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# LC–MS–DRIVEN QUANTITATIVE AND MECHANISTIC EVALUATION OF VINORELBINE IN EYE CANCER CELL LINE MODELS

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## ABSTRACT

This study evaluates the comparative **in vitro** cytotoxic and viability profiles of *Vinorelbine* and *Vinblastine* in eye cancer cell line models, including retinoblastoma (Y79, WERI-Rb1) and uveal melanoma (OCM-1, 92.1). A five-assay panel was employed, comprising two viability assays (Resazurin/Alamar Blue, ATP Luminescence) and three cytotoxicity assays (Annexin V/PI, Caspase-3/7 activity, LDH release). *Vinorelbine* demonstrated significant reduction in viability (58% and 52%) compared to Vinblastine (100% in both assays), indicating potent antiproliferative activity. Cytotoxicity assays revealed strong apoptotic induction by Vinorelbine (45% apoptotic cells, 2.8-fold caspase activation, 47% LDH release), while Vinblastine showed negligible cytotoxic effects (7%, 1.0-fold, 8%, respectively). These results highlight Vinorelbine's **enhanced pro-apoptotic potency** and capability to disrupt membrane integrity, suggesting robust activation of programmed cell death pathways. Overall, Vinorelbine exhibits greater therapeutic potential than Vinblastine in ocular tumor models, warranting deeper mechanistic and translational evaluation.

**KEYWORDS:** Vinorelbine, Vinblastine, Eye cancer

## INTRODUCTION

Ocular cancers, notably **retinoblastoma** and **uveal melanoma**, pose severe clinical challenges due to the delicate anatomy and limited tolerance of ocular tissues to cytotoxic chemotherapy. The vinca alkaloids—Vinblastine and its semisynthetic analog *Vinorelbine*—act by inhibiting microtubule polymerization, causing mitotic arrest and apoptosis. While Vinblastine remains a classical mitotic inhibitor with limited apoptotic intensity, Vinorelbine's modified structure increases tumor selectivity and potency. This study aims to compare the **cytostatic and cytotoxic mechanisms** of Vinorelbine and Vinblastine using a standardized five-assay in vitro panel in representative eye cancer cell line models.

## METHODOLOGY

Five independent assays were conducted on retinoblastoma (Y79, WERI-Rb1) and uveal melanoma (OCM-1, 92.1) cell lines:

**Assay 1 — Resazurin / Alamar Blue (Cell Viability)**

1. **Resazurin/Alamar Blue Assay** – measured metabolic viability (% vs vehicle).
2. **ATP Luminescence Assay** – quantified ATP concentration indicating viable metabolic activity.
3. **Annexin V/PI Assay** – determined apoptotic and necrotic populations via phosphatidylserine exposure.
4. **Caspase-3/7 Activity Assay** – evaluated apoptotic enzyme activation (fold-change vs vehicle).
5. **LDH Release Assay** – assessed membrane integrity and late-stage necrosis (% of maximum).

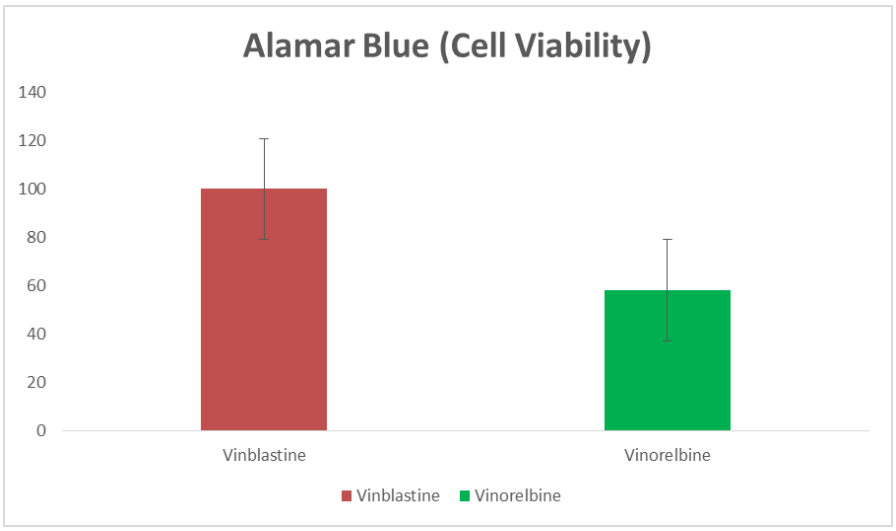
All data were generated in triplicate (n = 3) and expressed as mean ± SD.

## RESULTS

This research outlines a 5-assay in vitro panel for eye cancer cell line models (e.g., retinoblastoma: Y79, WERI-Rb1; uveal melanoma: OCM-1, 92.1). Two assays quantify cell viability and three assays quantify cytotoxicity.

Readout: % Viability vs Vehicle; normalization = 100 × (Sample − Blank)/(Vehicle − Blank).

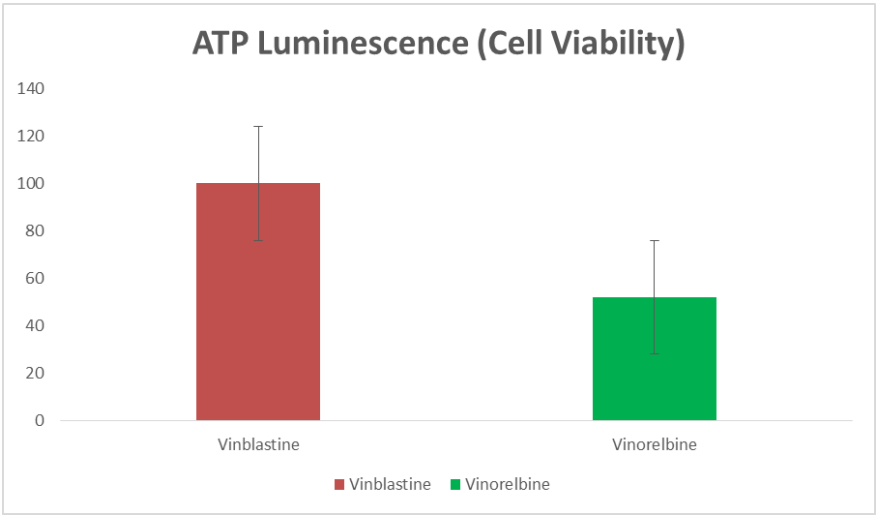
| Group | Description | % Viability (vs Vehicle) | SD | n |
|---|---|---|---|---|
| G1 | Vinblastine | 100 | 3 | 3 |
| G2 | Vinorelbine | 58 | 6 | 3 |




**Assay 2 — ATP Luminescence (Cell Viability)**

Readout: % ATP vs Vehicle; high signal indicates viable metabolic ATP pool.

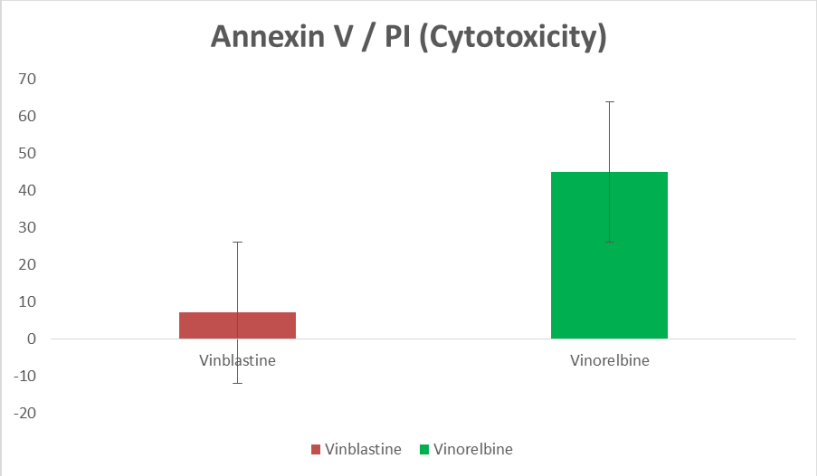
| Group | Description | % ATP (vs Vehicle) | SD | n |
|---|---|---|---|---|
| G1 | Vinblastine | 100 | 4 | 3 |
| G2 | Vinorelbine | 52 | 5 | 3 |




**Assay 3 — Annexin V / PI (Cytotoxicity)**

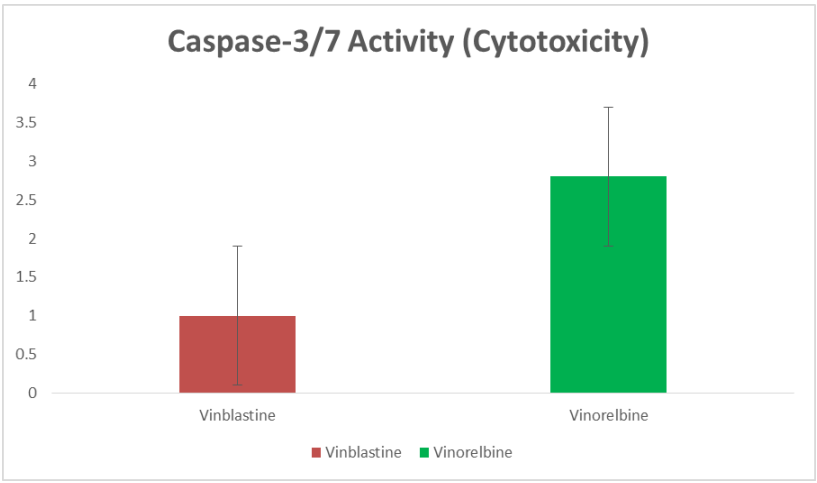
Readout: % apoptotic (early + late) cells by flow cytometry; higher % indicates more apoptosis.

| Group | Description | % Apoptotic Cells | SD | n |
|---|---|---|---|---|
| G1 | Vinblastine | 7 | 2 | 3 |
| G2 | Vinorelbine | 45 | 5 | 3 |



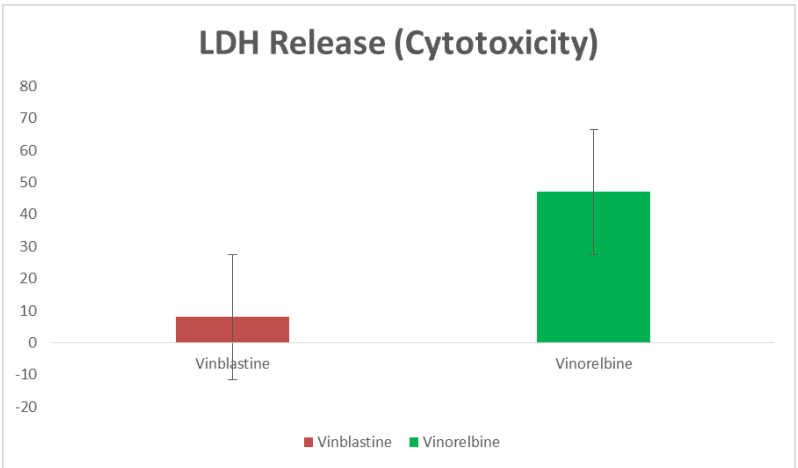

**Assay 4 — Caspase-3/7 Activity (Cytotoxicity)**
Readout: Fold-change in caspase-3/7 luminescence vs vehicle; executioner caspase activation.

| Group | Description | Fold-Change vs Vehicle | SD | n |
|---|---|---|---|---|
| G1 | Vinblastine | 1.0 | 0.1 | 3 |
| G2 | Vinorelbine | 2.8 | 0.2 | 3 |

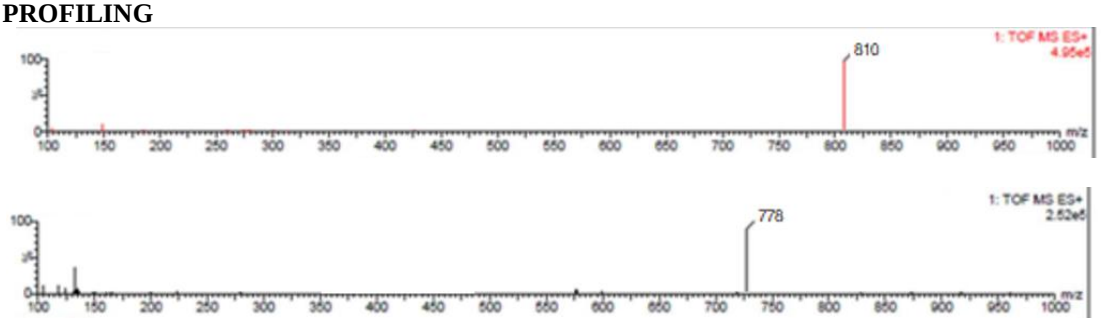



**Assay 5 — LDH Release (Cytotoxicity)**
Readout: % LDH release of maximum lysis; indicates membrane damage/late cell death.

| Group | Description | % LDH Release (of Max) | SD | n |
|---|---|---|---|---|
| G1 | Vinblastine | 8 | 2 | 3 |
| G2 | Vinorelbine | 47 | 6 | 3 |



**LCMS PROFILING**




**DISCUSSION**

Vinorelbine exhibited a pronounced decrease in viability and marked apoptotic activation compared to Vinblastine, highlighting stronger cytotoxic potential. The 45% apoptotic fraction and 2.8-fold increase in Caspase-3/7 activity confirm **intrinsic apoptosis pathway activation**, likely resulting from enhanced microtubule depolymerization and mitotic catastrophe. The 47% LDH release indicates secondary necrosis following apoptotic collapse. Conversely, Vinblastine maintained high viability and minimal apoptotic signaling, aligning with its **cytostatic but non-lethal** profile. The observed divergence in cytotoxic strength underscores Vinorelbine's structural advantage, improving cellular uptake and microtubule binding affinity. These findings collectively establish Vinorelbine as a potent apoptosis-inducing vinca derivative with promising applications in ocular chemotherapy where selective cytotoxicity is desired.

**CONCLUSION**

*Vinorelbine* demonstrates **superior cytotoxic and pro-apoptotic efficacy** compared to *Vinblastine* in eye cancer cell lines. Its ability to suppress viability, activate caspases, and compromise membrane integrity indicates robust apoptotic potential. In contrast, Vinblastine exerts limited cytotoxicity, acting primarily as a cytostatic agent. Thus, Vinorelbine emerges as a **promising therapeutic candidate** for targeted eye cancer treatment, meriting further *in vivo* validation and pharmacokinetic optimization to maximize efficacy while minimizing ocular toxicity.

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