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Selective anastasis induction by bee venom in normal cells: a promising strategy for breast cancer therapy with minimal impact on cell viability

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Anastasis is a phenomenon described as a cellular escape from ethanol-induced cell death. Although the relevant mechanism has not yet been fully elucidated, anastasis is thought to play a role in drug resistance in cancer cells. To date, the regulation of anastasis in normal and cancerous cells has not been clarified. The current cancer treatment strategies are expected to selectively attack cancer cells without negatively affecting normal cell proliferation. Inspired by the anti-cancer potential of bee venom, this study is the first to evaluate whether bee venom has similar selectivity in producing an anastatic effect. The results indicated that bee venom induces anastasis in normal cells (Michigan Cancer Foundation-10A (MCF10A), Adult Retinal Pigment Epithelium cell line-19 (ARPE-19), and National Institutes of Health 3T3 cell line (NIH3T3)) but causes irreversible cell death in breast cancer cells (M.D. Anderson-Metastatic Breast-231 (MDA-MB-231) and Michigan Cancer Foundation-7 (MCF7)). Liver cancer (HepG2) cells were moderately more resistant to permanent cell death after bee venom treatment compared to breast cancer cells. However, cisplatin caused permanent non-selective cell death in both normal and cancerous cells. The selectivity indices after bee venom treatment were higher compared to cisplatin. Taken together, bee venom was shown to induce selective anastasis only in normal cells, not in cancer cells, which suggests that bee venom has significant potential in selective cancer therapy, especially for breast cancer, via promoting the recovery and maintenance of viability of normal cells.

The human cervical cancer (HeLa) cells undergo anastasis after apoptosis in response to a chemotherapy drug, jasplakinolide (Tang et al., 2009). Ethanol-induced anastasis was previously shown in MDA-MB-231 and MCF7 cells as well as in normal breast (MCF10A) cells (Göker Bağca, 2022). The molecular mechanism for ethanol-induced anastasis was revealed by the time-dependent messenger RNA (mRNA) expression profiles. The expression of specific genes involved in the survival pathway was found to increase (Tang et al., 2012, 2022).

However, there are no studies that have assessed the selective induction of anastasis in normal cells over cancer cells. Bee venom is a promising natural product to induce selective cytotoxicity in cancer cells (Tu et al., 2008; el Sharkawi et al., 2015). Although bee venom has a strong cytotoxic potential, its cytotoxic specificity regarding the discrimination between anastatic and non-anastatic profiles in cancer and normal cells has not yet been revealed. This study showed that bee venom significantly induces anastasis in normal cells while triggering irreversible cell death in breast cancer cells. The detailed methodology is given in the supplementary materials and methods.

The matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) analysis of the bee venom determined the molecular weight of phospholipase A2 (PLA2) homologs with different N-linked carbohydrate chains to be about

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16 kDa (Hollander et al., 1993; Kubelka et al., 1993). Additionally, liquid chromatography-mass spectrometry (LC-MS) analysis of bee venom obtained the molecular weights of seven different peptide biomolecules that are the main peptide components of bee venom, as reported in previous studies (Baracchi and Turillazzi, 2010; van Vaerenbergh et al., 2014) (Table 1). The MALDI-TOF and LC-MS quadrupole TOF (q-TOF) spectra were given in Figs. S1–S8. Melittin was the most abundant component (50%–60%) of bee venom. It was eluted at about 20 min, and its monoisotopic mass-to-charge ratio (*m*/*z*) value was observed as 2844.806 Da. The other abundant components were melittin-F, apamin, mast cell-degranulating (MCD) peptide, secapin, secapin-1, and tertiapin. These results confirm that the crude bee venom samples used in this study were genuine.

Next, to reveal the cytotoxic doses for both bee venom and cisplatin, half maximal inhibitory concentration (IC_{50}) values were determined by methyl thiazolyl tetrazolium (MTT) assay for each cell line after bee venom or cisplatin. Cancer cells were more sensitive to bee venom with IC_{50} values of 8, 8, and 12 μg/mL in MDA-MB-231, MCF7, and HepG2 cells, respectively (Figs. 1a–1c); however, normal cells were more resistant to higher doses of bee venom with IC_{50} values as 36, 38, and 50 μg/mL in MCF10A, ARPE-19 and NIH3T3 cells, respectively (Figs. 1d–1f). Normal cells (except ARPE-19 cells) had a greater tendency towards cell death after treatment with low doses of cisplatin compared to bee venom. The IC_{50} values of MDA-MB-231, MCF7, and HepG2 cells were 12, 20, and 12 μg/mL, respectively (Figs. 1h–1j), and those of MCF10A, ARPE-19, and NIH3T3 cells were 25, 70, and 8 μg/mL, respectively (Figs. 1k–1m). The cell morphologies and population density of culture were shown by representative microscopy images after 24 h incubation of bee venom or cisplatin at different doses (Figs. 1g and 1n). Bee venom treatment resulted in higher selective index (SI) values than those detected after cisplatin (Table 2). This suggests a higher selectivity of bee venom for triggering cell death in cancer cells with a minimal cytotoxic effect on normal cells.

Cisplatin, as one of the most common chemotherapeutics clinically used in various cancers among the most preferred chemotherapeutic agents for comparison with new compounds/treatments in in vitro and in vivo cancer research. The IC_{50} values in MDA-MB-231 and MCF7 cells after cisplatin treatment for 24 h were found to be 11.08 and 21.08 μg, respectively (Kashyap et al., 2024), which are similar to our results. However, cisplatin (>50 μmol/L) treatment for 24 h was found cytotoxic for MCF7 and MDA-MB-231 cells (Mizielska et al., 2023). Another study reported that extended incubation with cisplatin (48 h) resulted in higher IC_{50} values than 24-h incubation for MDA-MB-231 and MCF7 at 38.6 and 83.1 μmol/L, respectively (Ben Hassen et al., 2023). Cisplatin showed cytotoxic effects on HepG2 cells with reported IC_{50} values after 24 h treatment of 7.5 μmol/L (Kntayya et al., 2018) and 26.71 μmol/L (Brito et al., 2012). Our study showed that ARPE-19 cells were more resistant to cisplatin-induced cytotoxicity with an IC_{50} value at 70 μg/mL. Consistently, a study suggested that the IC_{50} value of cisplatin in ARPE-19 cells was more than 30 μmol/L after 24 h of incubation (Sevim Nalkiran et al., 2023). However, prolonged incubation resulted in lower IC_{50} values, such as 25 μmol/L after 48 h (Saydam and Nalkiran, 2021) and 6 μmol/L after 96 h (Allison et al., 2017). NIH3T3 showed a time-dependent decrease in IC_{50} values, such as 98 μmol/L after 24 h (Demirbağ et al., 2024) and 3.42 μmol/L after 72 h (Zhang et al., 2025). Research indicates that the cytotoxic response of cells against cisplatin may show variation, which may depend on different parameters such as the passage number of cells, the stage of confluency

Table 1 Most abundant components found in the bee venom by liquid chromatography-mass spectrometry quadrupole time of flight (LC-MS qTOF)

Bee venom constituent	Number of amino acids	Calculated monoisotopic molecular weight (Da)	Observed monoisotopic molecular weight-deconvoluted (Da)
Melittin	26	2844.744	2844.806
Melittin-F	19	2206.332	2206.398
Apamin	18	2025.907	2025.923
Mast cell-degranulating (MCD) peptide	22	2585.412	2585.447
Secapin	25	2864.572	2864.615
Secapin-1	25	2821.566	2821.609
Tertiapin	21	2453.246	2453.262

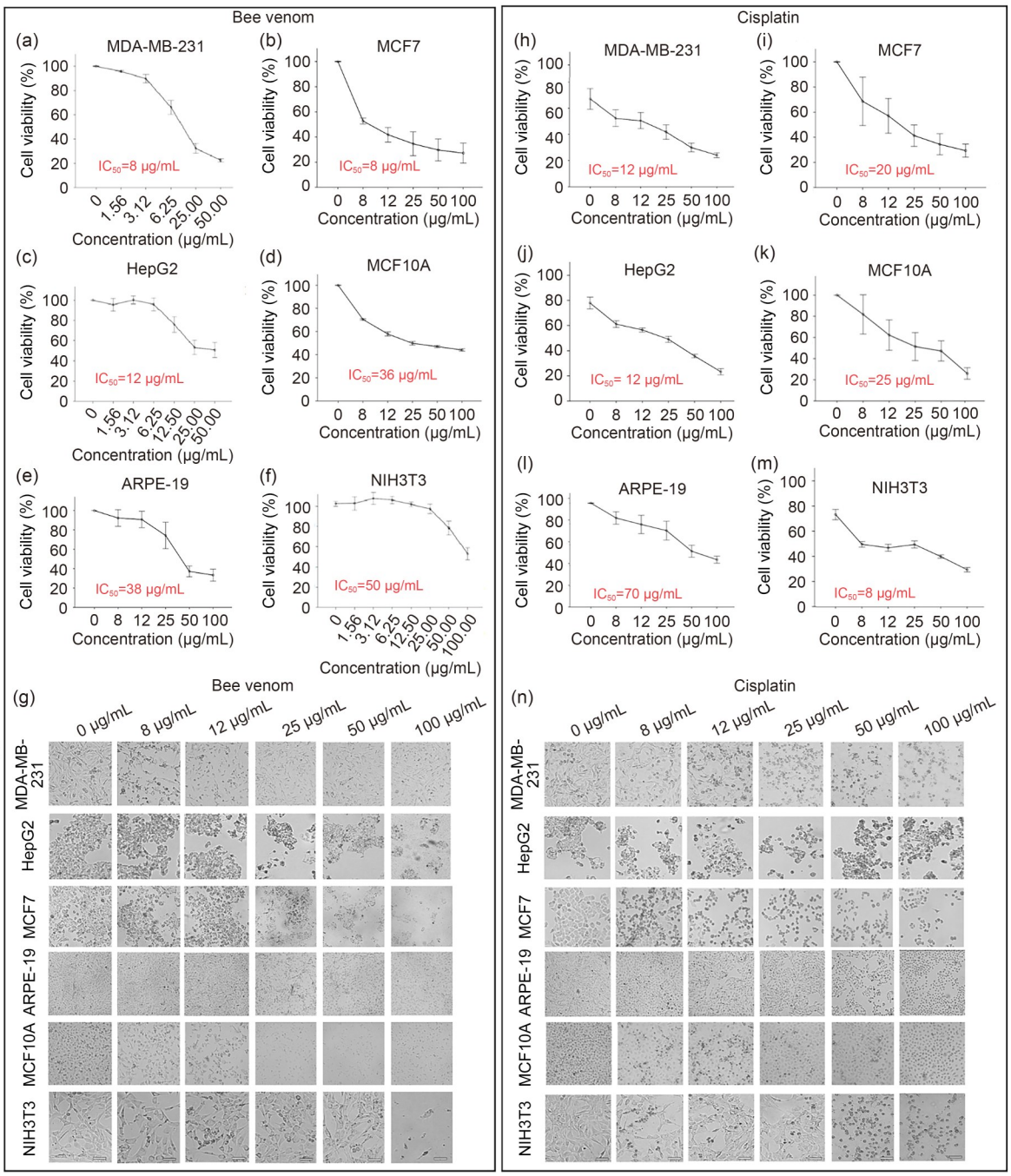


Fig. 1 Cytotoxicity profiles of bee venom (a–g) and cisplatin (h–n) in MDA-MB-231 (a, h), MCF7 (b, i), HEPG2 (c, j), MCF10A (d, k), ARPE-19 (e, l), and NIH3T3 (f, m) cell lines and representative microscopy images after bee venom and cisplatin treatment (g, n). Scale bar=10 μm. IC_{50}: half maximal inhibitory concentration; MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells.

when treated, and the total days of pre-culture/passage before treatment. For this reason, cisplatin should be included in each experiment during an MTT assay with the target compounds.

The anastatic response of cells against bee venom and cisplatin was next assessed. All cells were treated with bee venom or cisplatin to determine the number of living cells. A separate group of each cell line was left

untreated. Cells were washed after 24 h treatment and left to recover for up to 72 h (Fig. S9). MDA-MB-231 cells continued to die even if bee venom (≥25 μg/mL) was removed, and they entered anti-anastasis after 12 μg/mL of bee venom treatment (Fig. 2a). Another breast cancer cell line, MCF7, was sensitive to bee venom at each concentration after removal and each condition was anti-anastatic for MCF7 (Fig. 2b). However, HepG2 tended to enter anastasis at up to 25 μg/mL bee venom, and the minimum anti-anastatic dose was 50 μg/mL in liver cancer cells (HepG2) (Fig. 2c). MCF10A cells recovered at up to 12 μg/mL bee venom (Fig. 2d). NIH3T3 cells were anastatic at each concentration including 100 μg/mL (Fig. 2e). ARPE-19

Table 2 Selective index (SI) values after bee venom or cisplatin treatment

Agent	Cells	SI			
		MCF10A	ARPE-19	NIH3T3	Average
Bee venom	MDA-MB-231	4.50 (36/8)	4.75 (38/8)	6.25 (50/8)	5.17
	MCF7	4.50 (36/8)	4.75 (38/8)	6.25 (50/8)	5.17
	HepG2	3.00 (36/12)	3.17 (38/12)	4.17 (50/12)	3.45
Cisplatin	MDA-MB-231	2.08 (25/12)	5.83 (70/12)	0.67 (8/12)	2.87
	MCF7	1.25 (25/20)	3.50 (70/20)	0.40 (8/20)	1.72
	HepG2	2.08 (25/12)	5.83 (70/12)	0.67 (8/12)	2.87

IC_{50}: half maximal inhibitory concentration; SI: normal cell IC_{50}/cancer cell IC_{50}; MCF10A: Michigan Cancer Foundation-10A; ARPE19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M. D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells.

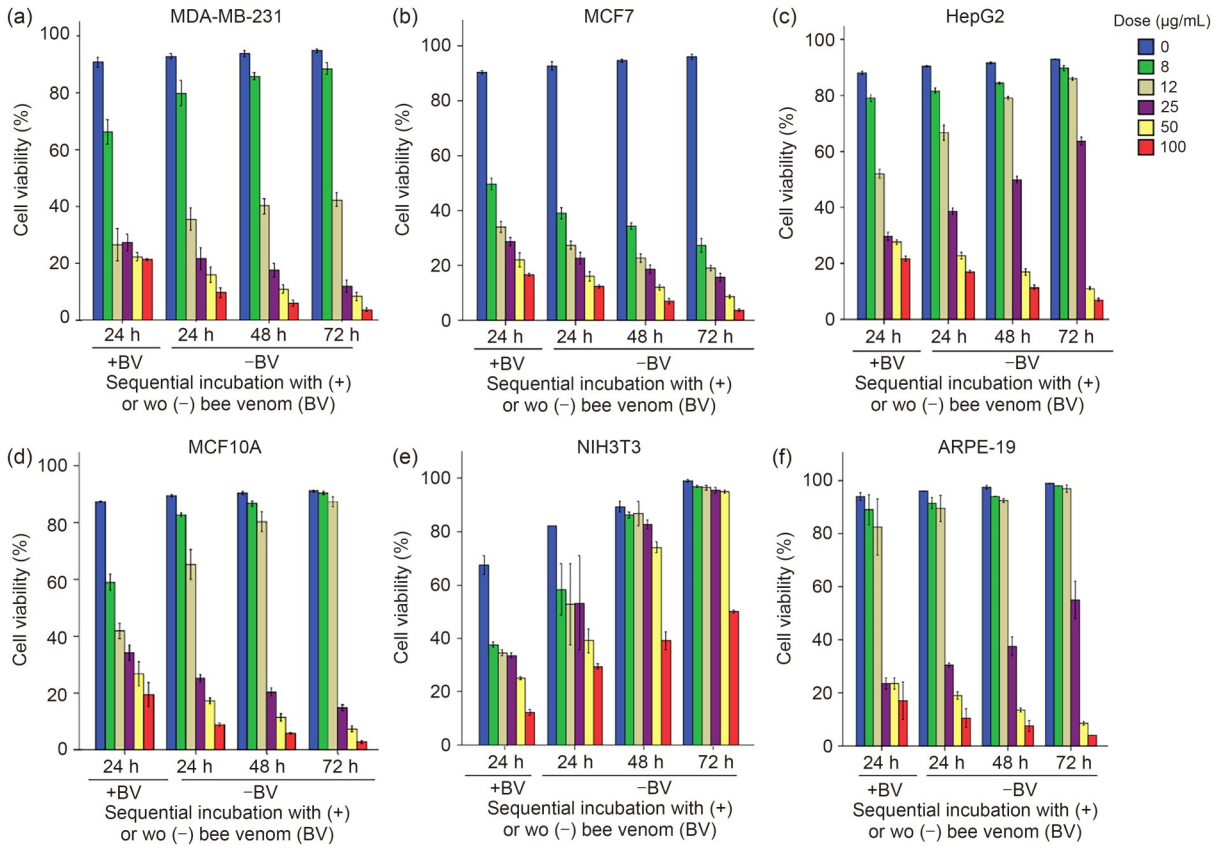


Fig. 2 Bee venom (BV)-induced cell viability in cancer (a–c) and normal (d–f) cell lines during anastasis. +BV: treatment with bee venom; −BV: post-treatment after bee venom; MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells; wo: without.

cells showed an anastatic profile at up to 25 μg/mL bee venom (Fig. 2f). Statistical comparisons indicated that 12 μg/mL of bee venom had an anastatic effect in normal cells (Figs. 3d–3f), but this was anti-anastatic in both breast cancer cells (MDA-MB-231 and MCF7) (Figs. 3a and 3b). HepG2 cells seemed more resistant to anti-anastasis since they entered permanent cell death after 50 μg/mL bee venom (Figs. 2c and 3c). These results suggest that bee venom significantly induced selective anastasis in normal cells compared to two breast cancer cell lines. However, none of the cells entered the anastasis process after cisplatin treatment (Figs. 4 and 5). Cisplatin was found to be selectively cytotoxic against HepG2 cells (compared to non-cancerous

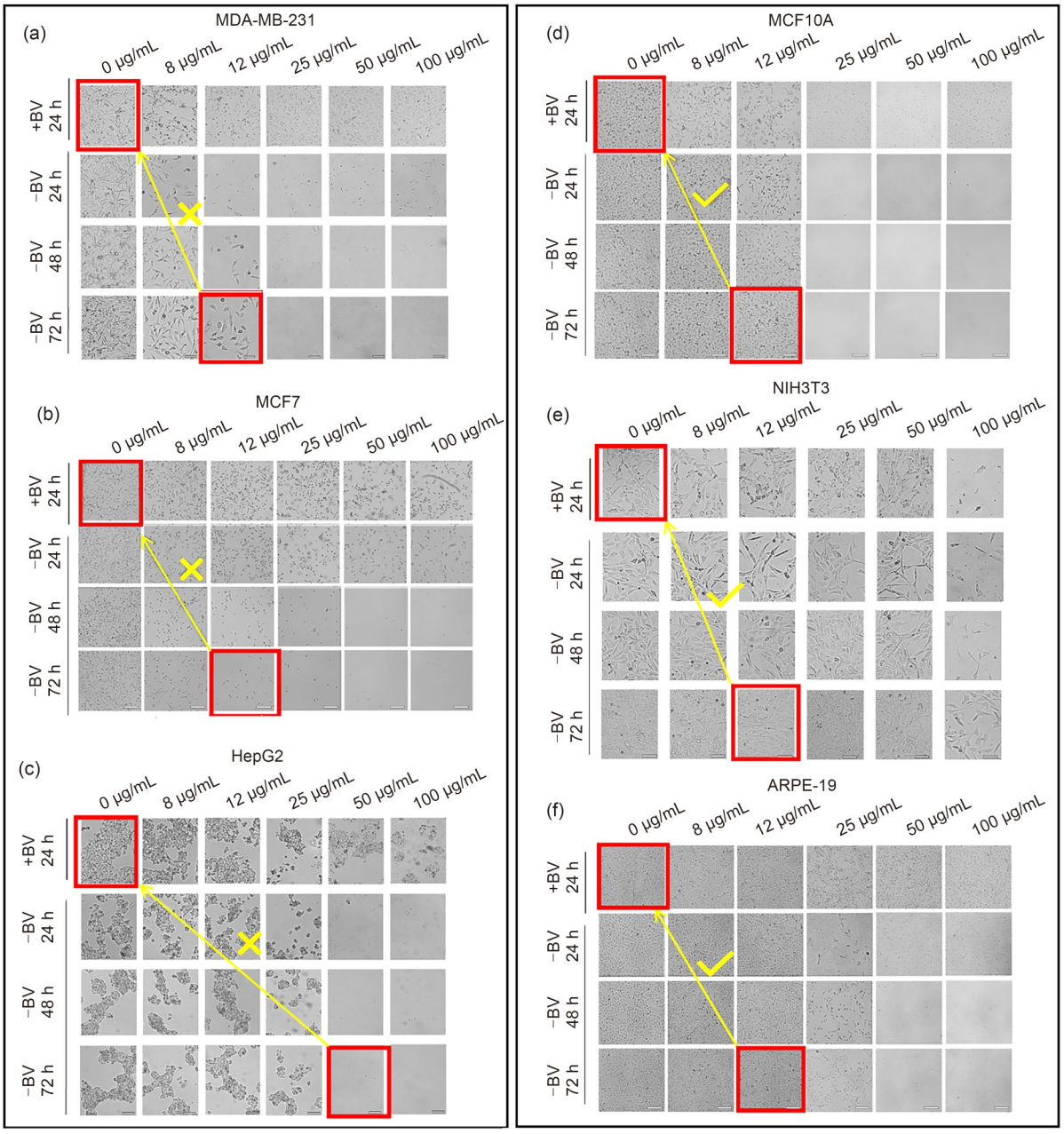


Fig. 3 Bee venom-induced anti-anastatic profiles in cancer cell lines (a–c) and anastatic profiles in normal cell lines (d–f). Scale bar=10 μm. The red square images represent the possible reversal of cell death to viable cells. ×: no reversal; √: reversal; +BV: treatment with bee venom; −BV: post-treatment after bee venom; MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells.

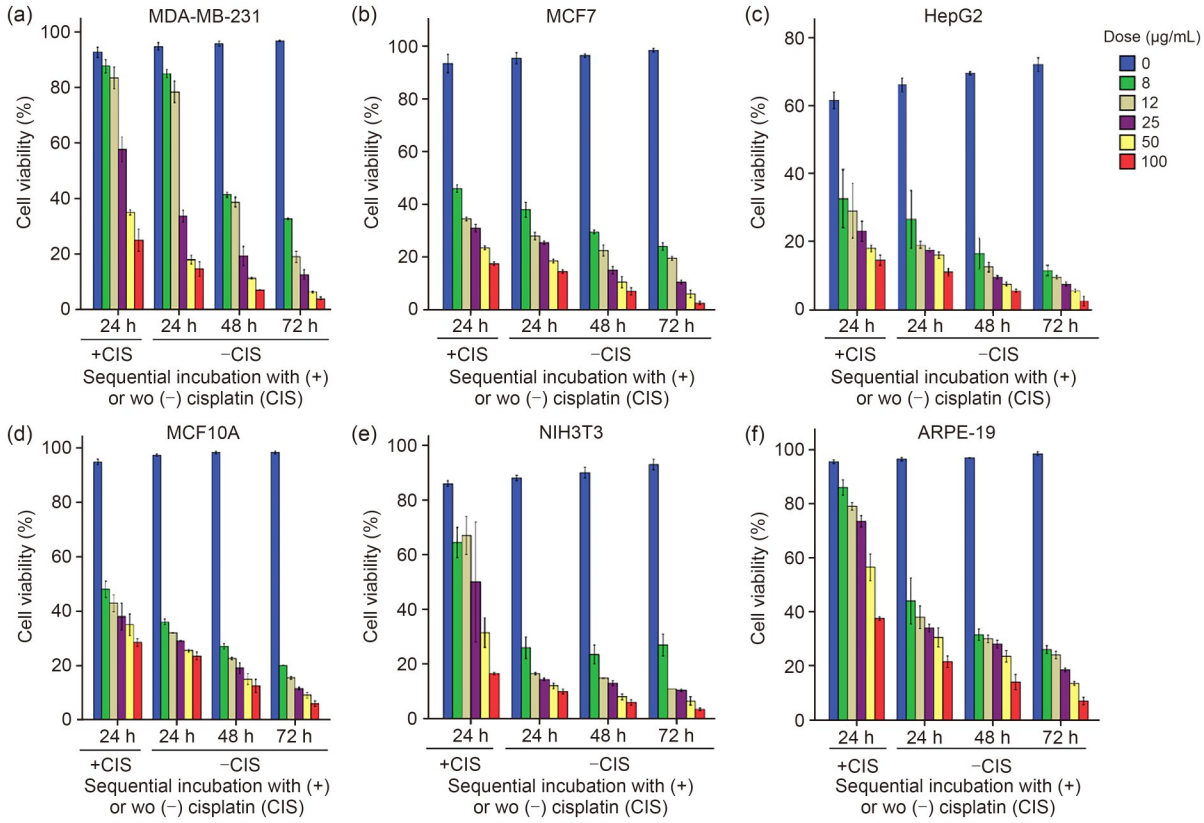


Fig. 4 Cisplatin (CIS)-induced cell viabilities (%) in cancer (a–c) and normal (d–f) cells in terms of anastatic expectation. +CIS: treatment with cisplatin; −CIS: post-treatment with cisplatin; MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson–Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells; wo: without.

epithelial cells, ARPE-19) with an SI value of 5.83 (Fig. 1, Table 2); however, it did not change the anastatic response of ARPE-19 cells compared to HepG2 cells. This indicates that cisplatin also harms normal cells in the long term, which cannot be recovered via induced anastasis. The development of resistance of cancer cells in chemotherapy treatment processes suggests that cancer cells can escape apoptosis by activating anastasis (Seervi et al., 2019; Wang et al., 2023). From this perspective, the anastasis event can well explain the developmental mechanisms that play a role in cancer recurrence. However, the potential of anticancer agents to trigger anastasis in normal cells while inducing cell death in cancer cells remains unrevealed. Therapeutic agents for cancer treatments are expected to have a highly cytotoxic effect on cancer cells while showing less cytotoxicity to healthy cells.

The significant dose intervals for anastasis are summarized in Table 3 for each cell line-agent combination. MCF7 was the most sensitive cancer cell line to both agents, with no anastatic trend under all conditions. The MDA-MB-231 cell line appeared to induce moderate anastasis only at the lowest dose of bee venom (8 μg/mL). MCF10A cells were more anastatic after bee venom at higher doses than the two breast cancer cells. However, HepG2 cells were the most resistant cancer cells to bee venom, with anastasis up to 25 μg/mL, which was similarly observed in normal epithelial ARPE-19 cells. The highest anastasis was observed in NIH3T3 cell line at up to 100 μg/mL. The trypan blue method or MTT method does not discriminate between the types of cell death; therefore, at this stage, these results cannot indicate any specific type of cell death for reversal.

We next analyzed the population doubling times for each cell after different doses/incubations with bee venom or cisplatin. Live cells were counted by trypan blue staining, and population doubling times (PDTs) were calculated using a formula given in the supplementary materials and methods. Fig. 6 shows each dose

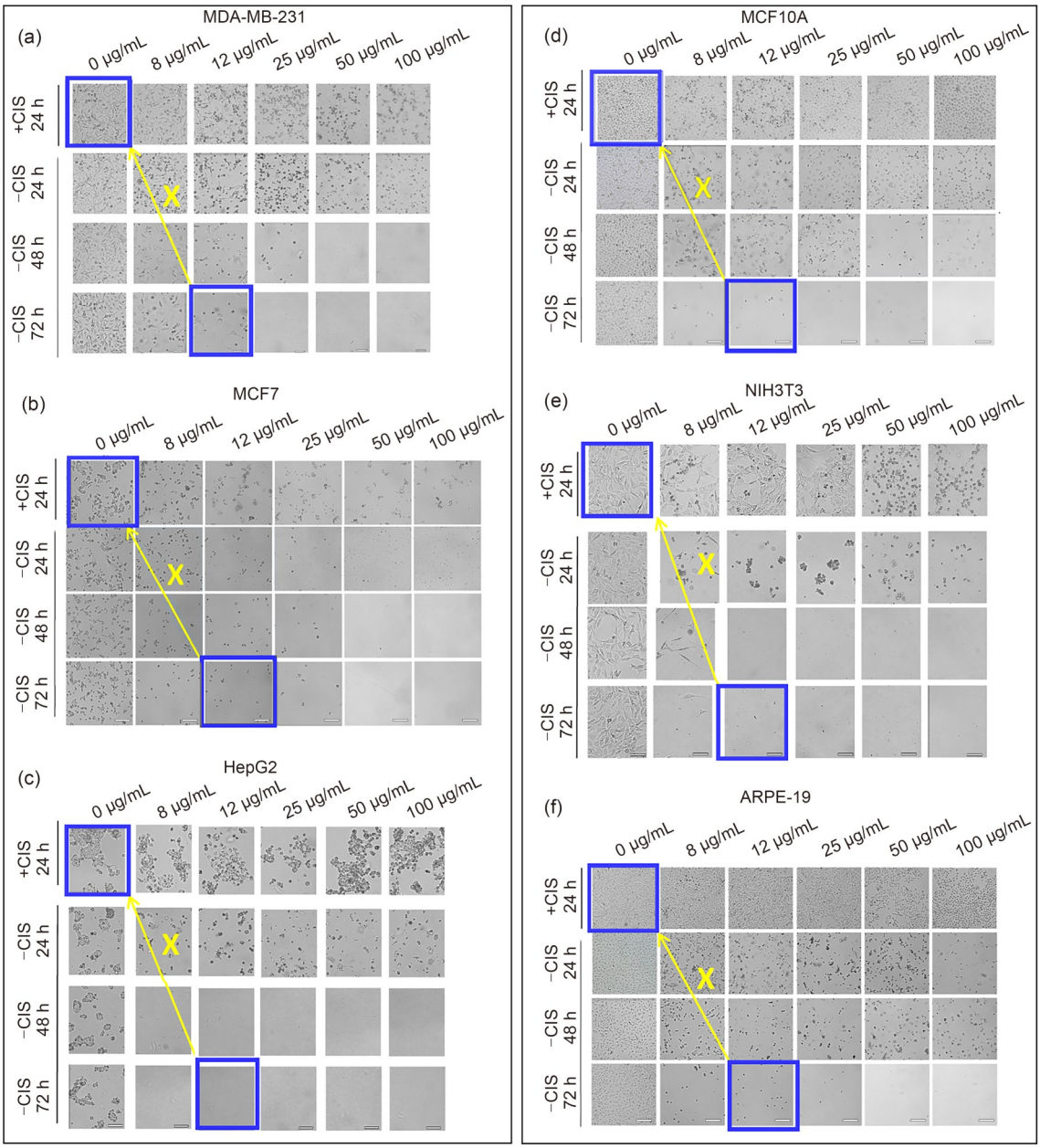


Fig. 5 Cisplain (CIS)-induced anti-anastatic profiles in cancer (a–c) and normal (d–f) cells. Scale bar=10 μm. The blue square images represent the possible reversal of cell death to viable cells. ×: no reversal; √: reversal; +CIS: treatment with cisplain; −CIS: post-treatment after cisplain; MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells.

Table 3 Significant anastatic dose interval in each cell line after bee venom or cisplatin treatment (at 72 h)

Agent	Significant dose interval for cancer cells (μg/mL)			Significant dose interval for non-cancerous cells (μg/mL)		
	MDA-MB-231	MCF7	HepG2	MCF10A	ARPE-19	NIH3T3
Bee venom	8	ND	8–25	8–12	8–25	8–100
Cisplatin	ND	ND	ND	ND	ND	ND

ND: not detectable. MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells.

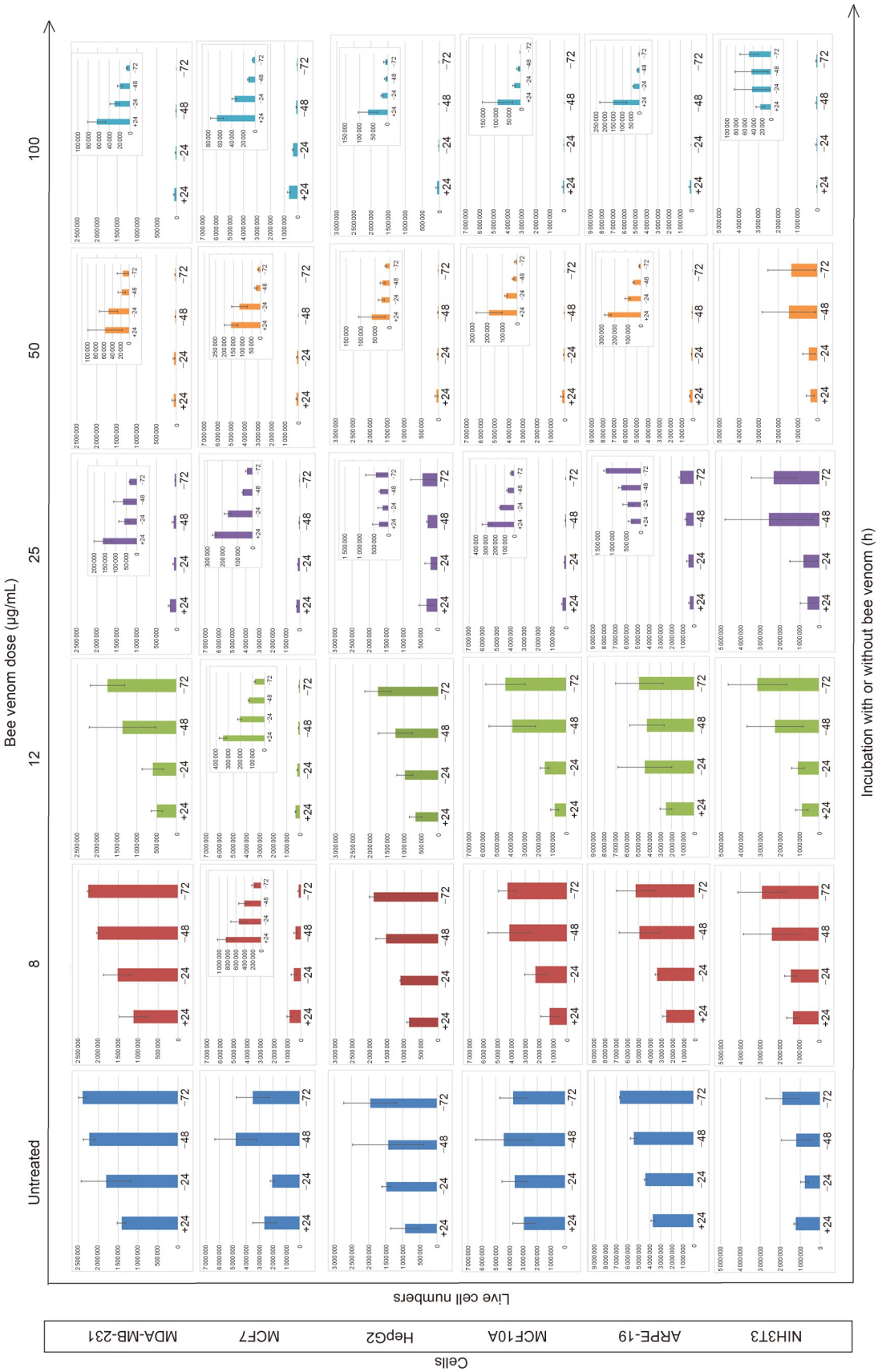


Fig. 6 Average live cell numbers in cancer and normal cells during anastasis-related response against bee venom.

Table 4 Average population doubling times (from the time for 24 h incubation with bee venom to anastatic incubation for 72 h)

BV dose (μg/mL)	Average population doubling times					
	MDA-MB-231	HEPG2	MCF7	MCF10A	ARPE-19	NIH3T3
0	406 676	375 204	459 007	652 756	832 831	386 427
8	713 494	631 007	ND	404 933	684 168	632 968
12	ND	514 698	ND	302 763	748 264	391 825
25	ND	162 155	ND	ND	406 186	375 684
50	ND	ND	ND	ND	ND	384 714
100	ND	ND	ND	ND	ND	701 518

BV: bee venom; MCF10A: Michigan Cancer Foundation-10A; ARPE-19: Adult Retinal Pigment Epithelium cell line-19; NIH3T3: National Institutes of Health 3T3 cell line; MDA-MB-231: M.D. Anderson-Metastatic Breast-231; MCF7: Michigan Cancer Foundation-7; HepG2: human hepatocellular carcinoma cells; ND: not detectable.

and incubation in cancerous and normal cells. Table 4 indicates the average PDT between incubation with an agent for 24 h and anastatic incubation for an extra 72 h.

The total live cell number increased at 8 μg/mL bee venom in MDA-MB-231 and 8–12 μg/mL in HepG2, whereas the live cell number did not increase at any dose in MCF7 cells (Fig. 6). HepG2 cells are the only cancerous cells that tend to a degree of cell proliferation at 25 μg/mL. Most MCF10A cells progressively lived in a time-dependent manner at up to 12 μg/mL bee venom, but both ARPE-19 and NIH3T3 cells were further alive at 25 μg/mL (Fig. 6). PDTs were consistent with the live cell trend (Table 4). MCF7 was the most sensitive cancer cell line that could not recover via anastasis, with a constant decrease in live cell number at each dose (Fig. 6 and Table 4). Bee venom resulted in higher PDTs in MDA-MB-231 and HEPG2 with higher doses; however, MCF10A and ARPE-19 normal cells proliferated faster after bee venom treatment than untreated counterparts (Table 4). PDT of NIH3T3 cells fluctuated after 8 and 100 μg/mL at a slow rate, but cells similarly proliferated at 12 and 25 μg/mL as fast as their untreated counterparts (Table 4).

Importantly, these results show that the anastasis mechanism can be activated in normal cells, but not in cancer cells, to escape the cytotoxic effect of treatment. Therefore, the anastasis mechanisms have a distinguishing function between normal and cancer cells and play a differential role in the response to treatment in favor of the survival of normal cells. Nonetheless, the prolonged effect of bee venom on the switch to anastasis from cell death should be tested in tumor tissues by in vivo models. Bee venom has been shown to inhibit the proliferation of different cancers, such as cervical cancer for up to four weeks (Lee et al., 2015), breast cancer for 21 d (Oršolić et al., 2003), and melanoma for up to 12 d (Liu et al., 2002) in mouse models. In vivo experimental designs are considered advantageous to conclude the long-term treatment of bee venom.

Bee venom is composed of many biologically active compounds, with melittin being the major component, exerting an anti-cancer effect (Cui et al., 2024; Honari et al., 2024; Wang et al., 2024). Phospholipase A is another important enzyme with an individual anticancer effect (da Cunha Recuero et al., 2024; Xie et al., 2024). Therefore, to standardize the anastatic effect of bee venom, each component should be individually evaluated for breast cancer specificity. Our study showed that anastasis induced by bee venom plays a distinctive role in breast cancer treatment. However, the molecular mechanism of anastasis and the main responsible component of bee venom for anastasis remain to be elucidated.

Data availability statement

All data about this work are included in the article and the supplementary data.

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Author contributions

Selcen CELIK UZUNER and Ugur UZUNER performed the conceptualization and writing – review & editing; Sinan TETIKOGLU, Muharrem AKCAN, and Selcen

CELIK UZUNER contributed to the data curation; Selcen CELIK UZUNER performed the funding acquisition; Sinan TETIKOGLU, Muharrem AKCAN, Ugur UZUNER, and Selcen CELIK UZUNER performed the investigation and methodology; Sinan TETIKOGLU, Muharrem AKCAN, and Selcen CELIK UZUNER performed the visualisation and writing – original draft; Selcen CELIK UZUNER performed the supervision and the resources.

Compliance with ethics guidelines

Sinan TETIKOGLU, Muharrem AKCAN, Ugur UZUNER, and Selcen CELIK UZUNER declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Supplementary information

Materials and methods; Figs. S1–S9