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In vitro cytotoxic and apoptosis-related effects of Liquidambar orientalis storax on MDAH-2774 human ovarian cancer cells

Eurasian Clinical and Analytical Medicine Original Research

L. orientalis storax and ovarian cancer

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Abstract

Aim: Liquidambar orientalis Miller (Altingiaceae) is a relict endemic tree whose resinous exudate, storax, is traditionally used for antiseptic and wound-healing purposes; however, its activity against gynecological cancers is poorly characterized. This study evaluated the cytotoxic, anti-invasive, and apoptosis-related effects of L. orientalis storax on MDAH-2774 human ovarian cancer cells.

Methods: Cell viability was assessed using the XTT assay. Clonogenic survival, migration, and invasion were evaluated using colony formation, wound-healing, and Matrigel invasion assays. Apoptosis was examined by TUNEL staining, and the expression of apoptosis- and cell cycle–related genes was analyzed by quantitative real-time PCR.

Results: The storax preparation reduced cell viability across the tested concentrations and exposure times, with a 24-h IC_{50} of 32.34 μg/mL. Treatment decreased colony formation by 24.5% and reduced the invasion rate from 72.4% to 38.4%, while wound-healing assays showed marked suppression of migration. The apoptotic index increased from 3.02% to 11.00%. Storax significantly upregulated the pro-apoptotic and death-receptor genes APAF1, BID, CASP10, FADD, FAS, TNF, and TRADD, and downregulated the anti-apoptotic gene BCL-XL.

Conclusion: L. orientalis storax preparation was associated with reduced cell viability, clonogenic growth, migration, and invasion in MDAH-2774 cells, along with an apoptosis-related response. These in vitro findings support further investigation of its selectivity and underlying mechanisms.

Keywords

apoptosis, cytotoxicity, Liquidambar orientalis, ovarian neoplasms, plant extracts

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Introduction

Ovarian cancer is the most lethal malignancy of the female reproductive tract, largely because it progresses silently and is often diagnosed at an advanced stage.[1] Despite standard surgery and platinum-based chemotherapy, disease recurrence remains a major clinical problem. Multidrug resistance further limits treatment success and contributes to mortality in advanced-stage disease.[2] Therefore, new agents capable of limiting tumor growth and metastatic progression are still needed, particularly for treatment-refractory disease.

Natural products remain an important source of compounds for anticancer drug discovery. Liquidambar orientalis Mill. (Altingiaceae), a Tertiary relict tree endemic to southwestern Anatolia and the Eastern Mediterranean, is of particular ethnopharmacological interest.[3] Its resin, storax (locally "sığla yağı"), has traditionally been used for chronic wounds, inflammatory skin lesions, and infections.[4,5] Experimental studies have also reported antibacterial, anti-inflammatory, and antioxidant activities of storax and its major cinnamate derivatives.[6,7] Because chronic inflammation, impaired apoptosis, and increased migration and invasion contribute to tumor progression, the traditional use of storax in inflammatory and tissue-repair disorders provides a rationale for investigating its effects on cancer-related processes.

Cytotoxic and apoptosis-modulating effects have been reported for other Liquidambar species and extracts,[8-10] but the antitumor activity of L. orientalis storax in gynecological cancers remains largely unexplored. This study therefore evaluated its in vitro effects on MDAH-2774 human ovarian cancer cells, focusing on viability, clonogenic growth, migration, invasion, apoptosis, and the expression of genes involved in intrinsic and extrinsic apoptotic signaling.

Materials and Methods

Plant Material and Preparation

Voucher specimens of Liquidambar orientalis were deposited in the Pamukkale University Chemical Ecology Laboratory Herbarium (accession no. GSE2557), and the plant material was taxonomically identified by co-author and botanist Prof. Gürkan Semiz. The resinous exudate (storax) of L. orientalis was collected from naturally growing trees in Köyceğiz (Muğla, Türkiye) and supplied by a producer licensed by the Turkish Ministry of Agriculture and Forestry. Traditional harvesting and production have been described previously.[6] A single batch of storax was used throughout all experiments and was stored at 4 °C in the dark.

Storax was dissolved in cold-pressed extra-virgin olive oil (Muğla, Türkiye; acidity <0.8%) to prepare a 100 mg/mL stock solution, diluted in DMEM (Gibco, USA) to 1 mg/mL, and sterilized through a 0.22 μm filter. Aliquots were stored in amber vials at 4 °C, and working solutions were freshly prepared before each experiment. The estimated olive-oil concentration in the culture medium ranged from approximately 0.01% to 0.50% (v/v) across the storax concentrations used in the XTT assay. At the 32.34 μg/mL dose used in the subsequent assays, the olive-oil concentration was approximately 0.032% (v/v). No concentration-matched olive-oil vehicle control was included, and untreated cells were used as controls. The storax batch used in this study had previously been characterized by GC–MS, as reported by Mutlu et al.;[11] therefore, no additional chemical analysis was performed.

Cell Culture and Treatments

MDAH-2774 human ovarian carcinoma cells (RRID: CVCL_0420; ATCC, Manassas, VA, USA) were cultured in DMEM supplemented with 10% heat-inactivated fetal bovine serum and antibiotics (20 U/mL penicillin and 20 μg/mL streptomycin) at 37 °C in 5% CO_2. Third-passage cells were used. Storax was freshly diluted in complete DMEM and applied at 10, 25, 35, 50, 75, 100, and 500 μg/mL for 24, 48, or 72 h.

Cell Viability Assay

Cell viability and the half-maximal inhibitory concentration (IC_{50}) were assessed using the XTT assay. Cells were seeded in 96-well plates at 1 × 10^4 cells/well, allowed to attach, and treated with storax for 24, 48, or 72 h. Untreated cells served as controls. XTT reagent was added according to the manufacturer's instructions and incubated for 4 h at 37 °C. Absorbance was measured at 450 nm using a microplate reader (BioTek Instruments, Winooski, VT, USA). The experiment was repeated three times.

Viability (%) = (Absorbance_treated / Absorbance_control) × 100

Colony Formation Assay

Logarithmically growing cells were detached with trypsin–EDTA, checked by trypan blue exclusion, and seeded at 1 × 10^3 cells/well in six-well plates in DMEM with 10% FBS. Cultures were maintained for 14–21 days with medium changed every 3 days. Once colonies of at least 50 cells formed, plates were fixed with cold methanol (10 min), stained with 0.5% crystal violet (15 min), and counted manually under a light microscope. The experiment was repeated three times.

Matrigel Invasion Assay

Invasion was assessed with Matrigel-coated transwell inserts (Thermo Scientific). MDAH-2774 cells (2 × 10^5) in serum-free DMEM were added to the upper chamber, while the lower chamber contained DMEM with 10% FBS as chemoattractant. After 24 h at 37 °C, non-invading cells on the upper surface were removed; cells that had crossed the Matrigel were fixed with cold methanol (10 min), stained with crystal violet, and counted in five random fields per insert. The experiment was repeated three times. Invasion was expressed relative to control inserts:

Invasion (%) = (N_Matrigel / N_control) × 100

where N_Matrigel and N_control are the numbers of invaded cells on Matrigel-coated and control inserts, respectively.

Wound Healing (Scratch) Assay

Cells were seeded in 60 × 15 mm dishes (1 × 10^6 cells/dish) and grown to ~90% confluence. A linear wound was made with a sterile 200 μL pipette tip, and detached cells were rinsed off with serum-free DMEM. Cells were then exposed to storax at the IC_{50} concentration (32.34 μg/mL) for 24 h. Images were captured immediately after scratching (0 h) and at 24 h. The experiment was repeated three times.

TUNEL Assay

Apoptosis was further assessed with the Cell Meter TUNEL Apoptosis Assay Kit (cat. no. 22844). Treated cells were fixed in 4% paraformaldehyde and processed per the kit protocol to detect DNA fragmentation, with Hoechst counterstaining of nuclei. Signals were examined on an Olympus fluorescence microscope (Tokyo, Japan). The apoptotic index was calculated as the percentage of TUNEL-positive nuclei among total nuclei in ten random fields per sample.

RNA Isolation, cDNA Synthesis, and Quantitative RT-PCR

After treatment at the IC_{50} concentration, total RNA was extracted with Trizol (Invitrogen, USA) and reverse-transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA). A panel of apoptosis- and cell cycle–related genes was analyzed. Cell cycle regulators: CDK2, CDK4, CDK6, CCND1, CCND2, RB1, CDKN1A (p21), and CDKN2A (p16). Apoptotic genes: CASP3, CASP8, CASP9, CASP10, BID, BCL-XL, BCL2, DR4, DR5, FAS, FADD, TNF, TRADD, APAF1, BAX, PUMA, and NOXA. Reactions used the SYBR Green PCR Kit (Thermo Scientific, USA) with gene-specific primers, and β-actin served as the housekeeping control. Primer sequences are given in Supplementary Table S1.

Ethical Approval

Ethics committee approval was not required because this in vitro study used a commercially available cell line and involved no human participants or animals.

Statistical Analysis

The effects of storax concentration and exposure time on cell viability were evaluated using two-way analysis of variance, followed by Tukey's multiple-comparison test. Differences in colony number, invasion rate, wound-closure percentage, and apoptotic index between untreated control and storax-treated cells were assessed using independent-samples Student's t-tests. The 24-h IC_{50} value was calculated from the concentration–response curve using GraphPad Prism 8. Relative gene expression was determined using the comparative Ct ($2^{-\Delta\Delta Ct}$) method after normalization to β-actin. For each gene, expression levels in the control and storax-treated groups were compared using Student's t-test in the RT^2 Profiler PCR Array Data Analysis platform. All experiments were repeated three times, and the results are presented as mean ± standard deviation. Additional statistical analyses were carried out using IBM SPSS Statistics version 25.0. Statistical significance was set at $P < .05$.

Reporting Guidelines

No specific reporting guideline was applicable to this in vitro experimental study.

Results

Cytotoxic Activity of Storax on MDAH-2774 Cells

Storax preparation reduced MDAH-2774 viability across 10–500 μg/mL at 24, 48, and 72 h (Figure 1A). At 24 h, viability generally decreased with increasing dose, reaching about 50% at 35 μg/mL. The effect was stronger at 48 h, where 35 μg/mL lowered viability to roughly 20%. At 72 h, viability recovered somewhat at lower concentrations, but the inhibitory trend persisted at higher doses. The apparent IC_{50} at 24 h, calculated in GraphPad Prism 8, was 32.34 μg/mL, and this concentration was used as the standard dose in all subsequent assays.

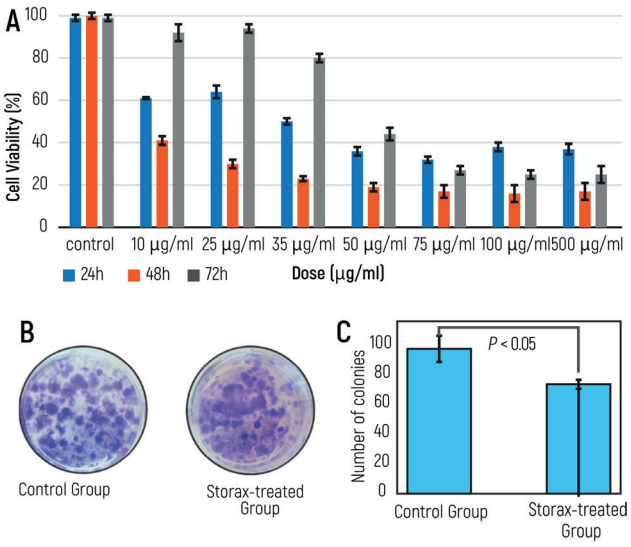


Figure 1. Effects of Liquidambar orientalis storax on cell viability and colony formation in MDAH-2774 cells.

(A) Cells were treated with 10–500 μg/mL storax for 24, 48, or 72 h, and cell viability was measured using the XTT assay. (B) Representative crystal violet–stained colonies from control and storax-treated groups after treatment at the 24-h IC_{50} concentration of 32.34 μg/mL. (C) Colony numbers decreased from 98.0 ± 9.0 in controls to 74.0 ± 3.0 after storax treatment. Data are presented as mean ± SD from three repeated experiments; $P < .05$ versus control.

Effects of Storax On Colony Formation

Colony formation was lower in cells exposed to the storax preparation than in untreated controls (Figure 1B–C). Colony numbers fell from 98.0 ± 9.0 in controls to 74.0 ± 3.0 at the IC_{50} concentration ($P < .05$), a 24.5% reduction. Treated colonies were also smaller and less compact, indicating reduced proliferative capacity among surviving cells.

Effects of Storax On Cell Invasion

In the Matrigel transwell assay, the invasion rate decreased from 72.4 ± 6.1% in untreated control cells to 38.4 ± 4.2% in cells exposed to the storax preparation at the IC_{50} concentration (Figure 2A–B; $P < .05$), corresponding to an approximately 47% decrease in invasion rate.

Effects of Storax On Cell Migration (Wound-Healing Assay)

Storax preparation also delayed wound closure. Control cultures nearly complete wound closure within 24 h, whereas wound closure was 41.2 ± 5.3% lower in treated group ($P < .05$), consistent with the reduced invasion seen in the Matrigel assay.

Pro-apoptotic Effect of Storax On MDAH-2774 Cells

TUNEL staining showed a clear rise in apoptotic nuclei after treatment, with DNA fragmentation and condensed chromatin typical of apoptosis (Figure 2C). The apoptotic index increased from 3.02 ± 1.02% in controls to 11.00 ± 1.20% (Figure 2D; $P < .05$). This nearly fourfold increase supports an apoptosis-related contribution to the observed reduction in cell viability.

Gene Expression Analysis of Cell Cycle and Apoptosis-Related Genes

To probe the underlying mechanisms, mRNA levels of apoptosis- and cell cycle–related genes were measured by RT-qPCR. Cell cycle regulators (CCND1, CDK2, CDK4, CDK6, and RB1) and several apoptosis-related genes (CASP3, CASP8, CASP9, DR4, DR5, BAX, PUMA, and NOXA) showed no significant change ($P > .05$; Supplementary Table S2). By contrast, eight apoptosis-related genes were significantly altered. Seven were upregulated, whereas BCL-XL was downregulated. ($P < .05$; Table 1). The pro-apoptotic and death-receptor genes APAF1 (8.71-fold), BID (15.46-fold), CASP10 (15.47-fold), FADD (2.89-fold), FAS (5.05-fold), TNF (8.25-fold), and TRADD (3.46-fold) were upregulated, whereas the anti-apoptotic gene BCL-XL was downregulated (−5.61-fold). These transcriptional changes were consistent with death receptor–related signaling and possible mitochondrial involvement; however, they did not establish direct pathway activation.

Table 1. mRNA expression changes in apoptosis-related genes in MDAH-2774 cells following storax treatment.

Gene	Description	Fold regulation	*P* value*
β-actin	Beta-actin	1	
APAF1	Apoptotic peptidase activating factor 1	8.7099	.04
BCL-XL	B-cell lymphoma-extra large	-5.6101	.02
BID	BH3 interacting domain death agonist	15.4591	.047
CASP10	Caspase 10, apoptosis-related cysteine peptidase	15.4659	.041
FADD	Fas (TNFRSF6)-associated via death domain	2.8869	.038
FAS	Fas (TNF receptor superfamily, member 6)	5.0488	.005
TNF	Tumor necrosis factor	8.24719	.044
TRADD	TNFRSF1A-associated via death domain	3.4607	.026

*P value less than .05 ($P < .05$) is statistically significant. Fold-regulation values represent mRNA expression relative to untreated controls. β-actin was used for normalization.

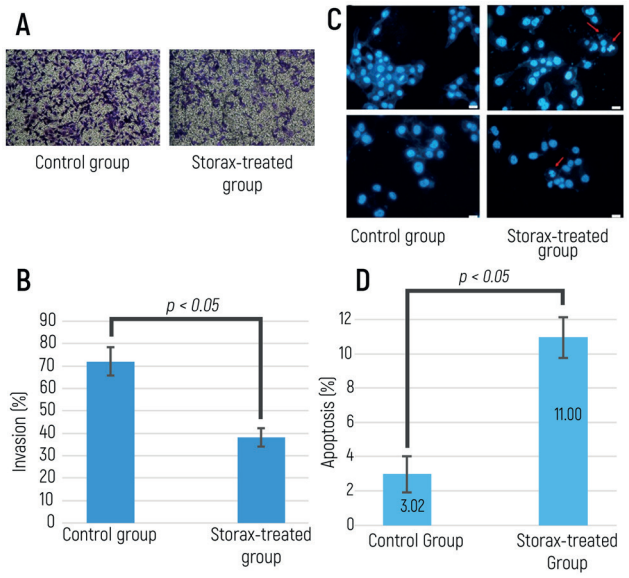


Figure 2. Effects of Liquidambar orientalis storax on invasion and apoptosis in MDAH-2774 cells.

(A) Representative images of crystal violet–stained cells that invaded through the Matrigel-coated membrane in control and storax-treated groups. (B) Storax treatment at the 24-h IC_{50} concentration reduced the invasion rate from 72.4 ± 6.1% to 38.4 ± 4.2%. (C) Representative TUNEL fluorescence images of control and storax-treated cells at 20× magnification. Arrows indicate TUNEL-positive nuclei. (D) The apoptotic index increased from 3.02 ± 1.02% in controls to 11.00 ± 1.20% after storax treatment. Data are presented as mean ± SD from three repeated experiments; $P < .05$ versus control.

Discussion

To our knowledge, this is one of the first studies to evaluate the effects of Liquidambar orientalis storax in an ovarian cancer cell model. Storax reduced cell viability, colony formation, migration, and invasion in MDAH-2774 cells, while increasing the number of TUNEL-positive cells. The accompanying gene-expression changes were also consistent with an apoptosis-related response. Together, these findings suggest that storax not only decreases cell survival but also limits several cellular behaviors associated with tumor progression.

The 24-h IC_{50} was 32.34 µg/mL. This value is close to the 28–43 µg/mL range reported for L. orientalis leaf extracts in colorectal cancer cells,[12] but lower than the approximately 125 µg/mL reported for resin-treated HEp-2 cells.[13] Such differences may reflect the cell line, preparation method, chemical composition, exposure time, or assay used. At 72 h, viability partly recovered at lower concentrations. This may be related to loss or degradation of active constituents during prolonged incubation, but this possibility was not tested and should be interpreted cautiously.

The storax batch used in this study had previously been characterized by GC–MS. Ethyl cinnamate and cinnamyl cinnamate were the main volatile components.[11] Cinnamic acid derivatives have been linked to antiproliferative and apoptosis-related effects in several experimental models.[14] These compounds may therefore contribute to the activity observed here. However, storax is a complex mixture, and the present study cannot identify which component, or combination of components, produced these effects.

Apoptosis appeared to be an important part of the cellular response to storax. BCL-2 family proteins largely regulate mitochondrial apoptosis, while caspases mediate the later stages of programmed cell death.[15] In our study, the apoptotic index increased from 3.02% in controls to 11.00% after storax treatment. APAF1, BID, CASP10, FADD, FAS, TNF, and TRADD were upregulated, whereas the anti-apoptotic gene BCL-XL was downregulated. In contrast, the main cell-cycle genes examined did not change significantly.

This expression pattern is consistent with death receptor–related apoptosis and possible mitochondrial involvement. FAS, FADD, TNF, TRADD, and CASP10 are associated with death receptor signaling, whereas BID may connect this pathway with mitochondrial apoptosis. Increased APAF1 expression and reduced BCL-XL expression may also favor an apoptotic response. Nevertheless, these results show transcriptional changes rather than direct pathway activation. TUNEL staining and RT-qPCR cannot confirm changes in protein expression, caspase activity, or the exact sequence of signaling events.

The findings are also consistent with studies of related Liquidambar species. Triterpenoids from L. formosana induced apoptosis in hepatocellular carcinoma cells through PI3K–AKT-related and mitochondrial signaling.[10] The present study extends this limited evidence to L. orientalis storax and ovarian cancer cells, although direct comparisons are difficult because the plant species, preparations, and tumor models differ.

Storax reduced Matrigel invasion from 72.4% to 38.4%, delayed wound closure, and decreased colony formation by 24.5%. These results suggest reduced motility, invasive capacity, and long-term proliferative survival. Migration and invasion are important steps in metastatic progression.[16] However, these assays were performed at the 24-h IC_{50} concentration, and reduced viability may have contributed to the lower migration and invasion values. Studies using subcytotoxic concentrations and parallel proliferation controls are needed to determine whether storax directly affects cell motility.

Limitations

This study has several limitations. Only one ovarian cancer cell line was used, and no non-tumorigenic ovarian epithelial control was included; therefore, selective toxicity remains unknown. A concentration-matched olive-oil vehicle control was not included. Therefore, a possible contribution of the vehicle to the observed effects, particularly at the higher concentrations used in the XTT assay, cannot be excluded. The estimated olive-oil concentration at the 32.34 µg/mL dose used in the subsequent assays was approximately 0.032% (v/v), but its independent effect was not assessed. Apoptosis was evaluated mainly by TUNEL staining and RT-qPCR, without protein analysis, caspase-activity assays, flow cytometry, or pathway-inhibition experiments. In addition, the in vitro model cannot reproduce metabolism, bioavailability, stromal interactions, or the tumor microenvironment. Validation in additional ovarian cancer models, normal-cell controls, matched vehicle controls and in vivo systems is required.

Conclusion

Liquidambar orientalis storax preparation was associated with reduced viability, clonogenic growth, migration, and invasion in MDAH-2774 ovarian cancer, along with an increased apoptosis and apoptosis-related gene changes. These findings provide preliminary evidence of anticancer activity, but further studies are needed to confirm its selectivity, mechanism, and in vivo relevance.

Declarations

Animal and Human Rights Statement

No animal or human studies were carried out by the authors for this article.

Informed Consent

Informed consent was not required for this study, as no human participants, patient data, or identifiable personal information were included.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare that there is no conflict of interest.

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Data Curation: C.K., M.S.
Writing – Original Draft Preparation: C.K., M.S., G.S., A.F.
Writing – Review & Editing: C.K., M.S., U.C., N.C., G.S., A.F.
All authors read and approved the final version of the manuscript.

Abbreviations
ATCC: American type culture collection
DMEM: Dulbecco's modified eagle medium
FBS: Fetal bovine serum
GC–MS: Gas chromatography–mass spectrometry
IC_{50}: Half-maximal inhibitory concentration
RT-qPCR: Reverse transcription quantitative polymerase chain reaction
TUNEL: Terminal deoxynucleotidyl transferase dutp nick-end labeling
XTT: Tetrazolium-based cell viability assay

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