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Cytotoxic activity of *Scrophularia variegate* extract against human prostate and ovarian cancer cell lines: An initial evaluation of antimicrobial properties

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Abstract

Background and Aims: Species within the genus *Scrophularia* are recognized in traditional medicine for their anti-inflammatory potential. *Scrophularia variegata*, in particular, has been historically employed for this purpose. This study sought to systematically evaluate the cytotoxic potential of a *S. variegate* extract against human prostate (PC3) and ovarian (SKOV3) adenocarcinoma cell lines, alongside a preliminary assessment of its antimicrobial activity against clinically relevant resistant strains.

Methods: Cytotoxicity was quantified via the MTT assay following exposure of PC3 and SKOV3 cells to the extract. Antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* was determined using standardized micro-broth dilution and disk diffusion methods.

Results: The *S. variegate* extract demonstrated a concentration-dependent cytotoxic effect on both PC3 and SKOV3 cell lines, significantly reducing cell viability. In contrast, the extract did not exhibit measurable antibacterial activity against the tested resistant bacterial strains at the concentrations employed.

Conclusion: Our findings indicate that *Scrophularia variegate* possesses pronounced cytotoxic activity against two distinct human cancer cell lines in vitro, suggesting its constituents may warrant further investigation as potential anticancer agents. The lack of observed antibacterial activity against resistant pathogens, however, highlights the specificity of its biological effects. Future studies are required to isolate the active cytotoxic compounds and elucidate their mechanisms of action.

Keywords: *Scrophularia variegate*, Phytochemicals, Cytotoxicity, Prostate cancer, Ovarian cancer.

Introduction

Reproductive cancers, including prostate cancer in men and ovarian cancer in women, represent a preeminent global cause of cancer-related mortality.[1] Ovarian cancer carries a particularly grave prognosis, with case-fatality rates exceeding those of breast cancer; this high lethality is often attributed to its frequently asymptomatic progression and late-stage diagnosis.[2] Similarly, prostate cancer is associated with significant mortality, largely due to its propensity for metastatic dissemination to sites such as bone and brain -a trait that underscores its characterization as a 'silent killer'.[3] Projections indicate a marked increase in the mortality burden of these malignancies by 2040, highlighting an urgent need for novel therapeutic strategies.[1]

Current standard treatments, including chemotherapy

and radiotherapy, are frequently compromised by debilitating side effects such as profound fatigue, myelosuppression, and opportunistic infections.[4] Consequently, the search for safer, more tolerable agents has intensified. Natural products and medicinal plants offer a promising avenue, having long served as a cornerstone for drug discovery due to their structural diversity and favorable safety profiles.[5] Indeed, several cornerstone chemotherapeutic agents, including vinca alkaloids and taxanes, are plant-derived.[6-10] The reduced toxicity often observed with crude plant extracts may stem from synergistic interactions among their complex phytochemical constituents.[5] These bioactive compounds -alkaloids, flavonoids, terpenoids, and phenolics- underpin the pharmacological value of traditional botanicals.

The genus *Scrophularia* is a rich source of such compounds, notably phenolics, flavonoids, and phenylpropanoids.[11] Various *Scrophularia* species have documented applications in traditional medicine for conditions ranging from eczema and psoriasis to inflammatory disorders and tumors.[13] Modern research supports these uses, revealing anti-inflammatory, immunomodulatory, and anticancer activities linked to mechanisms such as the inhibition of pro-inflammatory cytokines (e.g., TNF-α, IL-1) and matrix metalloproteinases.[11] For instance, *Scrophularia variegate* has been shown to induce apoptosis in breast cancer cells via the mitochondrial pathway.[11]

Despite this progress, the specific cytotoxic potential of *S. variegate* against prostate and ovarian cancers remains unexplored. Furthermore, given its traditional use in managing infectious diseases, the extract may also possess antimicrobial properties -an area warranting investigation against resistant pathogens.

Objectives

Therefore, this study was designed to evaluate the cytotoxic effects of a *Scrophularia variegate* extract on human prostate (PC3) and ovarian (SKOV3) cancer cell lines, while concurrently assessing its antibacterial activity against resistant strains of *Staphylococcus aureus* and *Escherichia coli*. Our work aims to contribute empirical evidence on the therapeutic potential of this plant, focusing on two clinically significant cancer types.

Methods

Plant Material and Extract Preparation

Leaves and roots of *Scrophularia variegate* were thoroughly rinsed with distilled water and air-dried in the shade at ambient laboratory temperature for ten days. The dried material was pulverized using an electric mill. A maceration process was then performed by soaking 100 g of the powdered plant in 350 ml of 70% ethanol for seven days, with intermittent agitation. The mixture was subsequently transferred to a percolator, and an additional 150 ml of 70% ethanol was added. The combined ethanolic percolate was collected and concentrated under reduced pressure at 40°C using a rotary evaporator (Heidolph, Germany), yielding a viscous, blackish-green residue. This crude extract was filtered through Whatman No. 1 filter paper and centrifuged at 4,000 × g for 15 minutes to remove particulate matter. The supernatant was then passed through a 0.22 µm cellulose acetate syringe filter (Membrane Solutions, USA). The resulting aqueous filtrate, constituting the final working extract, was stored at -20°C until use.

Cell Culture

The human ovarian adenocarcinoma cell line SKOV3 and the human prostate adenocarcinoma cell line PC3 were obtained as a generous gift from the Neuroscience Research Center of Iran University of Medical Sciences (original source: Pasteur Institute of Iran, Tehran). Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 IU/ml penicillin, and 100 µg/ml streptomycin. Cultures were incubated at 37°C in a humidified atmosphere of 5% CO_2. Cells were sub-cultured bi-weekly upon reaching 80-90% confluence using a cell scraper. For experiments, cells were seeded into 96-well plates at a density of 5×10^4 cells/ml and allowed to adhere for 24 hours prior to treatment [Figure 1].

Assessment of Cytotoxicity

The cytotoxic effects of the *S. variegate* extract on PC3 and SKOV3 cell lines were evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, which measures mitochondrial

dehydrogenase activity in viable cells. Cells were seeded in 96-well plates (15,000 cells/well in 100 µl medium) and incubated for 24 hours to form a monolayer. The culture medium was then aspirated and replaced with fresh medium containing serial dilutions of the extract (1.1, 10.2, 4.10, 6.10, and 8.10 µg/ml, prepared from a 10 mg/ml stock). Following a 24-hour incubation, the treatment medium was removed, and cells were washed once with phosphate-buffered saline (PBS). Subsequently, 100 µl of MTT solution (0.5 mg/ml in PBS) was added to each well, and plates were incubated for 3 hours at 37°C. The formazan crystals formed were solubilized by adding 100 µl of a solution containing 50% DMSO and 50% isopropanol, followed by gentle shaking for 15 minutes. Absorbance was measured at 570 nm using a microplate reader (BioTek, USA). Wells containing culture medium alone served as blanks, and wells with untreated cells served as viability controls (100%). Cell viability was calculated as: (Mean OD of treated well / Mean OD of control well) × 100.

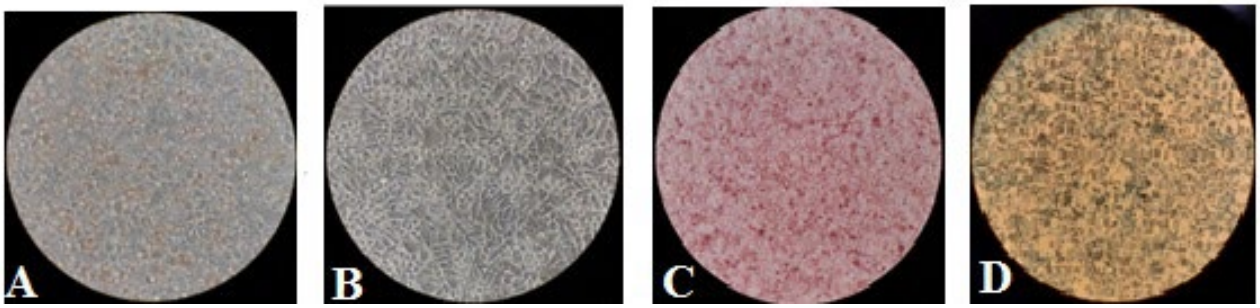

Figure 1. Representative microscopy of cell culture conditions. A) Cells treated with S. variegata extract in a 96-well plate. B) Untreated control cells. C) Uptake of neutral red dye by viable cells. D) Formation of purple formazan crystals following MTT reduction in viable cells.

Antibacterial Activity Assays

Disk Diffusion Method

Clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* were used. A bacterial suspension equivalent to a 0.5 McFarland standard (approximately 1.5×10^8 CFU/ml) was prepared in sterile saline and uniformly swabbed onto Mueller-Hinton agar plates. Sterile 6 mm blank paper disks were impregnated with 20 µl of the *S. variegate* extract (100 mg/ml) and placed onto the inoculated agar. Commercially available antibiotic disks (oxacillin for S. *aureus*, cefotaxime for *E. coli*) served as controls. Plates were incubated at 37°C for 18-24 hours. The diameter of the inhibition zones (including disk diameter) was measured in millimeters and interpreted according to CLSI (2016) guidelines.

Broth Microdilution for MIC and MBC Determination

The minimum inhibitory concentration (MIC) was determined using a standard broth microdilution method in 96-well plates. Briefly, a two-fold serial dilution of the extract was prepared in Mueller-Hinton broth across wells 1 to 11 (final volume 100 µl/well). Each well was then inoculated with 100 µl of bacterial suspension standardized to 5×10^5 CFU/ml (final inoculum ~5×10^5 CFU/well). Well 12 contained only broth and served as a sterility control. Positive growth controls consisted of broth with bacteria but no extract. Plates were incubated at 37°C for 24 hours without agitation. The MIC was defined as the lowest concentration of extract that prevented visible turbidity. To determine the minimum bactericidal concentration (MBC), 50 µl from each clear well and the first two turbid wells were sub-cultured onto fresh Mueller-Hinton agar plates and incubated for 24 hours at 37°C. The MBC was defined as the lowest extract concentration that resulted in ≥99.9% killing of the initial inoculum (no colony growth on subculture).

Statistical analysis

All cytotoxicity experiments were performed in triplicate and repeated independently at least three times. Data are presented as mean±SD. Statistical significance between treatment groups and the untreated control was determined using ANOVA followed by Dunnett's post hoc test for multiple comparisons. A p-value of≤0.05 was considered statistically significant. All analyses were conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical considerations

All experimental procedures involving cell lines were approved by the Institutional Animal Care and Use Committee of Iran University of Medical Sciences (Ethical Code: IR.IUMS.REC.1397.659).

Results

Cytotoxicity level on prostate cancer cell line

The *Scrophularia variegate* extract elicited a concentration-dependent cytotoxic response in PC3 prostate cancer cells, as assessed by the MTT assay [Figure 2]. Interestingly, at the two lowest dilutions tested (2/10 and 4/10), cell viability was significantly increased compared to the untreated control ($p<0.001$). The 4/10 dilution resulted in the highest viability (121.48 ± 3.06%), suggesting a potential proliferative or cytoprotective effect at these lower concentrations. This stimulatory effect was not sustained at higher concentrations. A pronounced and statistically significant decrease in viability was observed beginning at the 8/10 dilution (81.89 ± 3.52%, $p<0.001$), with the highest tested concentration (1/1) reducing viability to 33.25 ± 2.33% ($p<0.001$) [Table 1].

Table 1. Toxicity test results for SKOV3 ovarian cell line and PC3 prostate cell line using the neutral red method

Drug	SKOV3 cells			PC3 cells		
Concentration	Cell viability (%)	p (Dunnett's)	p (ANOVA)	Cell viability (%)	p (Dunnett's)	p (ANOVA)
Control	100	-	<0.001	100	-	<0.001
2/10	111.73 ± 10.18	0.621		117.12 ± 0.71	<0.001	
4/10	50.87 ± 11.68	0.001		121.48 ± 3.06	<0.001	
6/10	56.63 ± 13.29	0.003		111.24 ± 4.30	0.001	
8/10	64.48 ± 16.37	0.011		81.89 ± 3.52	<0.001	
1/1	79.83 ± 11.03	0.184		33.25 ± 2.33	<0.001	

* Significant difference compared to the control group

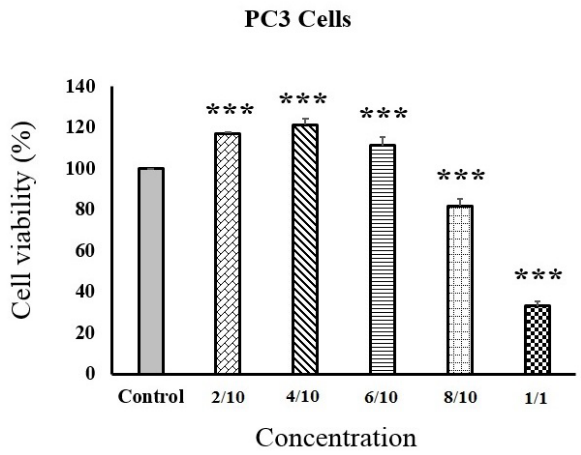

Figure 2. The concentration-response tests of Scrophularia variegata on PC3 human cancer cell line viability. The cell viability was determined by MTT assay. Data are presented as means ± SEM. *P<0.05, **P<0.01, ***P<0.001

3.2. Cytotoxicity level on ovarian cancer cell line

The extract demonstrated a more conventional cytotoxic profile against SKOV3 ovarian cancer cells [Figure 3]. The 2/10 dilution showed a non-significant increase in viability to 111.73 ± 10.18% ($p = 0.621$). However, all subsequent higher concentrations significantly reduced cell survival. The most potent effect was observed at the 4/10 dilution, which decreased viability by approximately 50% (50.87 ± 11.68%, $p = 0.001$). While the highest concentration (1/1) also reduced viability (79.83 ± 11.03%), this effect did not reach statistical significance against the control for this cell line ($p = 0.184$) [Table 1].

3.3. Antiseptic effects results

The extract was evaluated for activity against resistant clinical isolates of *Staphylococcus aureus* (MRSA) and *Escherichia coli* (ESBL-positive). In the disk diffusion assay, no zone of inhibition was observed around disks impregnated with the extract for either bacterial strain. This lack of activity was confirmed using the broth microdilution method, where visible turbidity, indicating bacterial growth, was present in all wells containing the extract across the tested concentration range. Consequently, no minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) could be determined. Together, these results indicate that the aqueous-ethanolic extract of *S. variegate* possesses no detectable antibacterial activity against the multidrug-resistant bacterial strains used in this study.

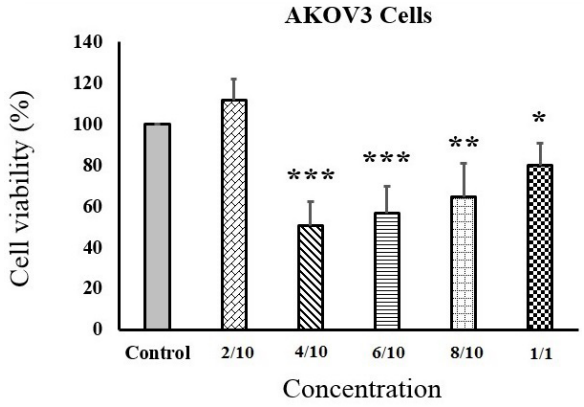

Figure 3. The concentration-response tests of Scrophularia variegata on SKOV3 human cancer cell line viability. The cell viability was determined by MTT assay. Data are presented as means ± SEM. *P<0.05, **P<0.01, ***P<0.001

Discussion

The present study evaluated the biological activity of an aqueous-ethanolic extract of *Scrophularia variegata*. Our primary finding is the concentration-dependent cytotoxic effect of this extract against two distinct human cancer cell lines: the androgen-independent prostate cancer line PC3 and the multidrug-resistant ovarian cancer line SKOV3. The latter is notably resistant to a range of agents, including tumor necrosis factor and cisplatin,[14] while PC3 cells are characterized by their androgen independence and lack of response to certain growth factors.[15] The observation of cytotoxicity against such resistant phenotypes highlights the potential of *S. variegate* as a source of novel bioactive compounds.

In the pursuit of safer and more effective cancer therapies, natural products remain a cornerstone of drug discovery. Their structural diversity, general tolerability, and historical use provide a valuable starting point.[16] Many current chemotherapeutic agents, including those for ovarian and breast cancers, are either derived from or inspired by plant metabolites.[17] Our work aligns with this paradigm, demonstrating that a crude extract from *S. variegate* can significantly impair the viability of cancer cells. However, cytotoxicity alone is not a sufficient criterion for an antitumor agent. Further mechanistic investigations are essential to determine whether this effect is selective for malignant cells and to elucidate the underlying pathways.

The phytochemical profile of *Scrophularia* species, rich in phenolics, flavonoids, and phenylpropanoids,[11] offers plausible candidates for the observed activity. Such polyphenolic compounds are widely implicated in cancer chemoprevention and therapy. For instance, epidemiological studies have suggested an inverse association between diets rich in plant polyphenols and the risk of prostate cancer in some populations.[18] Other common vegetables, like carrots and beetroot, exert chemoprotective effects attributed to compounds such as polyacetylenes and β-carotene, which can modulate apoptotic signaling and cell cycle progression.[19-21] Similarly, specific plant extracts have shown promise in modulating key cancer hallmarks. Extracts from *Carica papaya* L. leaves can suppress pro-inflammatory cytokines linked to tumorigenesis,[22] while crocin from saffron exhibits dose-dependent anti-proliferative effects against lung and colorectal cancer cells.[23] Its metabolite, crocetin, also shows activity against aggressive prostate and breast cancer lines, partly through the downregulation of matrix metalloproteinases.[24,25] The cytotoxic activity of *S. variegate* reported here may operate through analogous or distinct mechanisms involving its characteristic phenolic constituents.

Contrary to some traditional uses and reports on other *Scrophularia* species, our extract showed no antibacterial activity against resistant strains of *S. aureus* and *E. coli*. This discrepancy is not uncommon in phytochemical research, as biological activity is often extraction-dependent. Ayobi et al., demonstrated that while crude extracts and certain fractions of *S. striata* possessed antibacterial properties, the chloroform fraction did not.[26] This underscores a critical point: the solubility and concentration of active antimicrobial principles can vary dramatically with the solvent system. Our use of an aqueous-ethanolic extract may have selectively captured cytotoxic phenolics while leaving behind antimicrobial compounds soluble in other solvents. Therefore, the reported absence of antibacterial activity in this study should not be generalized to the whole plant or other extraction methods.

Conclusions

This *in vitro* investigation demonstrates that an aqueous-

ethanolic extract of *Scrophularia variegate* possesses significant cytotoxic activity against human prostate (PC3) and ovarian (SKOV3) cancer cell lines. The observed dose-dependent reduction in cell viability, particularly against the multidrug-resistant SKOV3 phenotype, identifies this plant as a promising candidate for further anticancer research. While the extract did not show antibacterial activity against the resistant bacterial strains tested under our experimental conditions, its selective cytotoxicity underscores a potential therapeutic value that merits deeper exploration.

Future studies should prioritize the bioassay-guided fractionation of the extract to isolate and characterize the specific bioactive compounds responsible for its cytotoxic effects. Subsequent research must also evaluate the selectivity of these compounds for malignant versus non-malignant cells and elucidate their precise molecular mechanisms of action, including pathways related to apoptosis, cell cycle arrest, and metastasis.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Methicillin-Resistant Staphylococcus aureus: MRSA; Extended-Spectrum Beta-Lactamase: ESBL; Colony Forming Units: CFU/ml; Clinical & Laboratory Standards Institute: CLSI; Minimum Inhibitory Concentration: MIC; Minimum Bactericidal Concentration: MBC; Dulbecco's Modified Eagle Medium: DMEM; Fetal Bovine Serum: FBS; 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide: MTT; Phosphate-Buffered Saline: PBS; Dimethyl Sulfoxide: DMSO; Optical Density: OD; Standard Deviation: SD; Analysis of Variance: ANOVA; Standard Error of the Mean: SEM; Tumor Necrosis Factor: TNF; Tumor Necrosis Factor-Alpha: TNF-α; Interleukin-1: IL-1.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

All experimental protocols involving cell lines in this study were approved by the Ethics Committee of Iran University of Medical Sciences (Ethical Code: IR.IUMS.REC.1397.659). The study was conducted in accordance with the relevant institutional guidelines and regulations.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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