Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2026; 43(1): 1-7
doi: 10.52142/omujecm.43.1.1

Hesperidin enhances the antiproliferative and apoptotic effects of oxaliplatin in AGS gastric cancer cells through modulation of apoptosis-related proteins

Ilker KILICCIOGLU[1,*], Gorkem DULGER[1], Basaran DULGER[2]

[1]Department of Medical Biology, Faculty of Medicine, Duzce University, Duzce, Türkiye
[2]Department of Biology, Faculty of Arts and Science, Duzce University, Duzce, Türkiye

Received: 22.08.2025 • **Accepted/Published Online:** 22.02.2026 • **Final Version:** 31.03.2026

Abstract

Gastric cancer remains a leading cause of cancer-related mortality worldwide, with poor prognosis and high rates of resistance to platinum-based chemotherapy. Hesperidin (HES), a citrus-derived flavanone glycoside, has demonstrated anticancer properties, but its potential as an adjuvant to oxaliplatin (OXA) in gastric cancer has not been fully explored. The cytotoxic effects of HES, OXA, and their combination were evaluated in AGS gastric cancer cells and HUVEC normal endothelial cells using WST-1 assays and morphological analysis. Wound healing assay was applied to assess antimigratory activity. Apoptotic mechanisms were investigated by ELISA-based quantification of caspase-3, -8, and -9, and Western blot analysis of Bax, Bcl-2, p53, and Survivin. HES inhibited the proliferation of AGS cells in a dose- and time-dependent manner (with IC50 values of 170.4 µM at 24 h and 92.06 µM at 48 h) and showed limited cytotoxicity in HUVEC cells. OXA exerted stronger antiproliferative activity (IC_{50}= 24.16 µM at 24 h), and its combination with HES produced a greater inhibition of proliferation and migration ($p < 0.0001$). Combination treatment significantly increased caspase activation: caspase-3, caspase-8, and caspase-9 levels increased by approximately 2.7-fold, 3.0-fold, and 2.8-fold, respectively ($p < 0.0001$). Furthermore, HES + OXA treatment downregulated Bcl-2 and Survivin (approximately 4.5- and 5-fold, respectively) while increasing Bax and p53 expression (approximately 9- and 5-fold, respectively), indicating significant ($p < 0.0001$) activation of both intrinsic and extrinsic apoptotic pathways. These findings suggest that HES may augment OXA-induced apoptosis and migration inhibition in gastric cancer cells.

Keywords: gastric cancer, hesperidin, oxaliplatin, apoptosis

1. Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide, particularly in East Asian and Eastern European populations, despite a gradual decline in incidence over recent decades (1). Among GC subtypes, adenocarcinoma of the stomach accounts for over 90% of cases. Due to the asymptomatic nature of early-stage disease and poor responsiveness to monotherapies, the prognosis for advanced GC remains dismal, with a 5-year survival rate below 30% (2). Although platinum-based chemotherapy regimens, such as oxaliplatin (OXA) in combination with fluoropyrimidines, have been the cornerstone of first-line treatment for advanced GC, drug resistance and systemic toxicity pose significant limitations to their efficacy (3).

OXA is a third-generation platinum compound that forms DNA adducts, leading to cell cycle arrest and apoptosis. It exhibits an improved toxicity profile compared to cisplatin, particularly regarding nephrotoxicity and ototoxicity (4). However, OXA resistance is frequently observed and is often associated with the deregulation of apoptotic signaling pathways, including the intrinsic mitochondrial pathway and anti-apoptotic proteins such as Bcl-2 and Survivin (5). To overcome this resistance and enhance therapeutic efficacy, the combination of OXA with bioactive natural compounds has gained increasing attention in recent years (6).

Hesperidin (HES), a naturally occurring flavanone glycoside abundantly found in citrus fruits, has demonstrated promising anticancer properties in a variety of malignancies, including breast, colon, lung, and GC (7,8). Mechanistically, HES has been reported to induce apoptosis, suppress proliferation, and inhibit migration and angiogenesis through modulation of oxidative stress, mitochondrial membrane potential, and apoptotic signaling cascades (9). Specifically, it can upregulate pro-apoptotic proteins such as Bax and p53 while downregulating anti-apoptotic regulators like Bcl-2 and Survivin (10). These properties suggest that HES may serve as an effective adjuvant to conventional chemotherapeutic agents.

Apoptosis, or programmed cell death, is a critical mechanism for maintaining cellular homeostasis and eliminating damaged or cancerous cells. Two principal apoptotic pathways whic are the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) are regulated by a balance between pro-apoptotic (such as Bax, p53) and anti-apoptotic

*Correspondence: ilkerkiliccioglu@duzce.edu.tr

(such as Bcl-2, Survivin) proteins, along with downstream activation of caspases, particularly caspase-3, -8, and -9 (11,12). Dysregulation of these pathways contributes significantly to tumor progression and chemoresistance in GC.

Given this background, the present study aims to investigate the improved apoptotic effects of HES in combination with OXA in AGS human gastric adenocarcinoma cells. We focused on key molecular markers of apoptosis, including Bax, Bcl-2, p53, and Survivin at the protein level using Western blot analysis, and evaluated caspase-3, -8, and -9 activity through ELISA-based quantification. This study aims to elucidate the potential of HES to increase the pro-apoptotic effects of OXA and contribute to the development of more effective therapeutic strategies for GC.

2. Matherials and Methods

2.1. Cell culture

The human gastric adenocarcinoma cell line (AGS; ATCC CRL 1739) and human umbilical vein endothelial cells (HUVEC; ATCC PCS-100-013) were used in this study. Cells were cultured in DMEM medium (Gibco, Thermo Fisher Scientific, USA) supplemented with 10% fetal bovine serum (FBS, Gibco), 100 U/mL penicillin, and 100 µg/mL streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. In all experiments, cells from passages 5 to 20 were used. Both cell lines were routinely tested for contamination from mycoplasma or other microorganisms and confirmed to be microorganism negative during the experiments. Cells were passaged every 2–3 days to maintain exponential growth.

2.2. Chemicals and reagents

HES (Merck KGaA, Darmstadt, Germany) and OXA (MedChemExpress LLC, USA) were prepared according to the manufacturer's procedures before use. Stock solutions of HES (100 mM) were prepared in dimethyl sulfoxide (DMSO), and OXA (10 mM) was prepared in sterile distilled water. Final working concentrations were obtained by dilution in culture medium. The final concentration of DMSO did not exceed 0.1% (v/v), which showed no cytotoxic effect on cells.

2.3. Cell viability assay (WST-1)

The antiproliferative effects of HES, OXA, and their combination were determined using the WST-1 assay (Abcam, Cambridge, UK). AGS and HUVEC cells were seeded in 96-well plates at a density of 5×10^3 cells/well and incubated overnight for attachment. Cells were treated with increasing concentrations of HES (25–500 µM) for 24 and 48 h, OXA (5–100 µM) for 24 h, or their combination (OXA 10–40 µM + HES 100 µM). After incubation, 10 µL of WST-1 reagent was added to each well and further incubated for 2 h at 37 °C. Absorbance was measured at 450 nm using a microplate reader (Allsheng Instruments, Hangzhou, China). The percentage of proliferation relative to control was calculated, and IC_{50} values were obtained by nonlinear regression analysis using GraphPad Prism 9.0 software. Each experiment was performed in three independent replicates.

2.4. Morphological evaluation

To assess cytotoxic effects on normal cells, HUVECs were treated with HES (75–200 µM) for 24 h. Then, morphological changes were visualized with an inverted microscope (Euromex, Arnhem, The Netherlands) equipped with a CMEX-5 Pro Camera at 20x magnification.

2.5. Wound healing assay

AGS cells were seeded in 6-well plates and grown to 90% confluence. A sterile 200 µL pipette tip was used to scratch a linear wound across the monolayer. Detached cells were removed by washing with PBS, and cells were treated with HES (100 µM), and combination with OXA (20 µM) in serum-reduced medium (1% FBS). Wound closure was recorded at 0, 24, and 48 h using an inverted microscope (Euromex, Arnhem, The Netherlands) equipped with a CMEX-5 Pro Camera at 20x magnification. The percentage of wound closure was quantified using ImageJ software (NIH, Bethesda, MD, USA) by comparing the initial wound area with that at subsequent time points.

2.6. Caspase activity assay

Caspase-3, -8, and -9 protein levels were quantified by ELISA kits (BT LAB, Shanghai, China) following the manufacturer's protocol. AGS cells were treated with HES (100 µM), and combination with OXA (20 µM) for 24 h. Cell lysates were prepared, and absorbance was measured at 450 nm. Protein concentrations were normalized to total protein content, and results were expressed as fold change relative to untreated control.

2.7. Western blot analysis

To evaluate apoptosis-related proteins, AGS cells were treated with HES (100 µM), and combination with OXA (20 µM) for 24 h. Cells were lysed in RIPA buffer supplemented with protease and phosphatase inhibitors. Equal amounts of protein (30 µg) were separated by SDS-PAGE (10–12%) and transferred onto PVDF membranes (Macherey-Nagel GmbH, Düren, Germany). Membranes were blocked with 5% non-fat dry milk in TBS-T (0.1% Tween-20) for 1 h at room temperature, followed by overnight incubation at 4 °C with primary antibodies against Bcl-2 (Affinity Biosciences, Cincinnati, USA), Bax (Affinity Biosciences, Cincinnati, USA), p53 (Affinity Biosciences, Cincinnati, USA), Survivin (Affinity Biosciences, Cincinnati, USA), and GAPDH (loading control). All primary antibodies were studied at 1:1000 dilution. After washing, membranes were incubated with HRP-conjugated secondary antibodies (1:5000) for 1 h at room temperature. Protein bands were detected using ECL reagent (ABP Biosciences, Beltsville, USA) and imaged using a chemiluminescence detection system (Pop-Bio Imaging, Cambridge, UK). and densitometric analysis was performed using ImageJ software.

2.8. Statistical analysis

GraphPad Prism 9.0 was used to perform the statistical analysis of the experiments results. Results were expressed as mean ± SD from three independent experiments. Statistical significance was determined using one-way ANOVA and two-way ANOVA followed by Dunnett's post-hoc test, with significance levels denoted as *p <0.05, **p <0.01, ***p <0.001, and ****p <0.0001.

3. Results

3.1. Hesperidin inhibited proliferation of AGS cells in a time- and dose-dependent manner

The cytotoxic potential of HES on AGS GC cells was evaluated using WST-1 assay. As shown in Fig. 1A, treatment with HES significantly suppressed AGS cell proliferation in a concentration-dependent manner. The calculated IC_{50} values were 170.4 µM at 24 h and 92.06 µM at 48 h, indicating that prolonged exposure increased the cytotoxic effect. Bar graph analysis further demonstrated a clear reduction in viability at concentrations above 100 µM ($p<0.05$), with a more pronounced inhibitory effect observed after 48 h of treatment (Fig. 1B). These results confirmed that HES exerts a time-dependent cytotoxic activity against AGS cells.

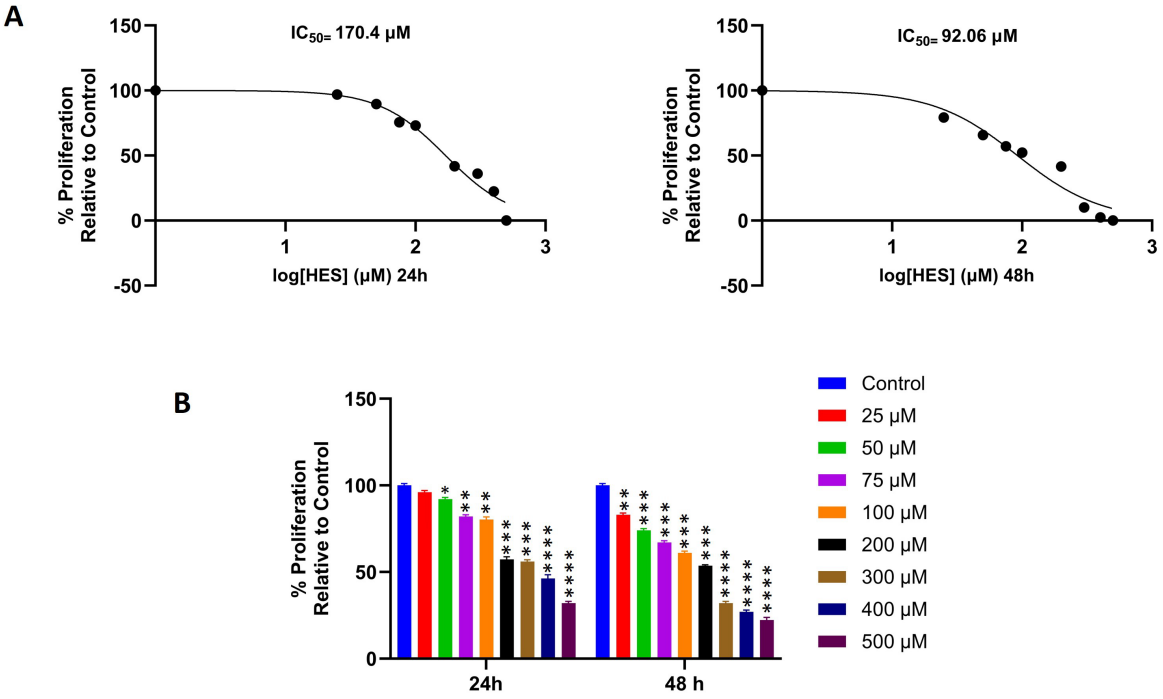


Fig. 1: Hesperidin inhibited proliferation of AGS gastric cancer cells

(A) Dose–response curves showing the effect of hesperidin (HES) on AGS cell viability after 24 h and 48 h treatment, with calculated IC_{50} values of 170.4 µM and 92.06 µM, respectively. (B) Bar graphs representing the percentage of proliferation relative to control at increasing concentrations of HES. Data are presented as mean ± SD of three independent experiments. (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs. control).

3.2. Oxaliplatin exerted stronger antiproliferative activity and showed potent effect with hesperidin

OXA markedly inhibited AGS cell proliferation in a dose-dependent manner with an IC50 value of 24.16 µM at 24 h (Fig. 2A). The reduction in cell viability was more substantial compared to HES alone. When combined with HES (100 µM), OXA exhibited an increased effect, producing significantly greater growth inhibition than either agent used individually (Fig.2C). This suggests that HES potentiates the cytotoxic efficacy of OXA, lowering the threshold concentration required for effective inhibition. 40 µM OXA and 100 µM HES reduced cell viability to 20%. Given that 100 µM HES alone showed 75–85% cell viability at 24-48 h (Fig. 1B), the combined effects exceeded the effects of either alone, indicating greater inhibition of the combination.

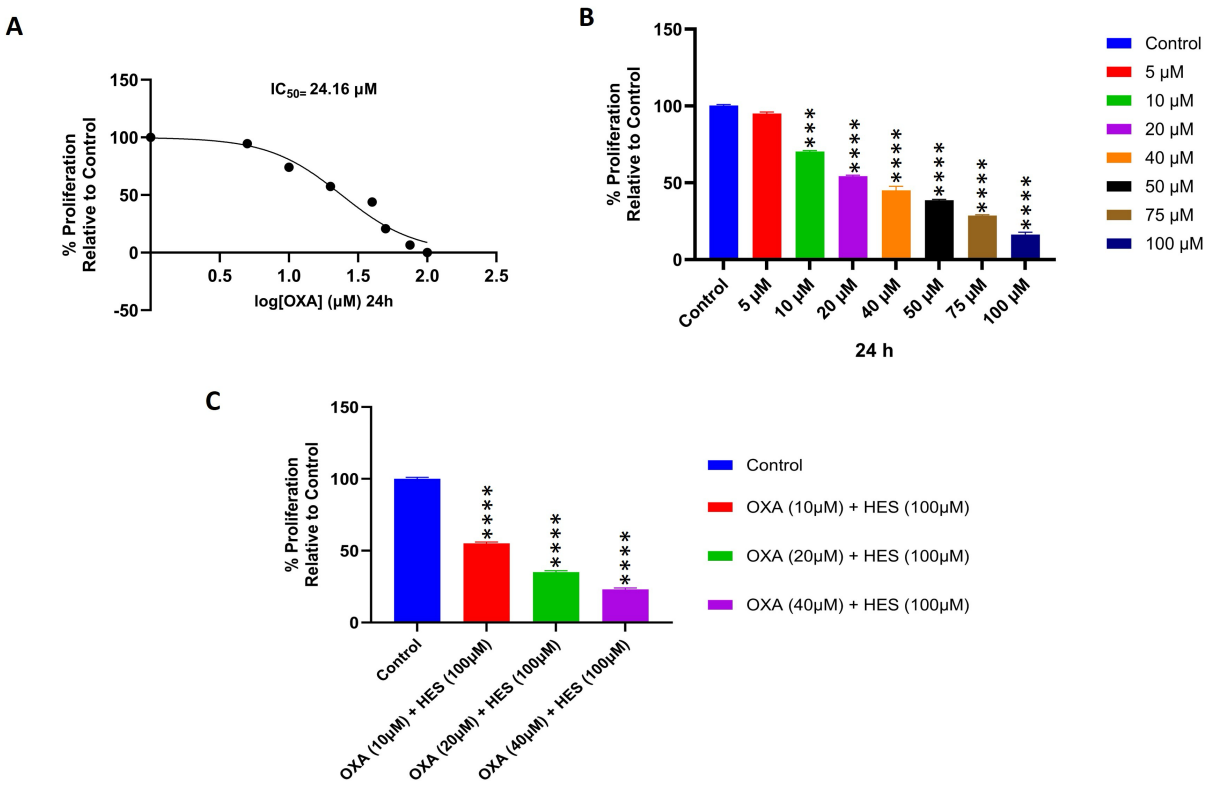


Fig. 2. Oxaliplatin suppressed AGS cell proliferation and synergizes with hesperidin
(A) Dose–response curve of oxaliplatin (OXA) on AGS cell viability after 24 h with IC_{50} value of 24.16 µM. (B) Bar graph illustrating the dose-dependent inhibitory effect of OXA on proliferation. (C) Combined treatment of HES (100 µM) with different concentrations of OXA significantly enhanced the antiproliferative effect compared to single treatments. Data represent mean ± SD of three independent experiments. (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs. control)

3.3. Hesperidin showed selective toxicity by protecting HUVEC cells

The effect of HES on normal human endothelial cells (HUVEC) was examined to assess selectivity. Morphological analysis revealed that HUVEC cells retained their normal spindle-like appearance at concentrations up to 100 µM, with only mild changes observed at higher doses (Fig. 3A). Consistently, WST-1 assay showed that cell viability remained largely unaffected at lower concentrations, with only moderate reductions detected at doses ≥200 µM (Fig. 3B). These findings indicate that HES exerts tumor-selective cytotoxicity, strongly inhibiting AGS cells while sparing normal endothelial cells at equivalent doses.

3.4. The combination of hesperidin and oxaliplatin inhibited AGS cell migration

The impact of HES and OXA on AGS cell migration was evaluated using wound healing assay. Control cells exhibited almost complete wound closure within 48 h, while cells treated with HES alone showed a marked reduction in closure (Fig. 4A). Notably, the combination of HES and OXA produced the strongest antimigratory effect, with minimal wound closure observed even after 48 h (Fig. 4B). These results indicate that the combined treatment significantly suppresses AGS cell motility, thereby potentially reducing the metastatic potential of these cells.

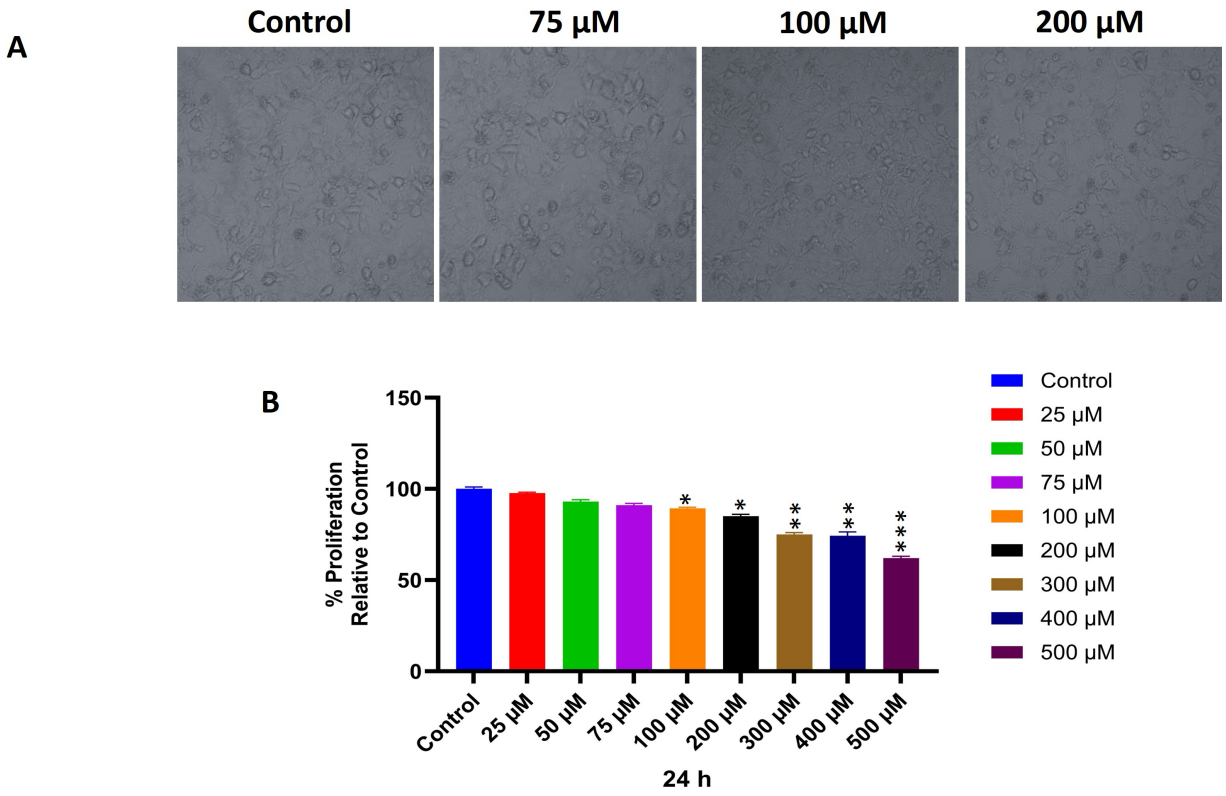


Fig. 3. Effects of hesperidin on normal HUVEC cells.
A) Representative inverted microscopy images showing HUVEC morphology after treatment with increasing concentrations of HES (75–200 µM, 24 h). (B) WST-1 assay results showing cell viability at different concentrations of HES. Data were expressed as percentage of proliferation relative to untreated control. (*p < 0.05, **p < 0.01 ***p < 0.001 vs. control)

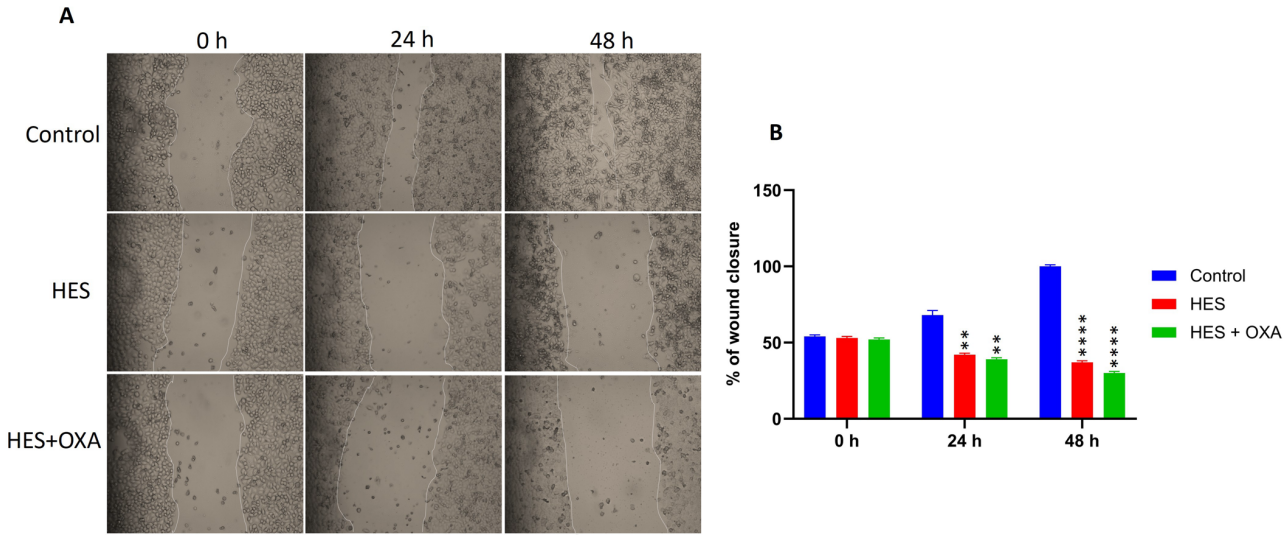


Fig. 4. Hesperidin and oxaliplatin combination inhibited AGS cell migration
(A) Representative wound healing images at 0, 24, and 48 h in control, HES, and HES + OXA groups. (B) Quantitative analysis of wound closure percentage. Combination treatment resulted in the strongest inhibition of migration. Data are expressed as mean ± SD from three experiments. (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs. control)

3.5. Combination treatment increased caspase-dependent apoptosis

To investigate the apoptotic mechanism, the expression of caspase proteins was investigated. As shown in Fig. 5, HES alone induced a moderate increase in caspase-3 and caspase-9 activity, while OXA in combination with HES markedly augmented the expression of caspase-3, -8, and -9. Compared to control, caspase-3 expression increased approximately 2.7-fold ($p<0.0001$) with HES+OXA treatment. Caspase-8 increased approximately 3-fold ($p<0.0001$) with HES+OXA treatment. Caspase-9 increased approximately 2.8-fold ($p<0.0001$) with HES+OXA treatment. The increase was particularly pronounced for caspase-8 and caspase-9, indicating activation of both extrinsic and intrinsic apoptotic pathways. The robust upregulation of caspases under combination treatment highlights the role of caspase-mediated

apoptosis in the observed cytotoxicity.

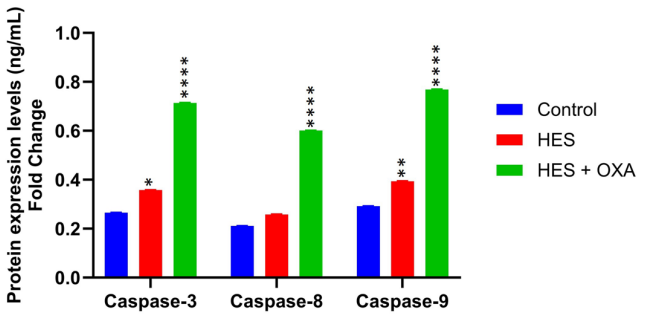


Fig. 5. Combination treatment induced caspase activation in AGS cells

Protein levels of caspase-3, caspase-8, and caspase-9 were measured by ELISA after treatment with HES (100 µM), OXA, or their combination. Combination of HES and OXA significantly enhanced the expression of caspases compared to single treatments. Data are expressed as fold change relative to control (mean ± SD). (*p < 0.05, **p < 0.01, ***p < 0.001 ****p < 0.0001 vs. control)

3.6. Modulation of apoptosis-related proteins by combination treatment

Western blot analysis revealed that HES alone downregulated the anti-apoptotic proteins Bcl-2 and Survivin, while upregulating Bax and p53 (Fig. 6A). These changes were significantly amplified in the combination group, where Bcl-2 and Survivin were strongly suppressed, and Bax and p53 levels were markedly elevated (Fig. 6B). Collectively, the combination decreased anti-apoptotic regulators (Bcl-2, Survivin) by approximately 4-5 fold ($p < 0.0001$) while increasing pro-apoptotic markers (Bax, p53) by approximately 2-9 fold ($p < 0.0001$), consistent with potent caspase activation and growth-inhibitory phenotypes. Taken together, these data suggest that the combination of HES and OXA promoted apoptosis through a shift in the balance between pro- and anti-apoptotic signaling, thereby increasing cell death in AGS cells.

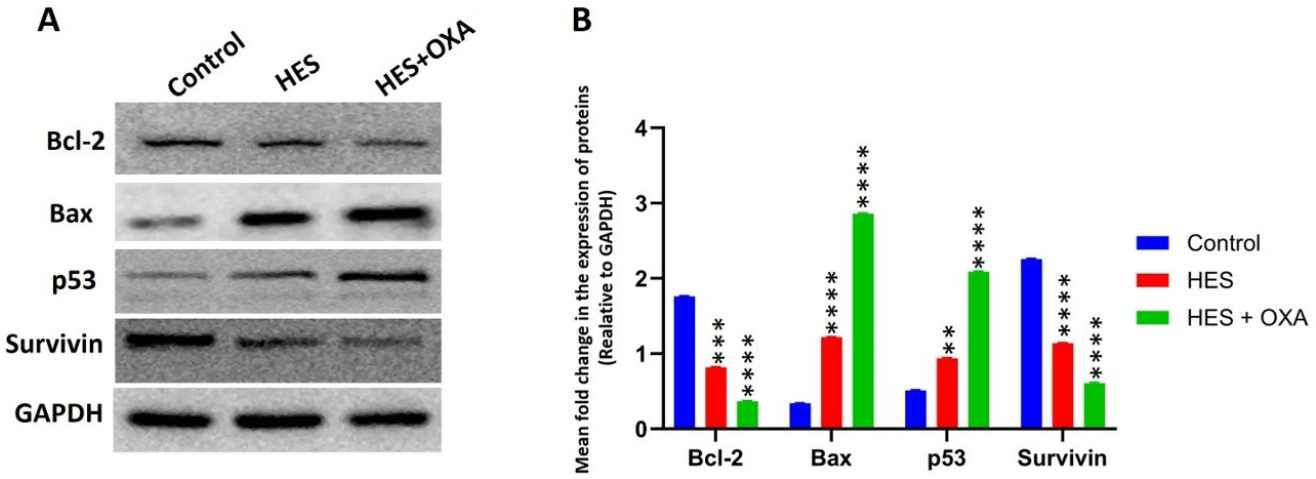


Fig. 6. Modulation of apoptosis-related proteins by hesperidin and oxaliplatin

(A) Western blot analysis showing expression levels of Bcl-2, Bax, p53, and Survivin in control, HES, and HES + OXA treated groups. GAPDH was used as loading control. (B) Densitometric quantification expressed as fold change relative to control. Combination treatment decreased Bcl-2 and Survivin while increasing Bax and p53 expression. Data represent mean ± SD. *p < 0.05, **p < 0.01, ***p < 0.001 vs. control

4. Discussion

The present study demonstrated that HES exerted significant antiproliferative, antimigratory, and pro apoptotic effects on AGS GC cells, and further potentiated the cytotoxic efficacy of OXA. Our findings suggested that the combination of HES and OXA could serve as a promising therapeutic strategy by increasing cancer cell death and potentially reducing the required dose of conventional chemotherapy.

Consistent with previous reports, HES inhibited proliferation of AGS cells in a dose- and time-dependent manner and displayed minimal cytotoxicity against normal HUVEC cells, indicating tumor selectivity. This aligns with the known pleiotropic actions of flavonoids on cell cycle, oxidative stress, and apoptotic signaling pathways (13).

OXA, a widely used platinum-based chemotherapeutic, demonstrated strong antiproliferative activity in AGS cells. However, drug resistance and dose-limiting toxicities often limit its clinical utility (14). Importantly, co administration of HES significantly augmented OXA's cytotoxicity and its antimigratory effects, suggesting chemosensitization is a phenomenon supported by prior evidence that HES can amplify the activity of chemotherapeutic agents in cancer cells (13, 15).

Mechanistically, the combination activated both intrinsic and extrinsic apoptotic pathways, as seen by elevated caspase 3, 8, 9 activities and modulation of Bcl 2 family proteins (downregulation of Bcl 2 and Survivin; upregulation of Bax and p53). This is consistent with studies showing hesperidin's ability to augment mitochondrial-mediated apoptosis via ROS generation and modulation of key apoptotic regulators (16).

The profound inhibition of AGS cell migration by HES plus OXA underscores the compound's potential to impair metastatic behavior. Flavonoids, including hesperidin, have been reported to suppress epithelial–mesenchymal transition (EMT) and metastatic potential in gastrointestinal cancers via modulation of signaling pathways (17, 18). In a study conducted by Arslan et al., they showed that HES increased the

sensitivity of HT-29 colon cancer cells to 5-fluorouracil, a conventional chemotherapeutic agent (19).

Furthermore, though not directly studied in our experiments, emerging evidence suggests that HES and its aglycone hesperetin may exhibit cardioprotective effects (20) when administered alongside chemotherapy, potentially mitigating chemotherapeutic cardiotoxicity without compromising antitumor efficacy. The fact that our findings were obtained using in vitro assays is a limitation. Future research should confirm these findings in vivo using GC xenograft or orthotopic models to assess tumor suppression, systemic toxicity, and potential cardioprotection (20). Further mechanistic studies should investigate the effects of HES on oxidative stress, DNA damage response, and drug resistance pathways, particularly in the context of OXA sensitivity.

In conclusion, our findings support the hypothesis that HES may improve the efficacy of OXA in GC cells by inducing apoptosis and inhibiting migration. Coupled with its low toxicity profile and possible cardioprotective effects, HES emerges as a promising adjunctive agent in GC therapy, warranting further preclinical and clinical exploration.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

None to declare.

Authors' contributions

Concept: I.K., G.D. Design: I.K., G.D., B.D., Data collection or Processing: I.K., G.D., Analysis or Interpretation: I.K., G.D., Literature Search: I.K., G.D., Writing: I.K., G.D., B.D.

Ethical Statement

Ethics Committee Approval: This study was conducted using commercial cell culture. Approval from an ethics committee is not necessary.

References

1. Smyth EC, Nilsson M, Grabsch HI, van Grieken, NC, Lordick, F. Gastric cancer. Lancet. 2020;396(10251): 635-648.

2. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA Cancer J Clin. 2021;71(3): 264-279.

3. Zhang SX, Liu W, Ai B, Sun LL, Chen ZS, Lin LZ. Current advances and outlook in gastric cancer chemoresistance: a review. Recent Pat Anticancer Drug Discov. 2022;17(1): 26-41.

4. Nath S, Datta A, Das A, Adhikari S. Metal-Based Drugs in Cancer Therapy. Int. J. Exp. Res. Rev. 2024; 37, 159-173.

5. Ye T, Wu C, Na, J, Liu X, Huang Y. Multi-Pathway Study for Oxaliplatin Resistance Reduction. Curr Issues Mol Biol. 2025;47(3): 172.

6. Wu J, Li Y, He Q, Yang X. Exploration of the use of natural compounds in combination with chemotherapy drugs for tumor treatment. Molecules. 2023;28(3): 1022.

7. Alam F, Mohammadin K, Shafique Z, Amjad ST, Asad MHHB. Citrus flavonoids as potential therapeutic agents: A review. Phytother Res. 2022;36(4):1417-1441.

8. Pandey P, Khan F. A mechanistic review of the anticancer potential of hesperidin,a natural flavonoid from citrus fruits. Nutr Res. 2021: 92:21-31.

9. Ahmad A, Afzaal M, Saeed F, Ali SW, Imran A, Zaidi SY, et al. A comprehensive review of the therapeutic potential of citrus bioflavonoid hesperidin against lifestyle-related disorders. Cogent Food Agric. 2023, 9(1), 2226427.

10. Aboraya DM, El Baz A, Risha EF, Abdelhamid FM. Hesperidin ameliorates cisplatin induced hepatotoxicity and attenuates oxidative damage, cell apoptosis, and inflammation in rats. Saudi J Biol Sci. 2022 May;29(5):3157-3166.

11. Zia Q, Azhar A, Hassan N, Jain P, Singh M., Mirza MA, et al. Cell death: a molecular perspective. Mol. Biol. Rep. 2021, 7(4), 41-66.

12. Meng X, Dang T, Chai J. From apoptosis to necroptosis: the death wishes to cancer. Cancer Control. 2021 :28: 10732748211066311.

13. Rahmani AH, Babiker AY, Anwar S. Hesperidin, a bioflavonoid in cancer therapy: a review for a mechanism of action through the modulation of cell signaling pathways. Molecules. 2023;28(13): 5152.

14. Tan Y, Wang H, Xu B, Zhang X, Zhu G, Ge Y, et al. Chinese herbal medicine combined with oxaliplatin-based chemotherapy for advanced gastric cancer: A systematic review and meta-analysis of contributions of specific medicinal materials to tumor response. Front Pharmacol. 2022:13: 977708.

15. Sohel M, Sultana H, Sultana T, Al Amin M, Aktar S, Ali M, et al. Chemotherapeutic potential of hesperetin for cancer treatment, with mechanistic insights: A comprehensive review. Heliyon. 2022;8(1): e08815.

16. He P, Ma J, Liu Y, Deng H, Dong W. Hesperetin promotes cisplatin− induced apoptosis of gastric cancer in vitro and in vivo by upregulating PTEN expression. Front Pharmacol. 2020:11: 1326.

17. Liu S, Li L, Ren D. Anti-cancer potential of phytochemicals: The regulation of the epithelial-mesenchymal transition. Molecules. 2023;28(13): 5069.

18. Liang Z, Song J, Xu Y, Zhang X, Zhang Y, Qian H. Hesperidin reversed long-term N-methyl-N-nitro-N-nitroguanidine exposure induced EMT and cell proliferation by activating autophagy in gastric tissues of rats. Nutrients. 2022;14(24): 5281.

19. Arslan A, Bircan B, Erden Y. Hesperidin potentiates the chemosensitivity of HT-29 colon cancer cells to 5-fluorouracil. Ann Med Res 2023;30(11):1416–1420.

20. Roohbakhsh A, Parhiz H, Soltani F, Rezaee R, Iranshahi M. Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. Life Sci. 2015:124: 64-74.