



Apple Seed Extract Alters Apoptosis-related Markers in HCT116 Cells and Uterine Tissues of an Exploratory Mouse Lesion Model

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ABSTRACT

Background: Apple seed extract (ASE) contains multiple bioactive constituents that may affect apoptosis-related cellular responses. This study evaluated ASE in HCT116 cells and an exploratory HCT116 exposure-based mouse uterine lesion-like model.

Methods: HCT116 cells were treated with amygdalin, phlorizin, their combination, or ASE. Female ICR mice were used to assess uterine histopathology and apoptosis-, proliferation-, inflammation-, angiogenesis- and extracellular matrix-related markers after ASE administration.

Results: ASE caused more pronounced morphological disruption and viability reduction than the single compounds, with increased Casp-3, decreased Bcl-2, altered TNF- α expression and altered MMP activity. In mice, ASE reduced uterine weight gain and attenuated histological abnormalities. ASE also decreased PCNA expression, increased Bax expression and reduced Bcl-2 expression, whereas VEGF and mTOR showed variable dose- and region-dependent patterns. These findings indicate that ASE modulates apoptosis-related responses in HCT116 cells and uterine tissues under the present exploratory model conditions.

Key words: Apoptosis, Apple seed extract, HCT116 cells, Mouse uterine lesion model, Uterine tissue.

INTRODUCTION

Female reproductive tissues are highly responsive to inflammatory, hormonal and metabolic disturbances and abnormal regulation of cell proliferation and cell death can contribute to uterine tissue dysfunction and lesion development. Endometrial cancer is one of the major gynecological malignancies associated with impaired apoptosis, abnormal survival signaling, angiogenic remodeling and extracellular matrix alteration (Morice *et al.*, 2016). Although surgery remains the primary treatment for many cases, apoptosis-related signaling has attracted attention because defective programmed cell death is closely linked to tumor progression and therapeutic resistance (Pistritto *et al.*, 2016).

Natural product-derived materials have been investigated as potential modulators of cancer-related cellular responses (Ngurthankhumi *et al.*, 2024; Suganya and Kalpana, 2026). Apples contain diverse phytochemicals, including polyphenols, flavonoids, cyanogenic glycoside-related seed constituents and phlorizin-related dihydrochalcones. Apple-derived bioactive compounds have been discussed for their onco-preventive and chemo-protective properties, but studies focusing specifically on apple seed-derived complex extracts remain limited (Nezbedova *et al.*, 2021).

Among apple seed constituents, amygdalin has been associated with antiproliferative and apoptosis-related responses, although its biological activity remains controversial and depends on dose, model system and experimental conditions (Jaszczak-Wilke *et al.*, 2021). Phlorizin, a dihydrochalcone compound found in *Malus*

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species, has also been linked to biologically relevant effects and related dihydrochalcone compounds have shown inhibitory activity in several human cancer cell lines (Qin *et al.*, 2015; Tian *et al.*, 2021). These findings suggest that apple seed extract (ASE), as a complex mixture, may influence apoptosis-related responses more broadly than isolated single compounds.

However, the biological effects of ASE have not been sufficiently evaluated in combined cellular and animal-model settings related to uterine tissue responses. In particular, it remains unclear whether ASE-associated apoptosis-

related changes observed in cancer cells are accompanied by histopathological and molecular alterations in uterine tissues under exploratory lesion-like conditions. Therefore, this study evaluated the effects of ASE in HCT116 cells and an exploratory HCT116 exposure-based mouse uterine lesion-like model. The study focused on apoptosis-, proliferation-, inflammation-, angiogenesis- and extracellular matrix-related markers and the animal experiment was interpreted as an exploratory uterine tissue response model rather than a validated endometrial cancer model. By combining HCT116 cell treatment with uterine tissue analysis after repeated HCT116 exposure, this study examined whether ASE-associated apoptosis-related changes were observed at both cellular and tissue levels.

MATERIALS AND METHODS

Ethics statements

All animal procedures were approved by the Institutional Animal Care and Use Committee of Hankyong National University (IACUC 2024-4) and performed according to institutional guidelines.

Study site and research period

The study was conducted from March to August 2024 at the Animal Developmental Biotechnology Laboratory, Hankyong National University, Republic of Korea.

Cell culture and treatment

HCT116 cells were used for the *in vitro* experiments. Cells were maintained in DMEM/F12 medium supplemented with 10% fetal bovine serum at 37°C under 5% CO₂. Cells were seeded at 3×10^5 cells/well and treated with amygdalin (A), phlorizin (P), a combination of amygdalin and phlorizin (AP), or apple seed extract (ASE) at concentrations of 20, 30, or 40 µg/mL for 48 h. Untreated cells served as controls.

Preparation of apple seed complex extract

Dried apple seeds were powdered and extracted with 80% ethanol (30 g/300 mL). Extracts were concentrated using a rotary evaporator (Eyela N-1300V-W, Tokyo, Japan) at 50°C and stored as a 15 g/50 mL stock at 5°C. ASE was diluted to working concentration immediately before treatment.

Animals and experimental design

Female ICR mice (8 weeks old) were obtained from Nara-Biotec (Pyeongtaek, Korea) and housed under standard conditions with free access to food and water. Thirty mice were assigned to six groups ($n = 5$ /group): normal control (NC), lesion-induced positive control (PC) and four ASE-treated lesion-induced groups receiving 50, 100, 150, or 200 mg/kg/day ASE (PA50, PA100, PA150 and PA200, respectively). Uterine lesion-like changes were induced in the PC and PA groups using an exploratory HCT116 exposure-based protocol modified from a previous study (Kim, 2022). Briefly, HCT116 cells (1×10^6 cells in 100 µL

of 1× PBS) were injected intraperitoneally into the lower abdominal region every 2 days for 2 weeks, whereas NC mice received 1× PBS. ASE was administered orally once daily for 13 consecutive days during the lesion-induction period. At the end of the experiment, uterine tissues were collected for gross, histological, molecular and protein-level analyses.

This model was used as an exploratory system for assessing uterine tissue responses after repeated HCT116 exposure.

Real-time PCR

Total RNA was extracted using TRIzol reagent (Invitrogen, MA, USA) and cDNA was synthesized according to the manufacturer's protocol. Relative expression was normalized to GAPDH. Primer sequences and annealing temperatures are provided in Table 1.

Gelatin zymography

MMP activity was analyzed in HCT116 cells. Equal amounts of protein (25 µg/10 µL) were separated on SDS-PAGE gels containing gelatin at 130 V for 90 min. Gels were washed with renaturation buffer and distilled water for 20 min and incubated in zymography reaction buffer at 37°C for 18 h. Gels were stained with Coomassie Brilliant Blue R-250 (Biosesang, Gyeonggi-do, Korea) and subsequently destained.

Relative protein analysis by in-house ELISA

After treatment, HCT116 cells and mouse uterine tissues were lysed using Pro-PREP™ solution (iNtRON Biotechnology, Gyeonggi-do, Korea). Relative protein signals associated with apoptosis, proliferation, angiogenesis and extracellular matrix/invasion responses were assessed using an in-house ELISA-based optical density assay. The following antibodies were used: caspase-3 (sc-373730), mTOR (sc-517464), PI3K (sc-365290), PCNA (sc-7907), IGF-related target (sc-712), BCL-2 (sc-492), MT1-MMP (sc-30074), TNF-α (sc-374186) and FSH (sc-7797) from Santa Cruz Biotechnology Inc. (Texas, USA); VEGF (PA5-16754) from Invitrogen (USA) and estrogen receptor (ab66102) and LH (ab180787) from Abcam (Cambridge, UK). Absorbance was measured using an Epoch microplate reader and data were expressed as relative OD values for comparison among groups.

Western blot

Equal amounts of protein (50 µg) were separated on 12% SDS-PAGE gels and transferred onto polyvinylidene fluoride (PVDF) membranes (Cytiva, Munich, Germany) using a semi-dry transfer system. Membranes were incubated with primary antibodies against β-actin, TNF-α, Casp-3 and BCL-2, followed by appropriate secondary antibodies. Signals were developed using Lumi-Light substrate solution and visualized with a KODAK Image Station 4000MM (Eastman Kodak, NY, USA). Band intensities were normalized to β-actin.

Immunofluorescence (IF)

HCT116 cells and uterine tissue sections were fixed with 4% formaldehyde and incubated with primary antibodies against TNF- α , Casp-3, BCL-2 and VEGF. Nuclei were counterstained with Hoechst 33342 (Sigma, MO, USA) and slides were mounted using H-1000 mounting medium (Vector Laboratories, CA, USA). Fluorescence images were acquired using an Eclipse C1 fluorescence microscope (Nikon, Tokyo, Japan). The distribution of Casp-3 and TNF- α was evaluated in the endometrium (EM) and myometrium (MY). Mean fluorescence intensity was quantified using ImageJ and normalized to the NC group.

Cell viability assay

HCT116 cells were seeded at 5×10^3 cells/well in 96-well plates and treated with the indicated compounds or ASE for 48 h. Cell viability was assessed using the QuantiMax™ WST-8 Cell Viability Assay Kit (Biomax, Gyeonggi-do, Korea). Absorbance was measured at 450 nm using an Epoch microplate reader.

Histopathological analysis

Uterine tissues were fixed, paraffin-embedded and sectioned at 5 μ m. Sections were deparaffinized, rehydrated and stained with hematoxylin and eosin (H&E; Muto Pure Chemicals Co. Ltd., Tokyo, Japan). Alcian Blue and Alizarin Red staining were performed using staining kits (American MasterTech Scientific, Lodi, CA, USA). Stained slides were examined using an AX70 microscope (Olympus, Tokyo, Japan).

Statistical analysis

In vitro experiments were performed with at least three independent replicates and animal data were obtained

from five mice per group. Data are expressed as mean $\pm$ SD. Statistical analyses were performed using IBM SPSS Statistics Ver. 21 (IBM, NY, USA). Group differences were analyzed by one-way ANOVA followed by Duncan's multiple range test. Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION**Morphological changes and viability reduction in HCT116 cells following compound treatment**

After 48 h of treatment, HCT116 cells showed reduced attachment, decreased cell density and rounded morphology (Fig 1A). These changes were more evident in the amygdalin plus phlorizin (AP) and apple seed extract (ASE) groups than in the amygdalin (A) or phlorizin (P) groups. The schematic summary showed a similar pattern of treatment-associated cellular damage (Fig 1B). Cell viability was most strongly reduced in the ASE group, followed by the AP group, whereas the A and P groups showed moderate and limited reductions, respectively (Fig 1C).

Consistent with the viability results, Casp-3 expression increased and Bcl-2 expression decreased in the AP and ASE groups (Fig 1D, F). Western blot analysis showed a concentration-associated increase in Casp-3 expression from the single-compound groups to the ASE group, accompanied by reduced Bcl-2 expression (Fig 1F). TNF- α expression increased with ASE concentration, whereas the other treatment groups showed limited or variable changes (Fig 1F). Gelatin zymography detected MMP activity in all treatment groups; active MMP-9 activity was lower in the ASE group and higher in the A group than in the other groups (Fig 1E). These findings indicate that ASE induced stronger viability reduction and apoptosis-related marker changes than either single compound.

Table 1: Gene primer information for real-time PCR analysis.

Genesymbol	NCBI Gene ID		Sequence	Annealing temp.
TNF- α	21926	Fw	5'- CCA CCA CGC TCT TCT GTC TAC-3'	61.8°C
		Rv	5'- AGG GTC TGG GCC ATAGAA CT-3'	59.3°C
Casp-3	12367	Fw	5'- CCT CAG AGA GAC ATT CAT GG-3'	57.3°C
		Rv	5'- GCA GTA GTC GCC TCT GAA GA-3'	59.3°C
IGF-1	16000	Fw	5'- TGT CGT CTT CAC ATC TCT TCT ACC TG-3'	63.2°C
		Rv	5'- CCA CAC ACG AAC TGA AGA GCG T-3'	62.1°C
BAX	12028	Fw	5'- GTG AGC GGC TGC TTG TCT-3'	58.2°C
		Rv	5'- GGT CCC GAA GTA GGA GAG GA-3'	61.4°C
BCL-2	12043	Fw	5'- CAG GTATGC ACC CAG AGT GA-3'	59.3°C
		Rv	5'- GTC TCT GAA GAC GCT GCT CA-3'	59.3°C
PCK	18534	Fw	5'- TGG GGT CCT GCT GTATGA GA-3'	59.3°C
		Rv	5'- TCAAAG TTT TCG CCA CTG CG-3'	57.3°C
mTOR	56717	Fw	5'- CTG GGA CTC AAA TGT GTG CAG TTC-3'	62.7°C
		Rv	5'- GAA CAA TAG GGT GAA TGA TCC GGG-3'	62.7°C
Casp-9	12371	Fw	5'- AGT TCC CGG GTG CTG TCT AT-3'	59.3°C
		Rv	5'- GCC ATG GTC TTT CTG CTC AC-3'	59.3°C
BCL-XI	12048	Fw	5'- AAC ATC CCA GCT TCA CAT AAC CCC-3'	62.7°C
		Rv	5'- GCG ACC CCA GTT TAC TCC ATC C-3'	64.0°C

Gross and histological changes in the exploratory mouse uterine lesion model following ASE treatment

Gross anatomical and histological changes were evaluated in the exploratory HCT116 exposure-based mouse uterine lesion-like model (Fig 2). In the normal control (NC) group, peri-reproductive tissues, uterine and ovarian morphology and uterine vascular patterns appeared relatively uniform. In contrast, the positive control (PC) group showed more pronounced peri-uterine tissue changes, altered uterine vasculature and abnormal uterine morphology (Fig 2A). The schematic summary also showed marked uterine morphological alterations in the PC group (Fig 2B).

Uterine weight was significantly increased in the PC group compared with the NC group, whereas ASE treatment significantly reduced uterine weight relative to the PC group (Fig 2C). Histological analysis supported these gross findings. H and E staining showed abnormal structural changes in the endometrial region of the PC group and these changes were alleviated in the ASE-treated groups (Fig 2D). In particular, the PA150 and PA200 groups showed reduced distortion of endometrial structures and more organized tissue architecture than the PC group. Alcian Blue and Alizarin Red staining also showed altered staining patterns in the ASE-treated groups, consistent with the reduction in uterine enlargement and histological abnormality (Fig 2D).

ASE treatment altered apoptosis- and proliferation-related marker profiles in uterine tissues

Protein and mRNA expression patterns in uterine tissues were evaluated using in-house ELISA-based analysis, immunofluorescence and real-time PCR (Fig 3 and 4C). VEGF and PCNA levels were higher in the PC group than in the NC group (Fig 3A). In the ASE-treated groups, PCNA and MT1-MMP levels tended to decrease, particularly in the PA50 and PA100 groups. In contrast, VEGF and mTOR did not show a consistent dose-dependent decrease and instead displayed variable responses, including partial re-elevation at higher ASE doses (Fig 3A). VEGF immunofluorescence showed region-dependent changes, with relatively reduced endometrial signals and stronger myometrial signals after ASE treatment (Fig 3B).

At the mRNA level, TNF- α expression was elevated in the PA100 group, whereas Casp-3 expression was higher in the PA50 and PA100 groups than in the PC group (Fig 4C). Bax expression increased in the PA100 and PA200 groups, whereas Bcl-2 expression decreased with increasing ASE dose. Casp-9 did not show a consistent pattern across the treated groups (Fig 4C). These results suggest that ASE treatment was associated with changes in uterine apoptosis-related markers, especially Casp-3, Bax and Bcl-2, while VEGF- and mTOR-related responses remained dose- and region-dependent.

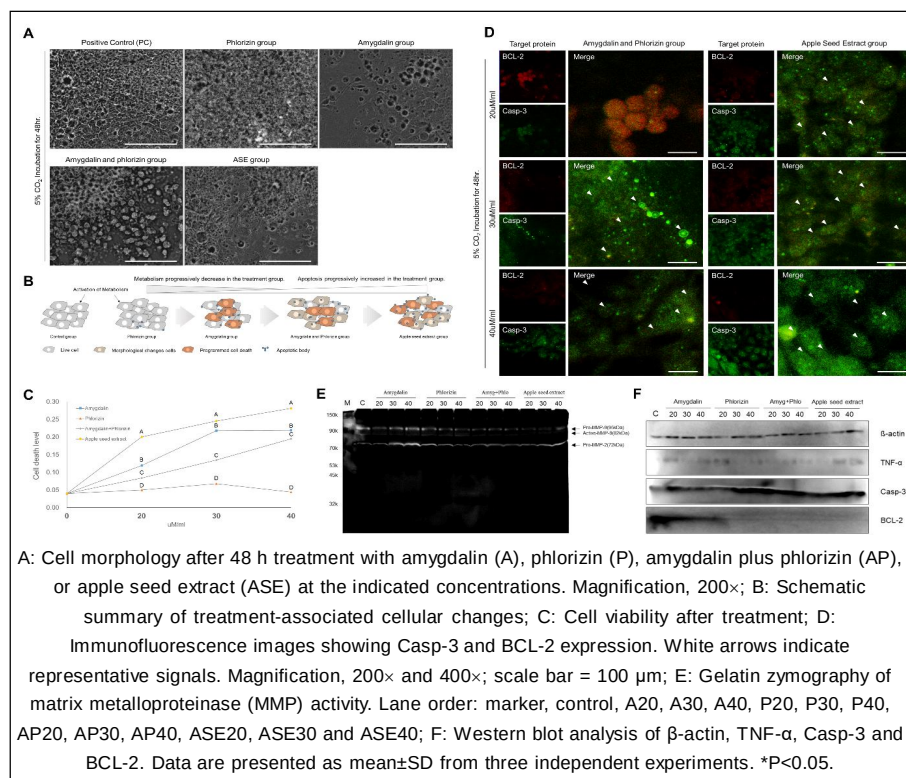


Fig 1: Morphological, viability and apoptosis-related changes in HCT116 cells treated with amygdalin, phlorizin, their combination, or apple seed extract.

Regional distribution of Casp-3 and TNF- α in uterine tissues following ASE treatment

The regional distribution of Casp-3 and TNF- α was evaluated in the endometrium (EM) and myometrium (MY) after ASE treatment (Fig 4A, B). In the NC group, Casp-3 and TNF- α signals were minimal or focally detected in both regions. In the PC group, these signals were broader

and stronger in the EM, particularly in structurally abnormal regions (Fig 4A).

In the ASE-treated groups, Casp-3-positive signals in the EM became more distinct than in the PC group, especially in the PA100 and PA200 groups. TNF- α signals were also mainly detected in the EM; however, unlike Casp-3, TNF- α did not show a consistent dose-dependent

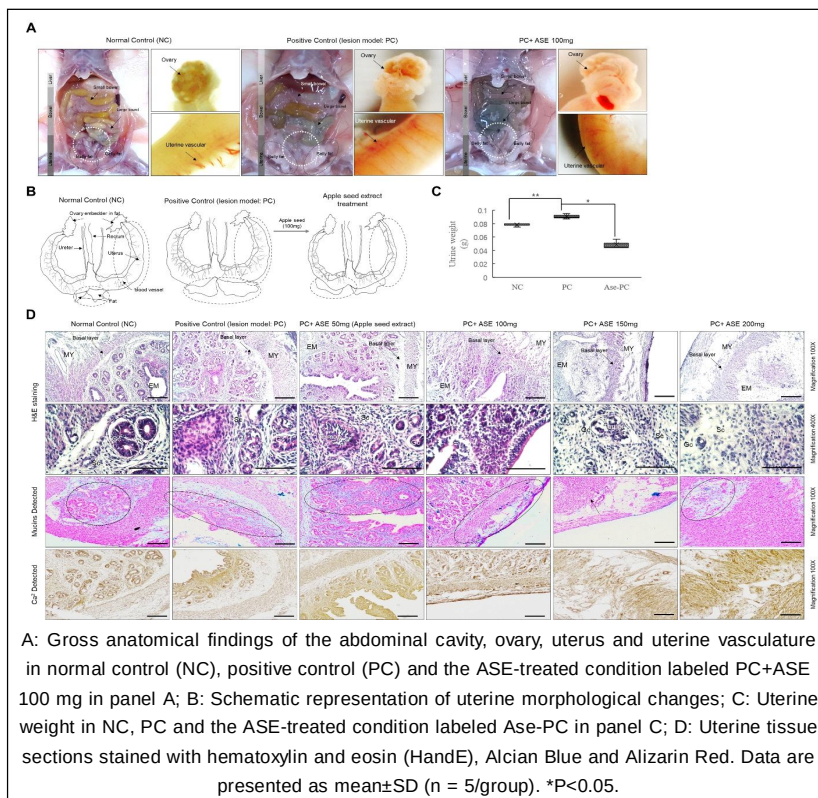


Fig 2: Gross and histological changes in the exploratory HCT116 exposure-based mouse uterine lesion-like model after ASE treatment.

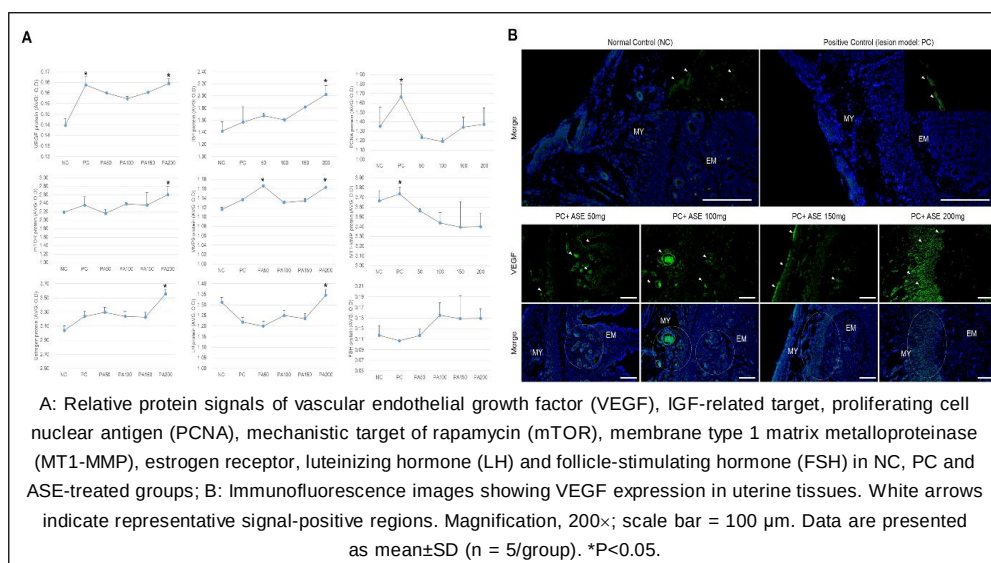


Fig 3: Protein-level changes in uterine tissues after ASE treatment in the exploratory mouse uterine lesion-like model.

increase and appeared enriched only in selected endometrial regions (Fig 4A). In the MY, Casp-3 and TNF- α signals were weaker than in the EM and were mainly localized near the EM-MY boundary. Quantitative fluorescence analysis confirmed higher Casp-3 intensity in the EM than in the MY after ASE treatment, whereas TNF- α intensity varied by region and treatment dose (Fig 4B). Together, these findings indicate that ASE-induced changes in Casp-3 and TNF- α distribution were more evident in the endometrium than in the myometrium.

Regulated apoptosis is essential for tissue homeostasis, whereas defective cell death contributes to abnormal cell survival and lesion progression (Morice *et al.*, 2016; Pistrutto *et al.*, 2016). The present study evaluated whether apple seed extract (ASE) modulates apoptosis-related responses in HCT116 cells and uterine tissues using an exploratory HCT116 exposure-based mouse uterine lesion-like model. Because this animal experiment was not designed as a validated endometrial cancer model, the findings are interpreted as cellular and uterine tissue responses under exploratory lesion-like conditions.

At the cellular level, ASE produced stronger morphological disruption and viability reduction than amygdalin, phlorizin, or their combined treatment. This response was accompanied by increased Casp-3 expression, decreased BCL-2 expression, altered TNF- α expression and changes in MMP activity. Amygdalin has been reported to show antiproliferative and apoptosis-related activities, but its biological effects remain controversial and are highly dependent on dose and model system (Jaszczak-Wilke *et al.*, 2021; Saleem *et al.*, 2018). Phlorizin-related dihydrochalcones have also been associated with inhibitory effects in cancer cell models (Qin *et al.*, 2015; Tian *et al.*, 2021). In this study, ASE produced a stronger response than amygdalin, phlorizin, or their combined treatment. Because ASE is a crude extract, this stronger response cannot be attributed to a single constituent and is more cautiously interpreted as a combined response to multiple apple seed-derived components. The apoptosis-related marker profile further supported the cellular response to ASE. ASE treatment produced clearer changes in Casp-3, Bax and Bcl-2 than in Casp-9, indicating that ASE was

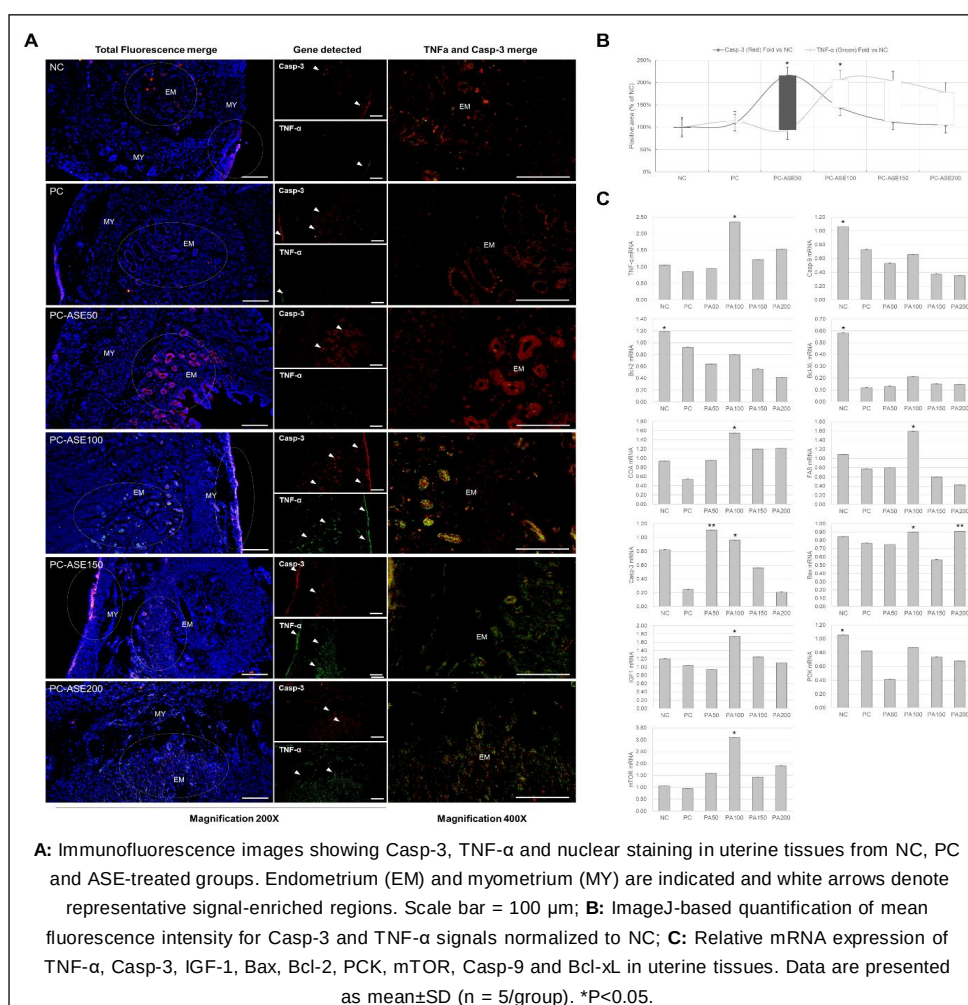


Fig 4: Effects of ASE on uterine gene expression and regional Casp-3/TNF- α protein distribution.

associated with apoptosis-related modulation but did not uniformly activate all measured apoptotic markers. The decrease in Bcl-2 together with increased Bax and Casp-3 is consistent with a shift toward a pro-apoptotic cellular state (Kharat *et al.*, 2024), although the present data do not establish a complete upstream pathway. Therefore, the results should be interpreted as marker-level evidence of apoptosis-related response rather than definitive proof of a specific apoptotic cascade.

In the animal model, the PC group showed increased uterine weight, endometrial structural abnormalities and altered peri-uterine tissue features compared with the NC group. ASE treatment reduced uterine weight gain and attenuated histological abnormalities, particularly in the endometrial region. These changes were accompanied by decreased PCNA expression and altered MT1-MMP expression, suggesting reduced proliferative and tissue-remodeling activity in ASE-treated uterine tissues. The regional immunofluorescence results further showed that Casp-3 and TNF- α changes were more evident in the endometrium than in the myometrium, indicating that the endometrium was the main uterine region affected under the present experimental conditions (Kim *et al.*, 2020; Kim, 2022).

VEGF and mTOR showed variable dose- and region-dependent responses rather than a uniform decrease. VEGF is closely related to vascular remodeling and tumor-associated angiogenic responses (Otrock *et al.*, 2007; Roskoski, 2007), but the present findings do not support a simple anti-angiogenic interpretation. Instead, the altered VEGF distribution between the endometrium and myometrium suggests that ASE may influence regional vascular or tissue-remodeling responses in a context-dependent manner. Similarly, the variable mTOR response indicates that ASE-associated tissue changes were not driven by a single linear survival pathway.

Overall, ASE induced stronger apoptosis-related changes than the single apple seed constituents in HCT116 cells and was associated with reduced uterine enlargement, improved histological appearance, decreased PCNA expression, increased Bax expression, reduced Bcl-2 expression and endometrium-dominant Casp-3 distribution in the mouse model. These findings support the interpretation that ASE modulates apoptosis-related cellular and uterine tissue responses under the present experimental conditions. Further validation using established uterine or endometrial cancer models will be required to clarify the tissue-specific mechanisms and active constituents responsible for these effects.

CONCLUSION

This study showed that apple seed extract (ASE) induced stronger apoptosis-related responses than amygdalin or phlorizin alone in HCT116 cells, as reflected by reduced cell viability, increased Casp-3 expression, decreased BCL-2 expression and altered MMP activity. In the exploratory

HCT116 exposure-based mouse uterine lesion-like model, ASE reduced uterine weight gain, attenuated histological abnormalities, decreased PCNA expression, increased Bax expression, reduced Bcl-2 expression and altered Casp-3/TNF- α distribution mainly in the endometrium. These findings suggest that ASE modulates apoptosis-related cellular and uterine tissue responses under the present experimental conditions. Further studies using validated uterine disease models are needed to clarify the active constituents and mechanisms of ASE.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily reflect those of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided but disclaim any liability for any direct or indirect losses resulting from the use of this content.

Ethical approval

All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC 2024-4) of Hankyong National University.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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