. At low concentrations, FA's antioxidant and cell-protective properties are prominent; however, at higher doses, it exhibits effects associated with suppression of the cell cycle, reduction of proliferative activity, and activation of apoptotic pathways (6–8). Despite its strong antioxidant and cytoprotective properties, ferulic acid has been reported to exhibit different biological effects in cancer cells depending on the dose and cellular context (9, 10). Notably, FA has different effects in hormone-dependent cancers, where the balance between proliferation and apoptosis is crucial for disease progression: low doses protect cellular integrity, while high doses suppress proliferation and enhance the apoptotic response (11–13). Given the biological characteristics of endometrial cancer, it is important to investigate the effects of ferulic acid on proliferation and apoptosis in this cell type to reveal its potential regulatory role.

Cell proliferation and apoptosis are two of the fundamental biological processes involved in the development and progression of endometrial cancer. Ki-67 is a nuclear protein that is expressed during active phases of the cell cycle. It is commonly used to assess cell proliferation and is considered a reliable indicator of proliferative activity (14). Bcl-2 family proteins play an important role in the regulation of apoptotic processes, with Bax exhibiting proapoptotic effects and Bcl-2 exhibiting antiapoptotic effects (15). The balance between Bax and Bcl-2 is crucial for activating the mitochondrial apoptotic pathway, and the Bax/Bcl-2 ratio is a widely used parameter for assessing apoptotic tendency (16, 17).

This study aims to determine the effects of FA on the balance between proliferation and apoptosis in Ishikawa endometrial cancer cells.

Material and Methods

Cell Culture

This study used the Ishikawa cell line, which was obtained from the European Collection of Authenticated Cell Cultures (ECACC). This cell line was developed by isolating it from a 39-year-old patient with endometrial adenocarcinoma who tested positive for oestrogen and progesterone receptors (18). The cells were cultured in a medium consisting of 90% high-glucose DMEM (HyClone, SH30022.01) containing 8% FBS (HyClone, SV30160.03) and 2% penicillin/streptomycin (HyClone, SV30010). The cells were maintained at 37 °C in a humidified incubator containing 5% CO_2.

MTT Analysis

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test is a

colourimetric method used to determine cell viability and proliferation, as well as the half-maximal inhibitory concentration (IC_{50}). The cytotoxic effects of FA on the Ishikawa cell line were analysed using the MTT assay. A stock solution was prepared by dissolving 5 mg of MTT powder (Bioshop MTT222.1) in 1 ml of distilled water. FA (Sigma-Aldrich, 128708) was dissolved in DMSO to achieve a final concentration of 4000 µM, taking into account its molecular weight. Ishikawa cells were seeded into a 96-well culture plate at a concentration of 1×10^4 cells per well. The plate was then incubated at 37 °C and 5% CO_2 for 24 hours to allow the cells to adhere to the surface. Then, increasing concentrations of FA were applied to the cells and the plate was incubated for a further 24 hours. After 24 hours, 10 µl of the prepared MTT solution was added to 100 µl of medium and cell mixture in each well. The cells were then incubated for a further four hours. After incubation, the medium in the wells was removed using a micropipette and 100 µl of MTT solvent solution (DMSO) was added. The cells were then incubated for a further 20 minutes. The proliferation activity of the cells after incubation was determined by measuring the absorbance intensity at a wavelength of 570 nm using a microplate reader spectrophotometer (Thermo, MULTISKAN SkyHigh). Measurements were performed in triplicate. Cell viability rates in all groups were calculated using a control group as a reference point of 100% viability.

Indirect Immunocytochemical Staining (ICC)

The intracellular distribution of the Ki-67, BAX and Bcl-2 proteins was determined using indirect immunocytochemical staining. $5x10^4$ cells were plated in each well of an 8-well cell culture slide. The cells were then cultured in an incubator at 37 °C and 5% CO_2 for 24 hours. After incubation, the culture media in the wells were removed. Fresh culture medium containing 800 µM FA was added to the FA group. After incubating the cells for a further 24 hours, the culture medium was removed from the wells and the slide was washed with PBS for five minutes. To fix the cells, 4% paraformaldehyde (PFA) was added to the wells, after which the slide was left at room temperature for 30 minutes. Following three 5-minute washes, the slide was treated with 3% H_2O_2 for 5 minutes at room temperature. After washing, 0.1% Triton X-100 was applied for 15 minutes. After washing with PBS, a block solution was added to the wells and left for one hour. The block solution was then removed and the wells were incubated overnight at 4°C with primary antibodies Ki-67 (AF0131 – 100 µl, 1/150), BAX (AF5239 – 100 µl, 1/200) and Bcl-2 (AF7013 – 100 µl, 1/200). The next day, the samples were washed and a biotin secondary antibody specific for the primary antibody (Abcam Rabbit Specific HRP/AEC IHC Detection Kit) was added and left for 30 minutes. Then, goat anti-rabbit HRP streptavidin antibody was added and left for 30 minutes. The wells were then washed three times with PBS for five minutes each. After adding AEC chromogen, the wells were left to infuse for approximately two minutes. After staining, the wells were treated twice with distilled water for five minutes each. After staining with Harris haematoxylin for three minutes, the slides were covered and examined under a light microscope.

Evaluation of Indirect Immunocytochemical Data

Light microscopy observations were performed by two histologists to evaluate the immunoreactivity of cells in the experimental groups. ImageJ v1.54, image processing and analysis software, was used to score and evaluate the images. Five different fields were determined at x20 magnification. One hundred cells were counted in each field and H-scores were calculated by assigning a value of 0 to unstained cells, 1 to lightly stained cells, 2 to moderately stained cells and 3 to heavily stained cells.

The data were statistically evaluated. H-score = $\sum(I + 1)$ x Staining % (I = staining rate of cells).

Statistical Analysis

The statistical analysis of the data was performed using GraphPad Prism 10.0 software. The normality of the data distribution was examined using the Shapiro–Wilk test. It was determined that the assumption of normal distribution was not met when p-values were below 0.05. Comparisons between two independent groups were investigated using the Welch-corrected unpaired t-test. All analyses were performed using the software, with a significance level of $p<0.05$.

Results

MTT Analysis Results

The MTT analysis, which examined the cytotoxic effects of ferulic acid (FA) on the Ishikawa cell line, revealed that the percentage of cell viability

in the control group was 100 after 24 hours. It was also observed that increasing FA concentrations reduced the percentage of viable cells. The closest IC50 value observed in the study was at a dose of 800 µM FA (Figure 1).

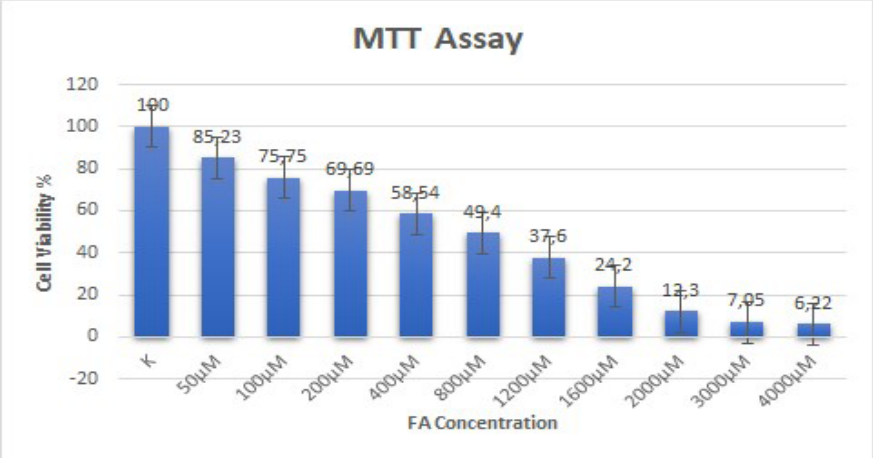

Figure 1. The effect of ferulic acid on cell viability in Ishikawa endometrial cancer cells. Cells were treated with different concentrations of FA, and viability was assessed using an MTT assay. Data were normalized to the control group and are presented as mean ± standard deviation (SD). Error bars indicate standard deviation.

Morphological Observations

In the control group, where no FA was applied, the Ishikawa cells formed a monolayer structure with good surface adhesion and a polygonal-oval morphology. The cells were also distributed evenly. High cell density, preserved cell-to-cell contacts and regular nuclear morphology were noted, alongside abundant mitotic figures (Figure 2).

In the FA-treated group, a decrease in cell density was observed, along with a tendency for cells to detach from the surface, compared to the control group. A significant proportion of cells in this group exhibited rounding, decreased cell-cell contacts and dispersed cell clusters (Figure 2).

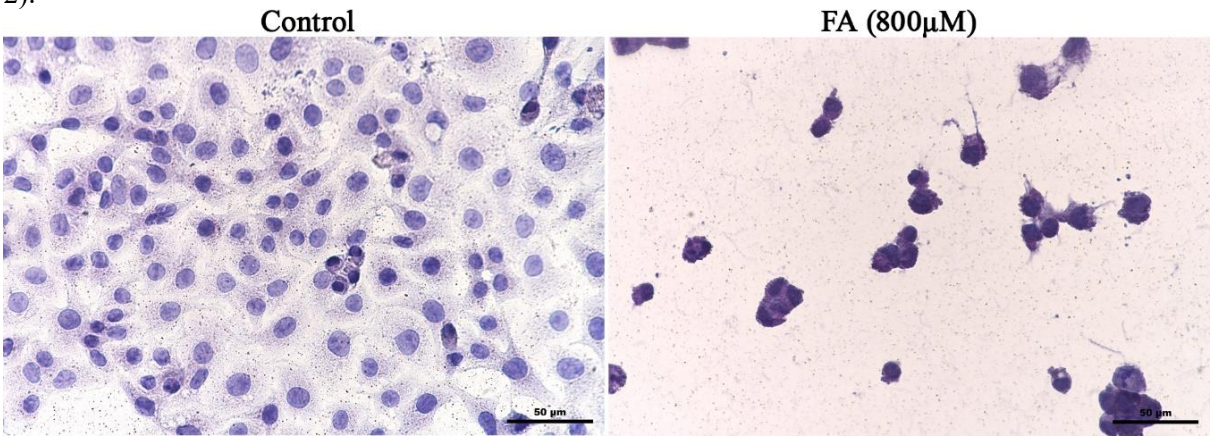

Figure 2. Effect of FA application on the morphology of Ishikawa endometrial cancer cells. Images were obtained using a light microscope at ×400 magnification. Scale bar: 50 µm

Indirect Immunocytochemical Staining Results

This study investigated the immunoreactivity (Ki-67, BAX and Bcl-2) of the control and FA groups. The expression levels of Ki-67 and Bcl-2 were found to be lower in the FA group than in the control group ($p = 0.007$ and $p < 0.0001$, respectively), while the BAX level and the BAX/Bcl-2 ratio were found to be higher in the FA group ($p = 0.002$ and $p = 0.0007$, respectively) (Figure 3, Figure 4, Table 1).

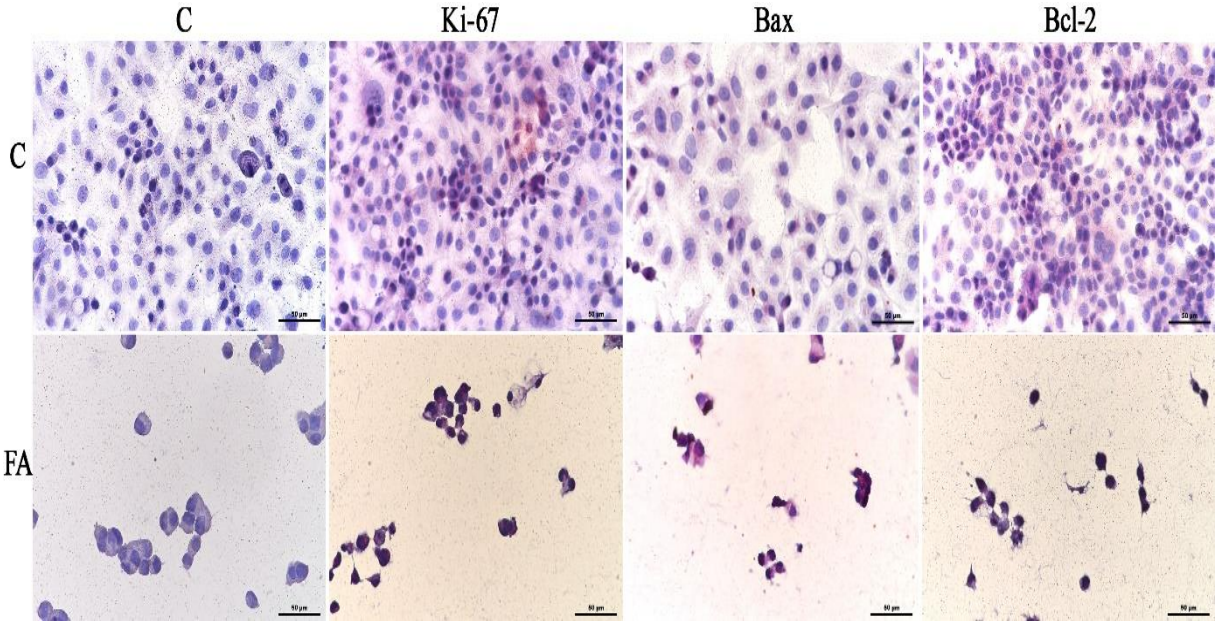

Figure 3. Immunoreactivities of Ki-67, Bax, and Bcl-2 in Control and FA-treated groups
C-C: Ishikawa cells (control) **C-FA:** Ishikawa cells treated with 800 µM FA Images were obtained using a light microscope at ×400 magnification. Scale bar: 50 µm

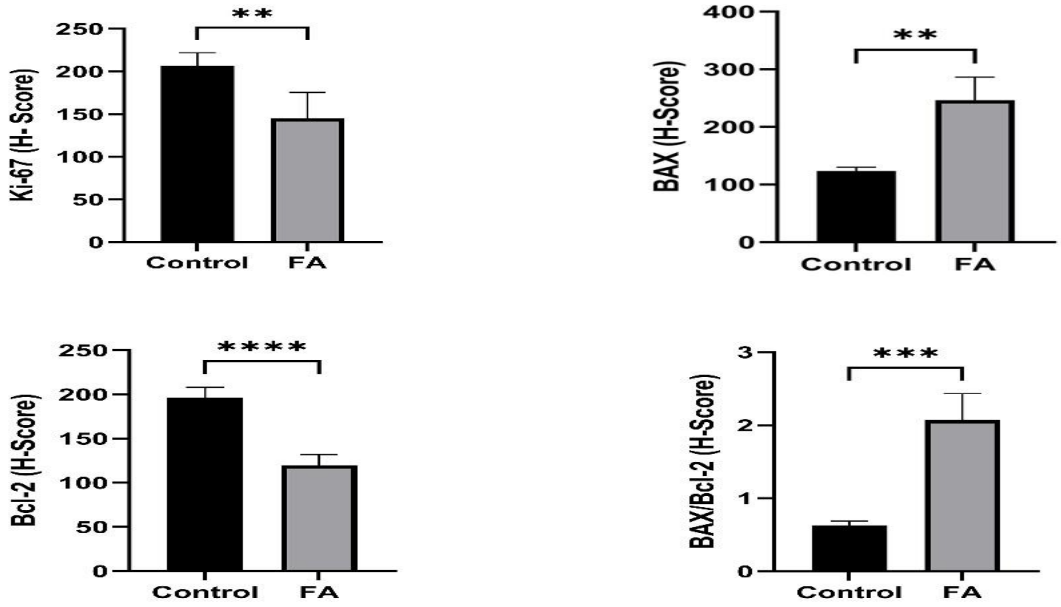

Figure 4. Graphical representation of Ki-67, Bax, Bcl-2 and Bax/Bcl-2 H-Score analysis.
****$p < 0.0001$, ***$p < 0.001$, **$p < 0.05$

Table 1. Immunocytochemical analysis H-scoring results of the groups (mean ± standard deviation)

	Control	FA (800 µM)	p value
Ki-67	206,6 ± 15,29	145,0 ± 30,43	0,0070
BAX	123,6 ± 6,73	246,4 ± 40,00	0,0020
Bcl-2	196,4 ± 11,63	119,6 ± 12,42	<0,0001
BAX/Bcl-2	0,63 ± 0,05	2,072 ± 0,36	0,0007

Discussion

This study evaluated the effects of FA on the viability, morphology and proliferation of Ishikawa cells. Previous studies have shown that the effects of FA can vary depending on the cell type, the dose applied, and the exposure time. FA has been shown to maintain cellular integrity and support cell viability by suppressing reactive oxygen species in normal cells and some tissue models (19). However, FA has also been reported to exhibit antiproliferative effects in various cancer cell lines. Janicke et al. applied 150 µM FA to Caco-2 cells for 24 hours, subsequently reporting an antiproliferative effect on the cell cycle (20). Another study in HepG2 cells showed that FA can reduce cell viability (21). In a further study, FA was found to significantly inhibit proliferation and disrupt the morphology of HepG2 cells (22). In experimental endometriosis studies in rats, a combined treatment involving FA, ligustrazine and tetrahydropalmatine was found to suppress proliferation markers and the Notch pathway in ectopic endometrium (23). In our study, we observed that FA caused a significant decrease in Ishikawa cells and affected their morphology. Morphologically, the cells rounded up, there was a decrease in cell-cell contact and the cells were distributed in scattered clusters. Experiments using FA in the literature show that the doses affecting cell viability have a very wide range. For example, in a study by Chen et al. on CT-26 cells, the IC_{50} value for FA was reported to be 800 µM after 24 and 48 hours, and it was stated that FA concentrations between 0 and 400 µM did not significantly affect cell proliferation (24). In contrast, another study on A549 and HT29-D4 cells tested the maximum FA concentration of 1000 µM and found that cell viability decreased by up to 30% (25). Another study conducted on MIA PaCa-2 human pancreatic cancer cells determined the IC50 dose of FA to be 500 µM/ml after 72 hours. As no studies using FA in Ishikawa cells were found in the literature, an MTT assay was planned in our study between 50 and 4000 µM. The concentration that reduced cell viability to 50% (49.4%) was determined to be an FA dose of 800 µM. These results are consistent with the dose-dependent effects of FA reported in different cancer cell lines, showing that the dose determined in our study was consistent with the literature.

The effects of FA on cell proliferation are known to vary depending on the cell type and the dose applied. Although it has been suggested that FA does not significantly suppress proliferative activity at low concentrations, and may even promote it in certain cell models, research has demonstrated that proliferative activity decreases as the cell cycle is suppressed at higher doses. This antiproliferative effect occurs through proliferation markers and cell cycle regulatory mechanisms. Gadelmawla et al. demonstrated in their study that FA reduces proliferation in rat colon cancer cells induced by 1,2-dimethylhydrazine (DMH) via Ki-67 (26). Another study reported that FA inhibited cell proliferation in MG63 osteosarcoma cells by reducing Ki-67 immunoreactivity (27). Consistent with the aforementioned antiproliferative effects observed in various cancer cell lines, our study revealed that FA suppressed cell proliferation in Ishikawa cells by reducing Ki-67 immunoreactivity. It has been emphasised that FA suppresses proliferation but does not significantly affect apoptotic activity at low concentrations; rather, it activates apoptotic pathways at higher doses. In a study by Eroğlu et al., FA application was reported to significantly reduce Bcl-2 gene and protein expression in LNCaP prostate cancer cells while increasing CYCS gene expression, which is associated with the apoptotic pathway (28). Another study, this time with the human renal carcinoma cell line

(ACHN), found that Bcl-2 gene expression levels were lower in ACHN cells treated with FA than in untreated cells, while Bax gene expression was increased (29). A study on HeLa and Caski human cervical cancer cells also found that FA decreased Bcl-2 and Mcl-1 levels, while increasing Bax levels (30). In our study, we detected a decrease in Bcl-2 immunoreactivity and an increase in Bax immunoreactivity in Ishikawa cells treated with FA. The higher Bax/Bcl-2 ratio found in the FA-treated group, a key indicator of the apoptotic index, suggests that FA enhances the apoptotic response in Ishikawa cells.

Conclusion

This study examined the impact of FA on the proliferation and apoptosis of Ishikawa cells. The findings show that FA application suppresses proliferative activity by decreasing Ki-67 immunoreactivity, and alters the apoptotic balance by increasing Bax and decreasing Bcl-2, resulting in an increased Bax/Bcl-2 ratio. Considering that FA may exhibit different biological effects at low and high doses, these results suggest that it may have dose-dependent antiproliferative and proapoptotic effects in Ishikawa cells. This study adds to the existing literature on the impact of ferulic acid on cellular responses in endometrial cancer cells.

Declarations

Ethical Approval Statement

This study was conducted using an in vitro cell culture model only, with no human- or animal-derived tissue, cells or clinical data being used. Therefore, approval from an ethics committee was not required.

Author Contribution Statement

CK: Conceptualization of the study, experimental design, execution of cell culture experiments, data analysis and interpretation, writing the original draft, and preparation of the final version of the article.
EA: Experimental design, execution of cell culture experiments, data analysis and interpretation and preparation of the final version of the article.

Funding Statement

No financial support was received from any public, commercial or non-profit organisation in relation to this study.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest in connection with this study.

Declaration on the Use of AI

In preparing this study, artificial intelligence tools were used solely for language support and spelling and grammar correction. The author is solely responsible for all scientific content, interpretations and conclusions in this study.

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