ARTICLE

Dual in vitro and in silico evaluation of the apoptosis-inducing and migration-inhibiting potential of *Capparis spinosa* methanol extract in prostate cancer cells

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Received: 11 January 2026 / Accepted: 23 February 2026 / Published online: 3 March 2026

Abstract

Background *Capparis spinosa L.*, rich in flavonoids and polyphenols, has limited mechanistic evidence regarding its anticancer effects. This study evaluated the methanol extract of *C. spinosa* in PC3 prostate cancer cells using combined in vitro and in silico analyses.

Methods Cytotoxicity in PC3 and HUVEC cells was assessed by MTT, followed by qRT-PCR and Western blot analysis of Bcl-2/Bax. Colony formation and wound-healing assays evaluated functional effects. Kaempferol and quercetin were analyzed via SwissADME, admetSAR, PASS Online and docking against apoptosis-related proteins.

Results The extract showed selective cytotoxicity toward PC3 cells (IC_{50}: 12.4 mg/mL at 24 h; 10.6 mg/mL at 48 h) with minimal HUVEC toxicity. Treatment suppressed Bcl-2 and increased Bax, reduced colony formation (~70%), and inhibited migration. Docking showed strong binding of kaempferol and quercetin to Bcl-2 (≈ −8.1 kcal/mol).

Conclusion *C. spinosa* extract induces mitochondrial apoptosis and inhibits PC3 proliferation, supporting its potential as a phytotherapeutic candidate.

Keywords *Capparis spinosa* L. · Prostate cancer · Apoptosis · Bcl-2/Bax · In vitro · In silico

Abbreviations

PC3	Human prostate cancer cell line
HUVEC	Human umbilical vein endothelial cells
IC_{50}	Half-maximal inhibitory concentration
DMSO	Dimethyl sulfoxide
DMEM	Dulbecco's modified Eagle's medium
FCS	Fetal calf serum
PBS	Phosphate-buffered saline
RIPA	Radioimmunoprecipitation assay buffer
SDS-PAGE	Sodium dodecyl sulfate–polyacrylamide gel electrophoresis
PVDF	Polyvinylidene difluoride

NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
Cyt c Cytochrome

Introduction

Cancer is the second leading cause of morbidity and mortality worldwide, increasing the need for various treatment approaches. Although chemotherapy is known to increase survival rates, its potential to cause significant acute toxicity necessitates further research. The literature shows that there is increasing interest in medicinal plants that have strong cytotoxic effects for cancer treatment (Reza et al. 2024). This interest has led to studies on the effects of plants. These compounds affect cancer-related cellular activities in multiple ways, including apoptosis proliferation and cell cycle arrest. They have also been reported to play a role in regulating cell function and gene expression (Singh and Yadav 2022; Hazafa et al. 2020; Kopustinskiene et al. 2020; Zhang and Ma 2018).

Capparis spinosa L. an aromatic shrub commonly referred to as caper, is widely distributed throughout the Mediterranean basin, where its flower buds are traditionally used in regional cuisine. Scientific studies have shown that it contains various glucosinolates as chemical components, as well as abundant phenolic acids and flavonoids. These compounds are known to have antimutagenic, anticancer, antibacterial, and antioxidant effective (Annaz et al. 2022a; Kdimy et al. 2022 a; Lo Bosco et al. 2019; Wojdyło et al. 2019; Zhang and Ma 2018; Bakr & El Bishbishy, 2016; Sezen et al. 2023).

The effects of extracts obtained from *C. spinosa* on various cancer cell lines have been investigated in some studies. A hydroalcoholic extract obtained from the flower buds and leaves of *C. spinosa* showed less effect on normal fibroblasts, whereas it significantly reduced the proliferation of cancer cell lines (HeLa, MCF-7, and Saos-2) (Moghadamnia et al. 2019). In another study, it was reported that the extract obtained from the flower buds and leaves of *C. spinosa* showed growth inhibitory effects on HT-29, a colorectal adenocarcinoma cell (Kulisic-Bilusic et al. 2012). Yu et al. (2010) asseted the cytotoxic effects of n-butanol extract on human gastric cancer SGC-790 cells using the MTT assay. After application at various doses between 5 and 400 µg/mL, significant inhibitory rates ranging from 24.1% to 75.4% were observed. It showed antiproliferative activity, with an IC_{50} value of 31.5 µg/mL (Yu et al. 2010). Saleem et al. (2021) examined the cytotoxic potential of methanol and dichloromethane extracts derived from both the aerial and root parts of the plant against the breast cancer cell lines MDA-MB-231 and MCF-7, reporting a 73.81% reduction in the survival of MDA-MB-231 cells. This resulted in a cell viability the inhibition of the survival of MDA-MB-231 cells by 73.81%. As a result of the analysis of the dichloromethane extract obtained fro the aerial parts, 55.36% viability rates were obtained for MDA-MB-231 cells and 55.72% for MCF-7 cells (Saleem et al. 2021; Annaz et al. 2022b). Interestingly, *C. spinosa* has been found to be safe and there is negligible scientific evidence regarding its adverse or toxic effects (Sher and Alyemeni 2010; Vahid et al. 2017). In the literature, no studies have been found for prostate cancer, but there are various studies in different cancer cell lines. The PC3 cell line was selected as an in vitro model due to its androgen-independent phenotype and high metastatic potential, characteristics that closely resemble advanced and castration-resistant prostate cancer. Unlike androgen-dependent models, PC3 cells lack functional androgen receptor signaling, making them particularly suitable for investigating therapeutic strategies targeting aggressive and hormone-refractory prostate cancer.

This study aimed to determine the effects of *C. spinosa* methanol extract on prostate cancer. For this purpose, we evaluated the cytotoxic effects on prostate cancer cell (PC3) and healthy Human umbilical vein endothelial cells (HUVECs) using MTT analysis to calculate the IC_{50} value. This specific concentration was then applied to PC3 cells for an in-depth molecular analysis (Fig. 3). These analyses included the examination of apoptosis-related gene expression, specifically Bcl-2 and Bax, using qRT-PCR and Western blotting, and the assessment of cell migration using wound healing assays and cell proliferation using colony formation assays (Figs. 4 and 5). Additionally, in silico analyses were conducted to assess various biological parameters for Kaempherol and

Quercetin, the most abundant active ingredients of the plant. This study will enable detailed molecular analysis of the methanol extract of *C. spinosa* in prostate cancer cells.

Materials and methods

Plant material and preparation of extracts

C. spinosa buds were obtained from Altınoluk/Balıkesir. *C. spinosa* was weighed on a precision scale and crushed to a powder using liquid nitrogen in a mortar before extraction. *C. spinosa* powder was collected using a spatula and placed in a falcon tube (Fig. 2). Fifty milliliters of 80% methanol was placed on it, which was kept at +4 °C for 15 days by turning it upside down at regular intervals. At the end of 15 days, *C. spinosa*, taken from +4 °C, was centrifuged at 13,500 rpm 15 min at 10 °C in a refrigerated centrifuge to remove the woody cellulose parts of the plant and obtain the liquid part containing the active substance. The samples were centrifuged twice. After centrifugation, the supernatant was filtered. The extract containing the active substance was prepared by transferring it into a 50 mL balloon and allowing the evaporation of methanol and water using an evaporator. For this process, the evaporator was set at 92 mbar, 100 rpm, and 35 °C. The prepared extract was dissolved in DMSO and passed through a 0.22 µm filter (Habib-Martin et al. 2017).

Cell culture and cell growth assay

In this study, the human prostate cancer cell line PC3 was obtained from the ATCC. These cells were cultured in 75 cm² flasks in DMEM containing 10% FCS, as recommended. The environmental conditions were maintained at 5% CO_2 and 37 °C. For cell counting, the cells were stained with trypan blue and counted on a Thoma Slide. Since dead cells appear blue after staining, live cells do not take up the dye, and the live cell concentration per milliliter was determined by counting the remaining unstained cells per milliliter.

Cell viability assay

The MTT assay, a colorimetric method, was employed to evaluate the cytotoxic effects of the methanol extract of *C. spinosa* on PC3 cells. PC3 cells were initially seeded in 96-well plates and incubated at 37 °C for 24 h, after which varying concentrations of the extract (62.5–1000 µg/mL) were added to the adherent cells. To minimize the influence of the extract color on the final readings, the medium containing the extract was removed, and the wells were gently washed with warm PBS. Subsequently, 100 µL PBS and 10 µL MTT stock solution (10 mg/mL) were added to each well, and the culture was incubated for 4 h at 37 °C. After incubation, the wells were emptied and the MTT formazan product was dissolved in 200 µL of isopropanol-HCl solution. Absorbance was measured at 550 nm using a spectrophotometer. Each treatment was assessed in at least four independent experiments, each performed in duplicate. The results are expressed as the optical density ratio of the treatment group to the control group. The IC_{50} values of the extracts were assessed using AAT Bioquest (Abdel-Rehim et al. 2024; Güngör et al. 2020; Hacıoğlu et al. 2021; Tokay et al. 2020).

RNA İsolation, qRT-PCR and real time analysis

Studies were conducted to determine gene expression at the mRNA level in cells treated with methanol extract of *Capparis spinosa*. PC3 cells obtained by applying *C. spinosa* extract in 25 cm^2 flasks were removed by trypsinization 24 and 48 h after applying the methanol extract. The samples were pelleted and thawed on ice for RNA

isolation. RNA was isolated from the control and experimental groups using a GeneJET RNA isolation kit. A Thermo Multiskan Go µDrop Plate Reader was used to measure the amount of isolated RNA. cDNA synthesis was performed using the isolated RNA and quantified by qRT-PCR. cDNAs was analyzed using semi-quantitative RT-PCR (Alper et al. 2025; Altuntaş et al. 2023; Aydemir et al. 2018). For real-time PCR studies, 5 µL of SYBR® Green PCR mixture solution, 1 µL of cDNA, and 0.5 µL of 100 ng/µL each of primers were obtained as a result of dilution (Hacıoğlu et al. 2020; Tokay 2021). The Livak method was used to evaluate these results.

Western blotting

PC3 cells were treated with the methanol extract of *C. spinosa* at effective concentrations for 48 h. Proteins were isolated using RIPA buffer. Protein concentration was calculated using the Bradford method. Total protein (50 µg) was subjected to SDS sulfate-polyacrylamide gel electrophoresis. SDS gel was run for 1 h at 120 V. The transfer was performed overnight at 15 V and 4 °C using PVDF membranes (Millipore). The membrane was incubated with antibodies against Bcl-2 (sc-7382; Santa Cruz), Bax (sc-7480; Santa Cruz) and β-actin (A3854; Sigma Aldrich) (Tokay et al. 2021; Tokay and Kockar 2016a, b). Densitometric analysis was performed by examining the protein bands in detail using the ImageJ software.

Scratch assay

A wound-healing assay was performed to determine the effect of the methanol extract of *C. spinosa* on the migration of PC3 cells. The cells (5×10^5 cells/well) were incubated at 37 °C until they adhered to the entire surface and were completely covered. A plus-shaped pipette was used for all wells as a standard. The first application (0 h) was then photographed and recorded. After 3, 6, 24, and 48 h, the cells were photographed to calculate the cell migration rate. The data were analyzed using ImageJ software in conjunction with the MRI Wound Healing Tool (Hacıoğlu et al. 2020).

Colony formation assay

The proliferative response of PC3 cells to the methanol extract of *C. spinosa* was examined using a colony formation assay. PC3 cells were exposed to the extract at the IC_{50} and incubated for 48 h. The cells were then trypsinized and seeded in six-well plates at 1×10^3 cells/well. The cell medium was continuously renewed during the 20-day incubation period. On day 20, the cells were fixed with 10% formaldehyde for 30 min and stained with 1% crystal violet for 5 min at room temperature. After staining, the wells were washed three times with PBS and colonies were counted using the cell counter plugin of the ImageJ software (Hacıoğlu et al. 2020).

In silico analysis

In this study, an in silico approach was employed to evaluate the pharmacokinetic properties, drug-likeness, and toxicity profiles of bioactive compounds found in *Capparis spinosa*. Initially, the phytochemical constituents of *C. spinosa* were identified through literature review (El Amri et al. 2025). Identified compound structures were sourced from PubChem and formatted in SMILES notation for further in silico analyses. SwissADME (http://www.swissadme.ch/index.php) was used to assess the blood-brain barrier (BBB) permeability, physicochemical properties, P-glycoprotein (P-gp) substrate prediction and gastrointestinal (GI) absorption. admetSAR (https://lmmd.ecust.edu.cn/admetsar1) provides ADMET-related predictions, including human intestinal absorption (HIA), Ames mutagenicity, hepatotoxicity and carcinogenicity potential. PASS Online (https://www.way2drug.com/passonline/) was used to estimate the potential biological activity spectra of the compounds based on structure-activity relationships (Abdolrahmat et al. 2025; Rivaldo and Chandra 2024). All results were compiled and comparatively analyzed to identify the major compounds of *C. spinosa* with promising pharmacological potential.

Potential molecular targets of the major *C. spinosa* constituents were identified using publicly available prediction tools and imported into the STRING database (organism: *Homo sapiens*) to construct protein–protein interaction (PPI) networks using high-confidence interaction scores. Network visualization and topological analyses were performed using Cytoscape software to identify key regulatory proteins. Functional enrichment analyses were conducted to characterize the biological relevance of the predicted targets. Gene Ontology (GO) analyses were performed for biological processes, cellular components and molecular functions, while pathway enrichment was carried out using KEGG and Reactome databases. Enriched terms related to apoptosis, cancer-associated signaling, inflammatory responses and cellular stress pathways were prioritized based on FDR-adjusted *p*-values. To integrate compound–target–pathway relationships, network-based visualizations, including Sankey diagrams, were generated to provide a comprehensive overview of the predicted pharmacological mechanisms of *C. spinosa* constituents. The integrated in silico findings were subsequently used to guide the design of in vitro experiments employing *C. spinosa* methanol extract.

Statistical analysis

For the cell proliferation and mRNA expression studies, all samples were studied in 3 replications. Data were analyzed using the Livak method in Microsoft Excel (Livak and Schmittgen 2001). *p*-values were calculated by One-way ANOVA using Mini Table 14 software (*$p<0.05$, **$p<0.01$ and ***$p<0.001$). All graphical representations were created in GraphPad Prism (version 8).

Results

In silico identification of apoptosis-related molecular targets of major *Capparis spinosa* constituents

Previous studies on the phytochemical profile of *C. spinosa* have shown that the plant's flavonoid content is largely dominated by kaempferol and quercetin, which are consistently reported as its major bioactive constituents. Therefore, to rationally predict the plant's biological effects at the molecular level, a comprehensive in silico analysis focusing primarily on these two dominant compounds was performed.

Sankey diagram analysis (Fig. 1a) revealed that kaempferol and quercetin interact with numerous common target genes, and these targets are particularly concentrated in key pathways of cancer biology such as apoptosis, the p53 signaling pathway, PI3K–Akt, MAPK, TNF and NF-κB signaling. Key regulators of intrinsic and extrinsic apoptotic mechanisms, such as CASP3, CASP8, CASP9, Bax, Bcl-2, and TP53, were found to be common targets for both compounds. This suggests that kaempferol and quercetin may exhibit a potential synergistic effect on key molecular networks regulating cell death. Protein–protein interaction (PPI) network analysis (Fig. 1b) revealed a highly linked and dense interaction network among the target proteins. The prominence of proteins such as TP53, AKT1, CASP3 and NF-κB1 as central nodes within the network suggests that these proteins may play key regulatory roles in kaempferol and quercetin-mediated biological effects. The network topology indicates that crosstalk between apoptotic signaling and proliferation and inflammatory responses can be simultaneously modulated by these compounds. Gene Ontology (GO) Biological Process enrichment analysis (Fig. 1c) revealed that the target genes were significantly enriched, predominantly in processes such as intrinsic apoptotic signaling pathways, cellular stress response, oxidative stress, and response to DNA damage. These findings demonstrate that kaempferol and quercetin can not only trigger cell death but also influence cellular stress adaptation mechanisms. In parallel, GO Cellular Component analysis (Fig. 1d) revealed that target proteins are concentrated in cellular structures directly associated with apoptosis, such as mitochondria, caspase complexes, Bcl-2 family protein complexes and NF-κB p50/p65 complexes. KEGG pathway enrichment analysis (Fig. 1e) showed that, in addition to apoptosis, cancer-related signaling networks and pathways linked to chemotherapy resistance are also prominently represented. Similarly, Reactome pathway analysis (Fig. 1f) confirmed that the intrinsic apoptotic

 https://doi.org/10.1007/s10616-026-00918-8

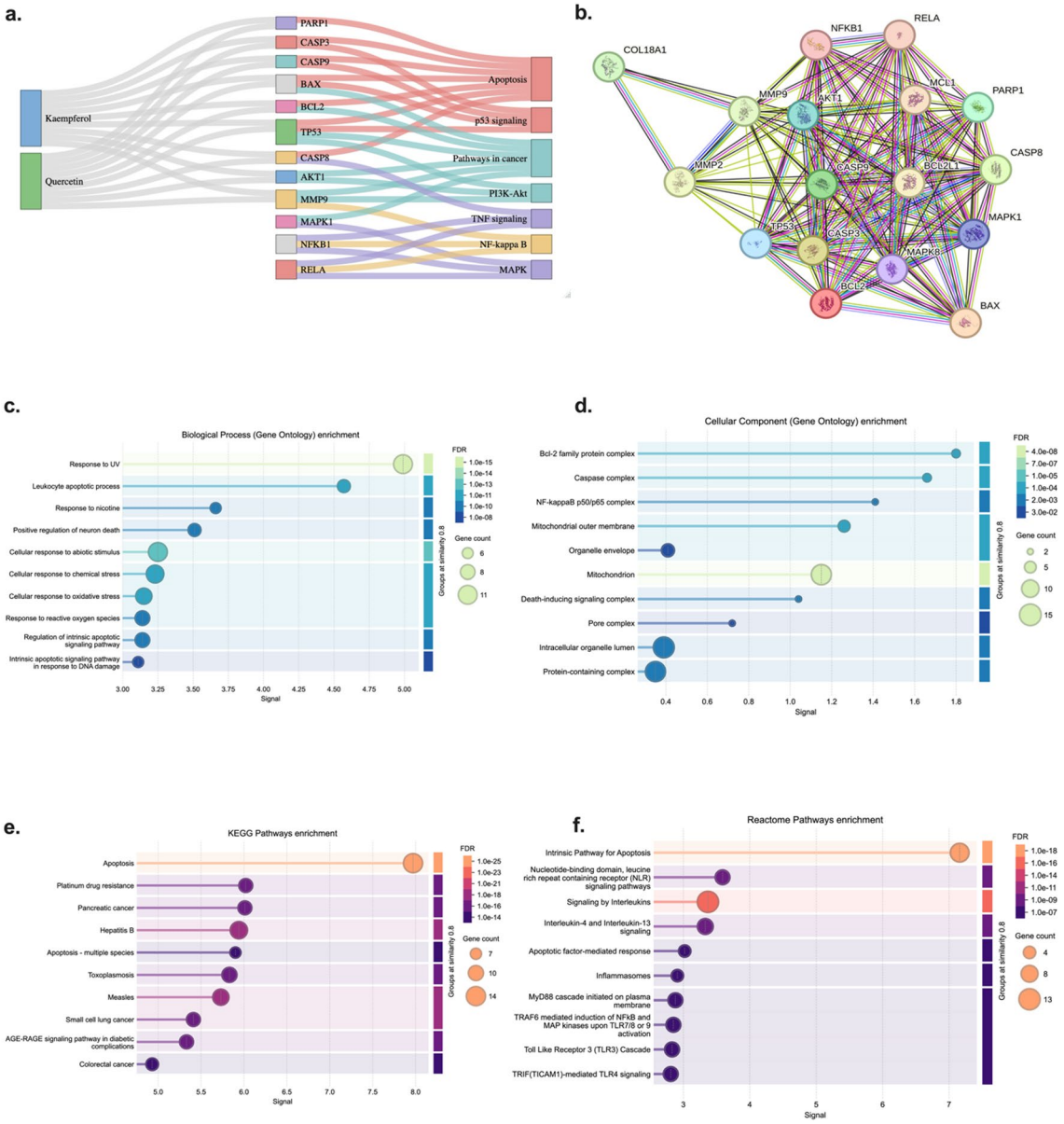

Fig. 1 Network pharmacology and pathway-level mechanistic analysis of the major flavonoids of *Capparis spinosa*. (**a**) Compound–target–pathway Sankey diagram illustrating the regulatory flow from kaempferol and quercetin to core apoptosis-associated targets (Bcl-2, Bax, CASP3/8/9, PARP1), survival and stress-related mediators (TP53, AKT1, MAPK1, NF-κB1, RELA) and the invasion-associated enzyme MMP9. These targets converge on cancer-relevant pathways including apoptosis, p53 signaling, PI3K–Akt signaling, MAPK signaling, NF-κB signaling, TNF signaling and general pathways in cancer. (**b**) STRING protein–protein interaction (PPI) network of kaempferol/quercetin-associated human targets showing high connectivity among apoptosis, stress-response and inflammatory regulators. (**c**–**d**) Gene Ontology enrichment demonstrating significant overrepresentation of biological processes related to intrinsic apoptotic signaling, oxidative stress response, cellular stress adaptation, cellular components linked to the Bcl-2 family complex, caspase complex, and mitochondrial outer membrane. (**e**) KEGG pathway enrichment highlighting apoptosis, p53, PI3K–Akt, MAPK and NF-κB signaling pathways as central routes modulated by the phytochemicals. (**f**) Reactome pathway analysis confirming activation of intrinsic apoptosis, apoptotic factor-mediated responses and TNF/TRAIL-related signaling cascades. Together, these multi-level analyses support a coordinated multi-target mechanism underlying the proapoptotic and anti-migratory effects of *C. spinosa* in prostate cancer cells

pathway, caspase-mediated signaling, and inflammatory response mechanisms stand out among the targets of kaempferol and quercetin. These results suggest that these compounds possess pleiotropic effects capable of simultaneously targeting multiple signaling pathways.

When these in silico findings are considered as a whole, it is seen that kaempferol and quercetin, the most abundant components of *Capparis spinosa*, have a strong regulatory potential on apoptosis, cellular stress response and key molecular pathways associated with cancer. However, it is known that the biological effects of plant extracts arise from the combined and potentially synergistic effects of multiple components rather than individual compounds. Therefore, in line with the in silico results obtained, the next stage of the study aims to experimentally evaluate the biological effects of *C. spinosa* methanol extract, which naturally contains kaempferol and quercetin, at the cellular level. Thus, whether the predictions based on individual compounds have a biological counterpart within the plant's holistic phytochemical matrix was investigated in in vitro models.

To further substantiate the pathway -and network- based findings, an extended in silico analysis was performed to predict the biological activity spectrum, pharmacokinetic behavior and toxicity profiles of kaempferol and quercetin, the predominant flavonoid constituents of *C. spinosa* (Table 1). Computational predictions were carried out using PASS Online (Way2Drug) for biological activity prediction, SwissADME for pharmacokinetic profiling and AdmetSAR for toxicity and drug-likeness assessments. PASS-based biological activity predictions revealed that both compounds exhibited high probability scores (Pa) for multiple anticancer-related activities. Kaempferol showed particularly strong predicted activities as an anticarcinogenic agent (Pa: 0.978), antineoplastic compound (Pa: 0.851) and TP53 expression enhancer (Pa: 0.877). Similarly, quercetin demonstrated high probabilities for apoptosis agonism (Pa: 0.887), TP53 modulation (Pa: 0.844) and antioxidant activity (Pa: 0.872). These predicted activities are highly relevant to prostate cancer biology, where dysregulation of TP53 signaling, oxidative stress imbalance and defective apoptotic pathways are recognized as major contributors to tumor initiation and progression.

Consistent with these mechanistic predictions, both compounds were computationally predicted to be effective in the treatment of prostate cancer (kaempferol: 0.643; quercetin: 0.642; $p = 0.005$), supporting their potential therapeutic relevance. These findings align with previous experimental studies reporting the anticancer activity of *C. spinosa* extracts in various cancer models, where phenolic compound–rich fractions were associated with growth inhibition and pro-apoptotic effects. (Yu et al. 2017).

Pharmacokinetic analyses using SwissADME indicated high gastrointestinal absorption for both compounds (kaempferol: 0.8041; quercetin: 0.9650), suggesting favorable oral bioavailability. Notably, both kaempferol and quercetin were predicted to localize predominantly to the mitochondria, a finding that closely aligns with the enrichment of intrinsic apoptotic signaling pathways identified in the preceding protein–protein interaction and pathway enrichment analyses. This mitochondrial localization supports a potential role for these compounds in modulating mitochondrial-mediated apoptosis. Toxicity predictions further demonstrated a favorable safety profile for both compounds. Neither kaempferol nor quercetin was predicted to be mutagenic (AMES-negative), hepatotoxic or hERG I inhibitors and acute and chronic toxicity values were within acceptable ranges. Although kaempferol was predicted as a potential hERG II inhibitor, the absence of hERG I inhibition suggests a manageable cardiotoxicity risk that warrants experimental confirmation.

Collectively, these in silico analyses indicate that kaempferol and quercetin exhibit robust anticancer-related biological activities, favorable pharmacokinetic properties, and acceptable safety profiles, particularly in the context of prostate cancer. Given that these compounds constitute the major phenolic fraction of *Capparis spinosa*, the present findings provide a strong mechanistic and pharmacological rationale for subsequent in vitro evaluation of *C. spinosa* methanol extract, enabling assessment of these predicted activities within the plant's natural phytochemical matrix.

 https://doi.org/10.1007/s10616-026-00918-8

Table 1 Comprehensive in silico prediction of biological activity, pharmacokinetic properties and toxicity profiles of kaempferol and quercetin, the major flavonoid constituents of *Capparis spinosa*

Activity	Parameters	Kaempherol	Quercetin
Prediction of biological activity	Membrane permeability inhibitor	Pa: 0,989 Pi: 0,000	Pa: 0,938 Pi: 0,003
	Membrane integrity agonist	Pa: 0,984 Pi: 0,001	Pa: 0,973 Pi: 0,002
	Proliferative diseases treatment	Pa: 0,943Pi: 0,001	Pa: 0,788 Pi: 0,004
	Histidine kinase inhibitor	Pa: 0,741 Pi: 0,006	Pa: 0,895 Pi: 0,002
	Antioxidant	Pa: 0,924 Pi: 0,003	Pa: 0,872 Pi: 0,003
	TP53 expression enhancer	Pa: 0,877 Pi: 0,006	Pa: 0,844 Pi: 0,008
	Hepatoprotectant	Pa0,958 Pi: 0,001	Pa: 0,706 Pi: 0,007
	Cancer-preventive	Pa: 0,978 Pi: 0,001	Pa: 0,757 Pi: 0,007
	Apoptosis agonist	Pa: 0,726 Pi: 0,013	Pa: 0,887 Pi: 0,005
	Antineoplastic	Pa: 0,851 Pi: 0,007	Pa: 0,797 Pi: 0,012
	Subcellular localization	Mitocondria	Mitocondria
	P-glycoprotein Substrate	Yes	Yes
	Human Intestinal Absorption	Yes (0.8041)	Yes (0.9650)
	CYP2D6 inhibitor	X	X
	CYP1A2 inhibitor	X	Yes
	CYP3A4 inhibitor	X	X
	Predicted bacterial targets	Streptococcus pneumoniae R6 Confidence: 0.4177	Streptococcus pneumoniae R6 Confidence: 0.4260
	Predicted antifungal action	Candida dubliniensis Confidence: 0.1426	Candida dubliniensis Confidence: 0.2325
HIV Targets prediction			
	Protease (HIV-1)	pIC_{50} Prediction: 6.018	pIC_{50} Prediction: 4.056
HIV Comorbidities activity spectra	Prostate cancer treatment	0.643 0.005	0.642 0.005
	Anti-inflammatory	0.607 0.019	0.627 0.017
	Antineoplastic (Breast cancer)	0.566 0.012	0.584 0.011
Prediction of toxicity	Mutagenic (AMES toxicity)	X	X
	Max. tolerated dose (Human)	0.481 (log mg/kg/day)	0.499 (log mg/kg/day)
	hERG II inhibitor	Yes	X
	hERG I inhibitor	X	X
	Oral Rat Chronic Toxicity (LOAEL)	3,569 (log mg/kg_bw/day)	2.612 (log mg/kg_bw/day)
	Skin Sensitisation	X	X
	T. Pyriformis toxicity (IGC50, ug/L)	0,285 (log ug/L)	0,288 (IGC50, ug/L)
	Minnow toxicity	6.252 (log mM)	3.721 (log mM)
	Oral Rat Acute Toxicity (LD50)	2,513(mol/kg)	2.471 (mol/kg)
	Hepatotoxicity	X	X

C. spinosa impedes PC3 cell proliferation

Based on the in silico predictions indicating that kaempferol and quercetin the major phenolic constituents of *C. spinosa* are strongly associated with apoptosis, TP53 regulation and cancer-related signaling pathways, we next sought to experimentally validate the anticancer potential of *C. spinosa* using an in vitro prostate cancer model. To this end, the cytotoxic effects of *C. spinosa* methanol extract (Fig. 2) were evaluated in PC3 cells and compared with healty HUVEC cells.

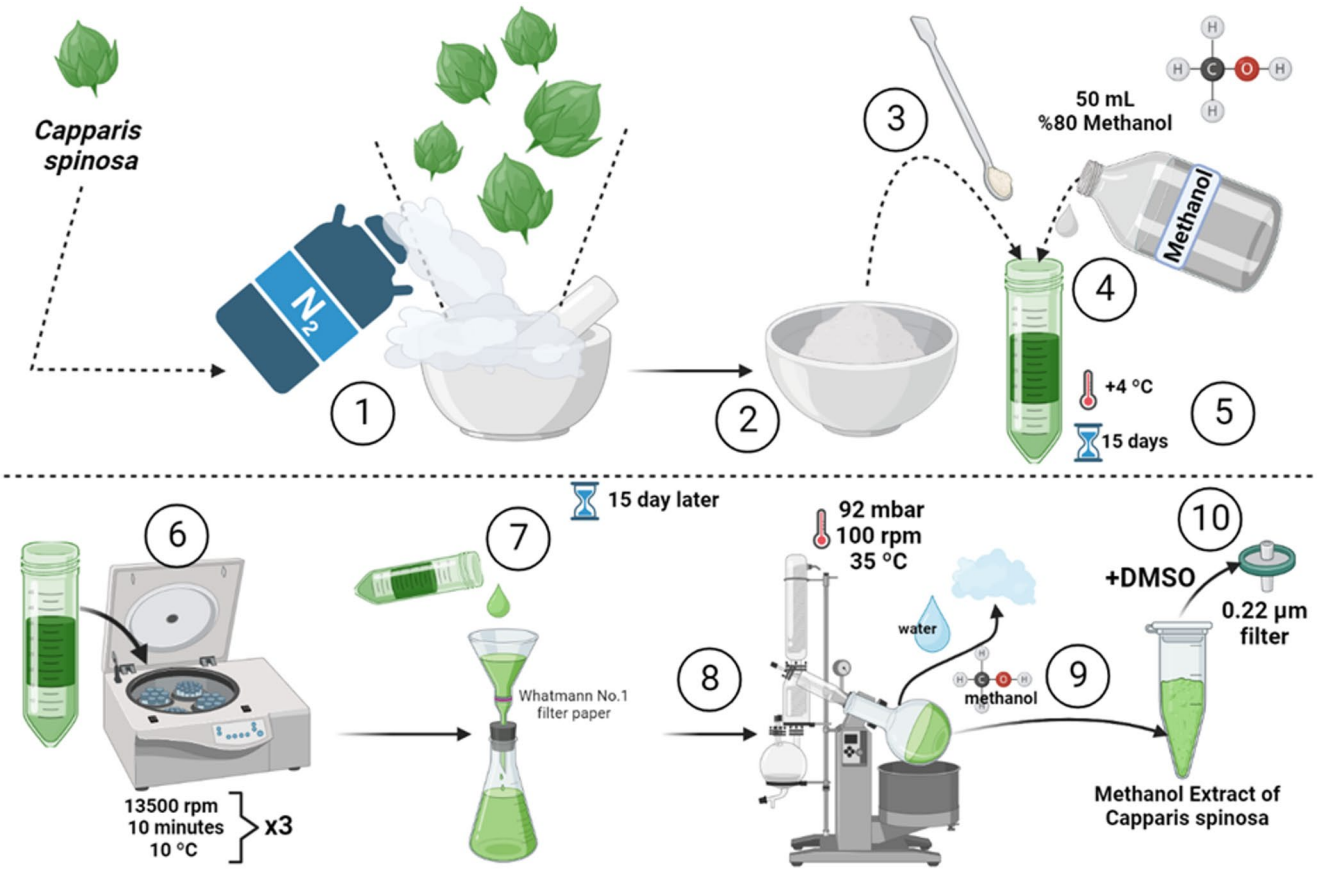

Fig. 2 Preparation of *C. spinosa* methanol extract. Schematic representation of the extraction procedure. *C. spinosa* buds were frozen with liquid nitrogen, ground into powder and incubated with 80% methanol at 4 °C for 15 days. The mixture was centrifuged, filtered and the supernatant was concentrated using a rotary evaporator. The dried extract was dissolved in DMSO and sterilized through a 0.22 µm filter for subsequent experiments

The effect of *C. spinosa* methanol extract on cell viability was evaluated in vitro using the MTT assay, which assesses cytotoxicity based on the reduction of tetrazolium salts by metabolically active cells. As shown in Fig. 3a, treatment of HUVEC cells with increasing concentrations of the extract for 24 and 48 h did not result in a significant reduction in cell viability compared with the DMSO control. Accordingly, no IC_{50} value could be determined for HUVEC cells within the tested concentration range, indicating that the extract did not exert notable cytotoxic effects on healthy endothelial cells.

In contrast, exposure of PC3 prostate cancer cells to *C. spinosa* methanol extract led to a marked, dose-dependent decrease in cell viability at both 24 and 48 h (Fig. 3b). The cytotoxic effect was more pronounced following 48 h of treatment, suggesting a time-dependent enhancement of growth inhibition. Based on these results, the half-maximal inhibitory concentration (IC_{50}) values for PC3 cells were calculated as 12.4 mg/mL at 24 h and 10.6 mg/mL at 48 h. These IC_{50} concentrations were subsequently used as reference doses for downstream molecular analyses.

Importantly, the absence of a measurable cytotoxic effect in HUVEC cells across all tested concentrations (Fig. 3a), together with the pronounced dose- and time-dependent reduction in PC3 cell viability (Fig. 3b), demonstrates a selective cytotoxic effect of *C. spinosa* methanol extract toward prostate cancer cells. This selectivity suggests that the extract preferentially targets malignant cells while sparing non-tumorigenic endothelial cells under the same experimental conditions.

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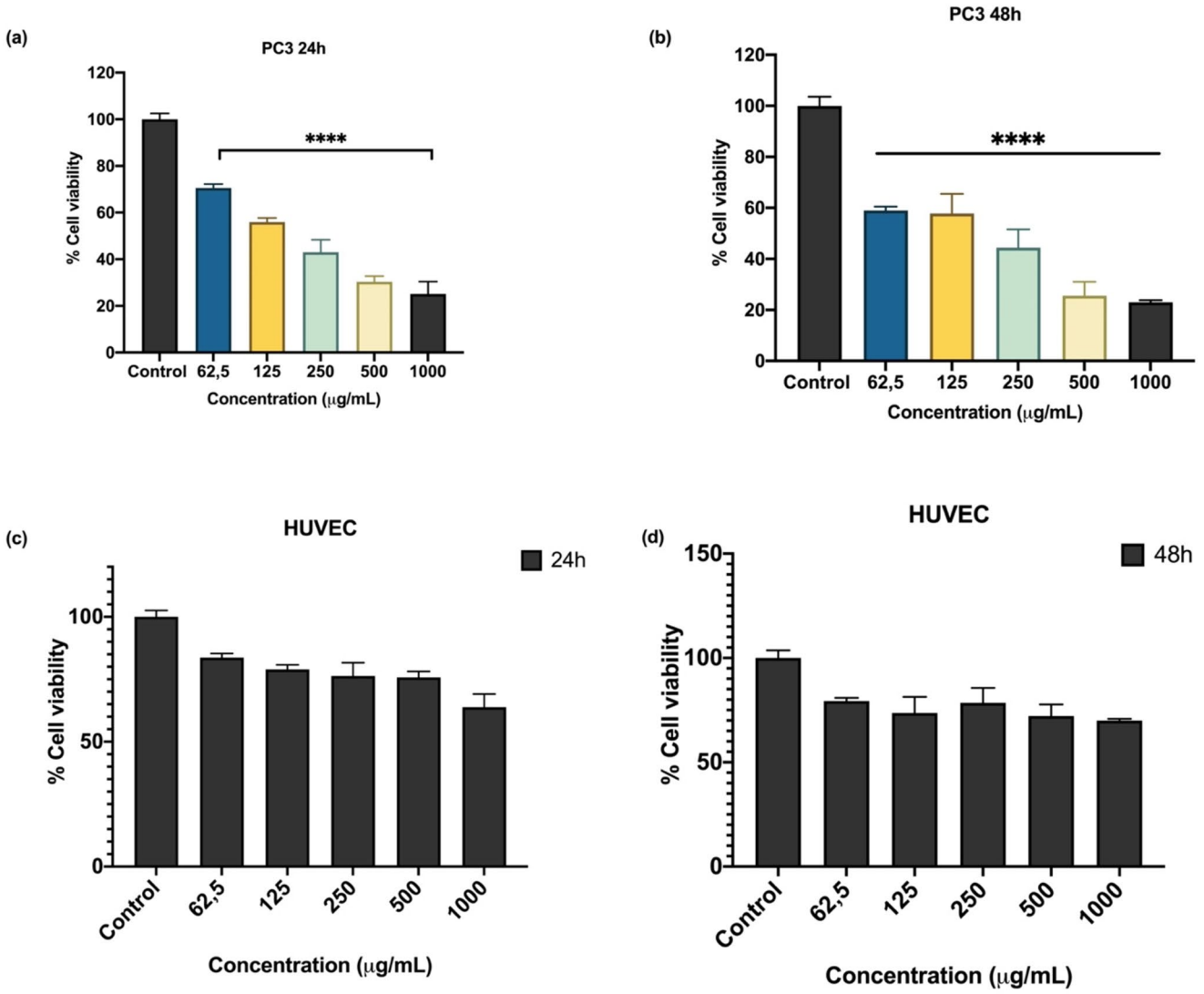

Fig. 3 Effects of *C. spinosa* methanol extract on the viability of PC3 and HUVEC cells. In vitro cytotoxicity of *C. spinosa* methanol extract was evaluated in (**a**) HUVEC and (**b**) human PC3 cells. Cells were exposed to various concentrations of the extract or DMSO control. Viability was measured by MTT assay and presented as mean ± SD from three independent experiments

C. spinosa causes a cell death in PC3 cells

To determine the molecular and cellular effects of *C. spinosa* methanol extract on prostate cancer, RT-qPCR, Western blot, wound healing and colony formation analyses were performed on PC3 cells.

In this context, the expression profiles of apoptotic (Bax) and anti-apoptotic (Bcl-2) genes were examined to elucidate the mechanisms of cell death. PC3 cells were treated with *C. spinosa* methanol extract for 24 and 48 h using previously determined IC_{50} concentrations (10 and 20 µg/µL) and gene expression levels were analyzed by RT-qPCR. Bcl-2 an anti-apoptotic protein, plays a role in maintaining cell viability by suppressing cytochrome-c release from mitochondria. In this study, a statistically significant decrease in Bcl-2 mRNA levels (Fig. 4a) was observed after both 24 and 48 h of treatment compared to the control group ($p < 0.05$). Specifically, at a dose of 10 µg/µL, a 12-fold decrease in Bcl-2 expression was detected at 24 h and a 40-fold decrease at 48 h. Similarly, at a dose of 20 µg/µL, Bcl-2 expression decreased 14-fold at 24 h and 55-fold at 48 h. When the expression of the

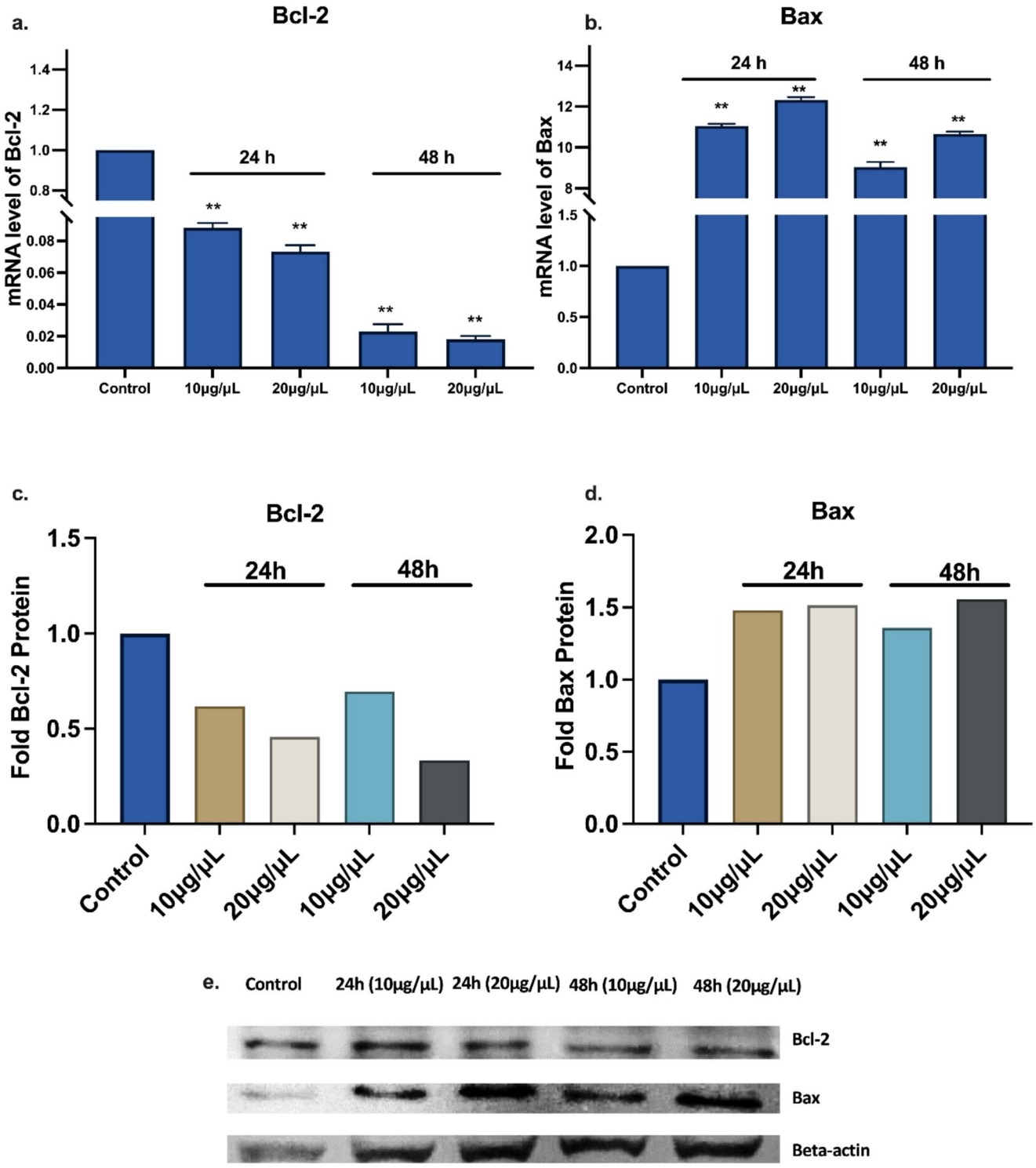

Fig. 4 Effects of *C. spinosa* methanol extract on apoptotic markers in PC3 cells. (**a**, **b**) Relative mRNA expression levels of Bcl-2 and Bax after 24 h and 48 h of treatment with 10 µg/µL and 20 µg/µL extract concentrations. (**c**, **d**) Corresponding protein expression levels of Bcl-2 and Bax determined by Western blot analysis. (**e**) Representative Western blot images showing decreased Bcl-2 and increased Bax expression, confirming induction of apoptosis. Data are presented as mean ± SD ($p < 0.01$)

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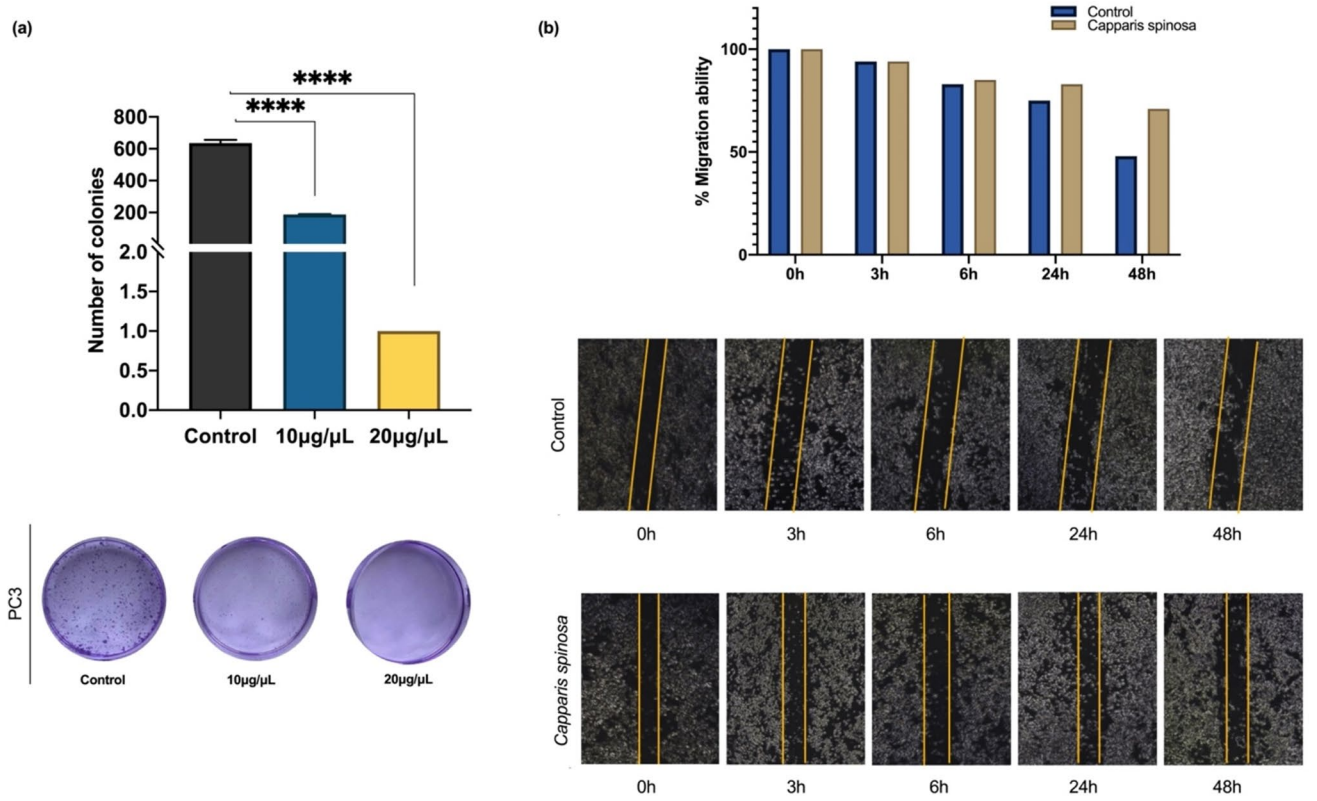

Fig. 5 Effects of *C. spinosa* methanol extract on colony formation and migration ability of PC3 cells. (**a**) Colony formation assay showing a dose-dependent reduction in the number and size of colonies following treatment with 10 and 20 µg/µL of *C. spinosa* extract for 48 h. Representative images of crystal violet–stained colonies are presented below the graph. (**b**) Wound healing assay illustrating decreased migration capacity in *C. spinosa*–treated cells compared with the control group at 3, 6, 24, and 48 h. Quantitative analysis of migration ability is shown in the accompanying bar chart. Data are expressed as mean ± SD (****$p < 0.0001$)

Bax gene a key indicator of apoptosis, was examined, it was determined that the application of *C. spinosa* methanol extract significantly increased Bax mRNA levels (Fig. 4b). At a dose of 10 µg/µL, Bax expression increased 11-fold and 9-fold at 24 and 48 h, respectively, while at a dose of 20 µg/µL, these increases were 12-fold at 24 h and 10-fold at 48 h.

To confirm the observed changes in gene expression levels, Bcl-2 and Bax protein levels were evaluated using Western blot analysis (Fig. 4). The results, consistent with mRNA findings, showed a dose- and time-dependent decrease in Bcl-2 protein levels. After 24 h of application, Bcl-2 protein levels decreased (Fig. 4c) 1.6-fold at the IC_{50} dose and 2.2-fold at the $2\times IC_{50}$ dose. After 48 h, this decrease was determined to be 1.4-fold at the IC_{50} dose and 3-fold at the $2\times IC_{50}$ dose. When Bax protein levels were examined, it was observed that the extract application had an apoptosis-promoting effect. After 24 h of application, Bax protein levels increased (Fig. 4d) 1.4-fold at the 10 µg/µL dose and 1.5-fold at the 20 µg/µL dose compared to the control group.

To evaluate the cellular counterparts of the molecular findings, colony formation and wound healing experiments were performed. In the colony formation experiment, groups treated with *C. spinosa* methanol extract showed approximately a 70% reduction in colony count after 14 days compared to the control group (Fig. 5). This result indicates that the extract significantly suppresses the long-term proliferation capacity of PC3 cells. In a wound healing experiment conducted to evaluate cell migration, it was determined that after 48 h, 48% of cells migrated in the control group, while this rate reached 72% in the extract-treated group. These findings reveal that *C. spinosa* methanol extract significantly limits the migration ability of PC3 cells.

Taken together, these findings demonstrate that *C. spinosa* methanol extract effectively suppresses antiapoptotic signaling while activating apoptotic pathways in PC3 prostate cancer cells, leading to a marked inhibition of cell proliferation and migratory capacity and ultimately resulting in the induction of cancer cell death.

Discussion

C. spinosa is known to be rich in a wide range of bioactive phytochemicals, including alkaloids, terpenoids, isothiocyanates, glucosinolates, polyphenols, carotenoids, and phenolic compounds. This chemical diversity substantially enhances the therapeutic potential of the plant and underlies its broad biological activity spectrum. Previous studies have consistently reported antioxidant, anti-inflammatory and antiproliferative effects of *C. spinosa*, supporting its relevance as a natural source of pharmacologically active compounds (Jamal et al. 2018; Kdimy et al. 2022; Saleem et al. 2021; Shahrajabian et al. 2021; Bacchetti et al. 2022).

The anticancer potential of *C. spinosa* has been demonstrated in various experimental models. Lectins isolated from caper seeds have been shown to inhibit cancer cell proliferation by inducing apoptosis in hepatoma and breast cancer cells (Lam & Ng 2009), while fruit extracts exhibit anti-inflammatory properties that may be beneficial in cancer-associated inflammation (Zhou et al. 2010). Moreover, nano emulsion formulations of *C. spinosa* oil have displayed enhanced cytotoxic effects against multiple cancer cell lines compared to the native oil (Eid et al. 2023). In addition to direct anticancer effects, *C. spinosa* extracts have been reported to alleviate chemotherapy-induced nephrotoxicity and hepatotoxicity, highlighting their potential role as supportive agents during cancer treatment (Tir et al. 2019). Collectively, these findings suggest that the anticancer activity of *C. spinosa* arises from both direct tumor-suppressive effects and modulation of cellular stress and inflammatory responses.

In the present study, a comprehensive in silico strategy was employed to investigate the molecular mechanisms underlying the anticancer potential of *C. spinosa*, with particular emphasis on its major phenolic constituents, kaempferol and quercetin. The integration of biological activity prediction, pharmacokinetic and toxicity profiling, target prediction, protein–protein interaction network analysis, and functional enrichment analyses provided a mechanistic framework that guided subsequent experimental validation. PASS-based predictions indicated that both kaempferol and quercetin possess high probabilities for apoptosis induction, TP53 modulation, antioxidant activity and antineoplastic effects mechanisms that are highly relevant in prostate cancer, where dysregulated apoptosis, oxidative stress imbalance and TP53 dysfunction are key drivers of disease progression.

Target prediction and PPI network analyses revealed that the predicted targets of kaempferol and quercetin form a densely interconnected network involving central regulators such as TP53, AKT1, CASP3, and NF-κB1. Functional enrichment analyses using GO, KEGG and Reactome databases consistently highlighted pathways related to intrinsic apoptosis, cancer-associated signaling, inflammatory regulation and cellular stress responses. Importantly, the predicted mitochondrial localization of both compounds provides a mechanistic link to intrinsic apoptotic signaling, given the pivotal role of mitochondria and Bcl-2 family proteins in regulating cytochrome c release and caspase activation. The identification of these pathways across multiple independent in silico platforms strengthens the biological plausibility of the proposed mechanisms.

Based on these computational predictions, in vitro experiments were designed to evaluate the biological effects of *C. spinosa* methanol extract in a prostate cancer model. The extract selectively reduced the viability of PC3 prostate cancer cells while exerting minimal cytotoxic effects on non-tumorigenic HUVEC cells, indicating a favorable selectivity profile. The IC_{50} value determined for PC3 cells further supported the antiproliferative potential of the extract. Molecular analyses demonstrated that the extract suppresses antiapoptotic signaling and activates proapoptotic pathways, as evidenced by the downregulation of Bcl-2 and upregulation of Bax at both mRNA and protein levels. These findings are in strong agreement with the mitochondrial and TP53-associated apoptotic mechanisms predicted by the in silico analyses.

In addition to molecular alterations, functional assays revealed that *C. spinosa* methanol extract significantly impaired the colony-forming ability and migratory capacity of PC3 cells. The marked reduction in colony formation

suggests long-term inhibition of proliferative potential, while restricted cell migration indicates a possible role in limiting tumor progression and metastatic behavior. Similar antiproliferative and cell cycle–modulating effects of *C. spinosa* extracts have been reported in other cancer models, further supporting the generalizability of these findings (Kulisic-Bilusic et al. 2012; Yu et al. 2010). Taken together, these results demonstrate that apoptosis-driven growth inhibition represents a central mechanism underlying the anticancer activity of *C. spinosa*.

Overall, the integrative in silico–in vitro approach employed in this study enabled the identification of kaempferol and quercetin as key bioactive contributors to the anticancer potential of *C. spinosa* and provided a mechanistic roadmap that was successfully validated at the cellular level. While in silico predictions cannot fully capture the complexity of multicomponent plant extracts, the consistency between computational predictions and experimental outcomes underscores the utility of network-based approaches in rationalizing plant extract–based anticancer research. These findings support further investigation of *C. spinosa* as a promising natural source for prostate cancer–oriented therapeutic strategies.

Conclusion

In conclusion, this study demonstrates that *C. spinosa* methanol extract exerts selective anticancer effects against PC3 prostate cancer cells by suppressing antiapoptotic signaling and activating apoptosis-related pathways. The integrative in silico analyses identified kaempferol and quercetin as major bioactive constituents and highlighted apoptosis, TP53 regulation and mitochondrial signaling as central mechanistic axes. These predictions were subsequently validated through in vitro experiments, which confirmed apoptosis induction, inhibition of proliferation and migration and selective cytotoxicity toward cancer cells. While in silico predictions cannot fully capture the complexity of multicomponent plant extracts, the combined computational–experimental approach employed herein provides a robust and rational framework for elucidating the anticancer potential of *C. spinosa*. Overall, these findings support *C. spinosa* as a promising natural source for prostate cancer research and warrant further investigation in advanced experimental and in vivo models.

Author contributions The authors contributed to drafting the manuscript. The authors approved the final version of the manuscript.

Funding This work was supported by the The Scientific and Technological Research Council of Türkiye [Grant number:1919B011903677].

Data availability The data generated and analyzed during this study are available from the corresponding author upon reasonable request. All in vitro experimental data and in silico analysis results supporting the findings of this study are included within the article and its supplementary materials.

Declarations

Conflict of interest The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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