ORIGINAL CONTRIBUTION

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HOMOERIODICTYOL INHIBITS SURVIVAL AND MIGRATION OF ANDROGEN-RESISTANT PROSTATE CANCER CELLS IN VITRO

Background. Flavonoids, naturally occurring compounds found in plant-based products, are being investigated as potential non-invasive treatments due to their ability to inhibit cell growth, induce apoptosis, and prevent cell migration. **Aim.** This study aims to investigate the effects of homoeriodictyol, a member of the flavanone group, both alone and in combination with docetaxel on the survival, apoptosis, migration, and proliferation of prostate cancer cells. **Materials and Methods.** Androgen-resistant prostate cancer PC3 cells were treated with various concentrations of homoeriodictyol, docetaxel, or a combination of both for 72 h. The treatment effects on cell survival, migration, apoptosis, and gene expression were evaluated using the MTT test, wound healing assay, Hoechst staining, and real-time PCR. **Results.** Homoeriodictyol induced apoptosis in PC3 cells in a concentration-dependent manner, with a more potent effect in combination with docetaxel. Apoptosis occurred through both intrinsic and extrinsic caspase pathways, leading to the upregulation of *CASP3, CASP8, TP53, BAX*, and *CYCS*, and downregulation of *BCL2* mRNA expression. Homoeriodictyol also exhibited antimigratory effects via upregulating *CDH1*, while decreasing *CDH2* expression levels. It suppressed epithelial-mesenchymal transition by downregulating the expression of *TWIST, SNAIL*, and *ZEB1*, which correlated with the observed antimigratory effects in wound healing assays. **Conclusion.** Homoeriodictyol exerted potent effects and inhibited prostate cancer cell proliferation and migration, especially when used in combination with docetaxel.

Keywords: homoeriodictyol, docetaxel, PC3, prostate cancer, chemotherapy.

Prostate cancer, with 1,414,259 cases reported by the WHO in 2020, is the second most commonly diagnosed cancer in men after lung cancer [1]. There are several treatment options available for patients diagnosed with prostate cancer [2]. Although treatment strategies used currently are considered successful in terms of the survival rate, they can lead to several complications, resulting in numerous health problems such as impotence and urinary problems after surgical intervention and radiation therapy [3]. Androgen deprivation therapy is a commonly used treatment option for advanced metastatic carcinoma, but it has limited clinical outcomes in androgen-resistant prostate

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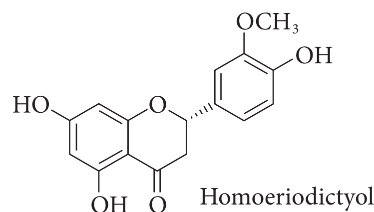
cancer [4]. Chemotherapy is a common treatment for prostate cancer; however, it causes many serious side effects [5]. Therefore, research has focused on new treatment approaches that can more effectively protect prostate function and minimize the side effects.

Flavonoids are a diverse group of plant-derived compounds known for their antioxidant properties and potential health benefits, including anticancer effects. Several flavonoids, such as apigenin, quercetin, and naringin have been studied for their potential role in cancer therapy [6—8]. It has been reported that certain flavonoids when used in conjunction with traditional chemotherapy, enhance the effectiveness of the treatment and help mitigate the side effects [7, 9]. Flavonoids, derived from phenylalanine and acetate metabolism, serve as secondary metabolites. These aromatic compounds are commonly present in fruits, vegetables, cocoa products, as well as green and black tea [7, 9]. These molecules exhibit antioxidant, anti-inflammatory, and antibacterial properties, particularly in low concentrations. Moreover, at high concentrations, flavonoids exhibit antiproliferative effects by inducing the apoptosis pathway, halting the cell cycle [6, 7, 9]. Here, we explore the effects of homoeriodictyol in vitro using prostate cancer cells and discuss the key experimental studies.

Homoeriodictyol ($C_{16}H_{14}O_6$) belongs to the flavanone group, a subset of flavonoids (Fig. 1, *a*) [10]. The studies have shown that their antimetastatic effects could be exerted via reducing cell migration and inhibiting epithelial-to-mesenchymal transition (EMT) pathways [11—13], therefore these compounds could be useful in cancer therapy [14, 15]. Despite extensive research of other flavonoid subclasses, studies on the anticancer effects of homoeriodictyol are limited. The study by Saquib et al. [10] highlighted the potential of homoeriodictyol, which affects intracellular signaling pathways and reactive oxygen species, leading to apoptosis induction and inhibition of cell proliferation in breast, colon, and cervical cancer cells.

The objective of this study was to investigate the effects of homoeriodictyol, both alone and in combination with the chemotherapeutic agent docetaxel, on the survival, apoptosis, migration, and proliferation of prostate cancer cells.



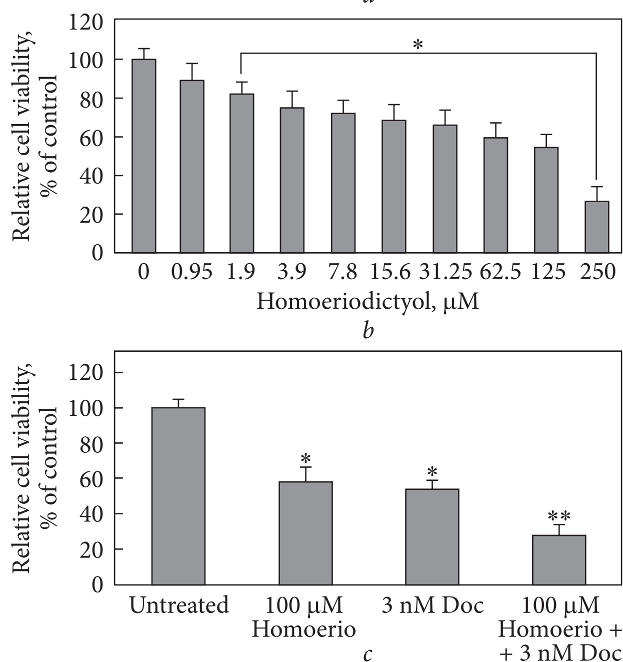


Fig. 1. Homoeriodictyol inhibits the growth of prostate cancer cells in a concentration-dependent manner: (*a*) molecular structure of homoeriodictyol; (*b*) prostate cancer PC3 cells were exposed to various concentrations of homoeriodictyol for 72 h, and cell viability was determined using the MTT assay; (*c*) the cells were treated with homoeriodictyol alone, docetaxel alone, or a combination of both for 72 h, and cell viability was assessed using the MTT assay. Data are presented as percentage changes relative to the untreated cells. $^{*}p < 0.05$ compared to untreated cells; $^{**}p < 0.05$ compared to cells treated with docetaxel

Materials and Methods

Cell culture. The androgen-resistant human prostate cancer cells of the PC3 line were purchased from ATCC (USA). The cells were cultured in sterile polystyrene cell culture dishes containing DMEM/F12 (50/50 mix, Multicell, Canada) complete liquid medium supplemented with 10 % fetal bovine serum (FBS) (GIBCO, UK) and 100 U/mL penicillin + 100 µg/mL streptomycin (Sigma-Aldrich, USA). The cells were maintained in a sterile incubator at 37 °C with 5 % CO_2 and 95 % air. Cell proliferation and passage were monitored, and cell numbers were determined using trypan blue staining in a hemocytometer before each passage. All experiments were

conducted in triplicate, and each experiment was repeated three times. The cells between passages 5 and 15 were used for experiments. All plastic containers used in the study were sourced from Wuxi NEST Biotechnology Co. (China).

Dose response determination. PC3 cells were seeded into 96-well culture plates at a density of 10,000 cells per well. After ensuring proper cell adhesion, they were treated for 72 h to determine the optimal concentration and exposure times for homoeriodicytol (Boc Sciences, USA). The concentrations of homoeriodicytol ranged from 0.95 μM to 250 μM. Homoeriodicytol was dissolved in dimethyl sulfoxide, and the final concentration of the solvent in the culture media did not exceed 0.1%. Subsequently, 3 nM docetaxel (Cayman Chemicals, USA) was administered alone and in combination with the optimal dose of homoeriodicytol for 72 h. Cell survival rates following the treatments were quantitatively assessed using the MTT (thiazolyl blue tetrazolium bromide) (Sigma-Aldrich) assay and analyzed spectrophotometrically. The absorbance was measured at 570 nm using a plate reader (Multiscan GO, Thermo Scientific, Finland).

Hoechst staining. The cells were cultured overnight in 12-well plates at a density of 2.5×10^5 per well in 1 mL of medium containing 10 % FBS. Subsequently, the cells were treated with 100 μM homoeriodictyol, 3 nM docetaxel, or a combination of both for 72 h. After the treatment, the cells were washed twice with PBS and stained with 5 μg/mL Hoechst 33342 dye (Sigma—Aldrich) at 37 °C for 5 min. The cells with fragmented nuclei were then immediately observed for morphological changes under an inverted fluorescence microscope (ZEISS, Axio Vert A.1, Germany) at 340—510 nm emission and 40× magnification, and images were captured. The assessment was conducted twice and performed in three replicates.

Cell migration analysis. The impact of the treatments on cell migration was assessed using the

The primer sequences used in the study

Gene	Primer sequences
BAX	F: 5′-CATGGGCTGGACATTGGACT-3′ R: 5′-AAAGTAGGAGAGGAGGCCGT-3′
BCL-2	F: 5′-TTGTGGCCTTCTTTGAGTTCGGTG-3′ R: 5′-GGTGCCGGTTCAGGTACTCAGTCA-3′
CASP3 (Caspase-3)	F: 5′-TGGTTCATCCAGTCGCTTTG-3′ R: 5′-CATTCTGTTGCCACCTTTCG-3′
CASP8 (Caspase-8)	F: 5′-CTGCTGGGGATGGCCACTGTG-3′ R: 5′-TCGCCTCGAGGACATCGCTCTC-3′
CYCS (Cytochrome c)	F: 5′-TGGGCCAAATCTCCATGGTC-3′ R: 5′-AGGCAGTGGCCAATTATTACTCA-3′
TP53	F: 5′-GAGGTTGGCTCTGACTGTACC-3′ R: 5′-TCCGTCCCAGTAGATTACCAC-3′
SNAİL	F: 5′-CAACCCACTCAGATGTCAA-3′ R: 5′-CATAGTTAGTCACACCTCGT-3′
TWİST	F: 5′-GGGAGTCCGCAGTCTTAC-3′ R: 5′-CCTGTCTCGCTTTCTCTTT-3′
ZEB1	F: 5′-AGTGTTTGTGATTGTGTTTGA-3′ R: 5′-GATGAAGGCGGGTTAGAG-3′
CDH1 (E-cadherin)	F: 5′-TTGACGCCGAGAGCTACAC-3′ R: 5′-GTCGACCGGTGCAATCTT-3′
CDH2 (N-cadherin)	F: 5′-TGTTTGACTATGAAGGCAGTGG-3′ R: 5′-TCAGTCATCACCTCCACCAT-3′
GAPDH	F: 5′-TTGGTATCGTGGAAGGACTCA-3′ R: 5′-TGTCATCATATTTGGCAGGTTT-3′

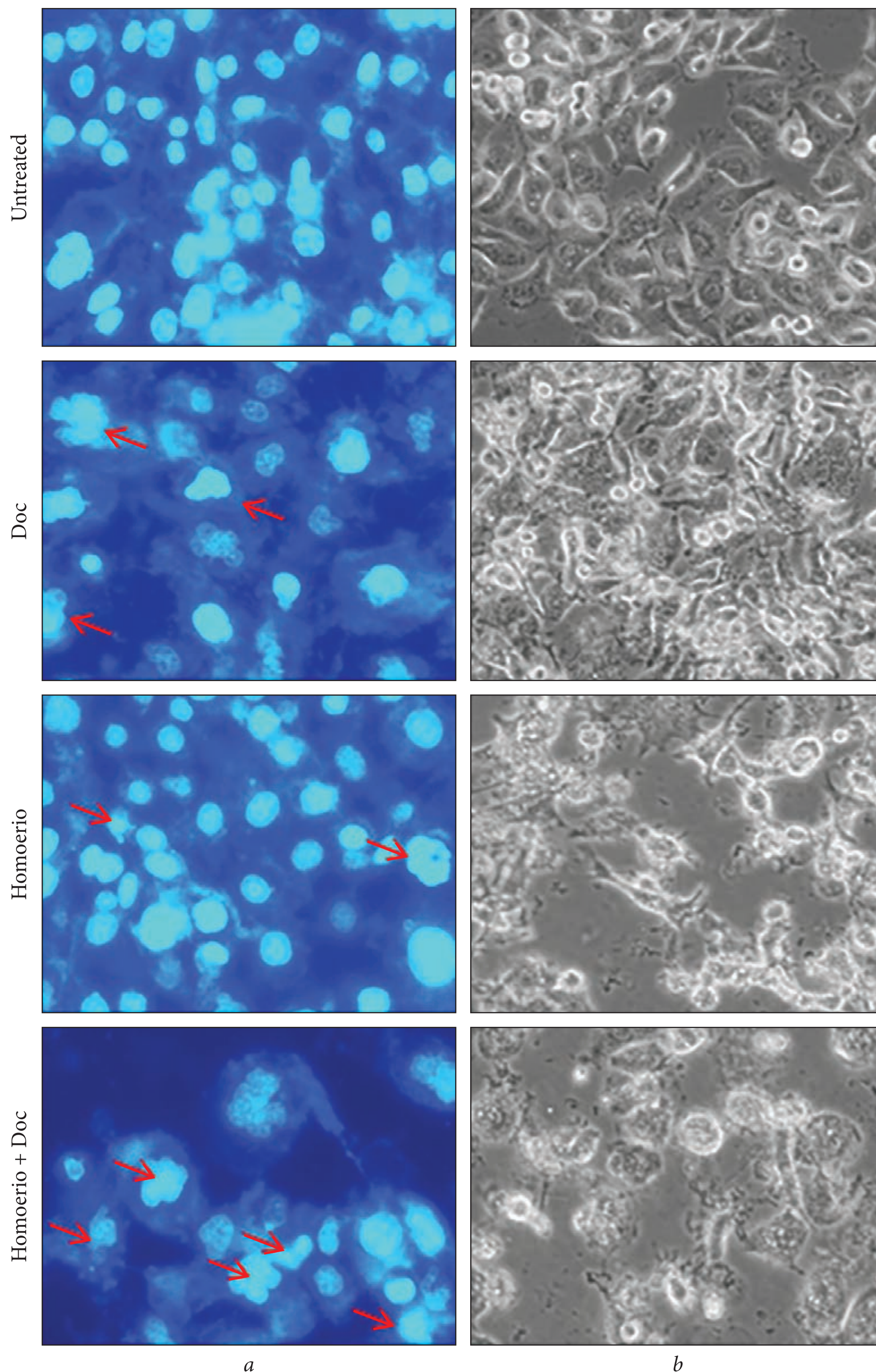


Fig. 2. Combination of docetaxel with homoeriodictyol increases the rate of apoptosis. PC3 cells were incubated for 72 h with 100 μM homoeriodictyol, 3 nM docetaxel, or both: (*a*) cells were stained with Hoechst dye, and apoptosis was evaluated using fluorescence microscopy; (*b*) phase contrast microscopy. Arrows indicate apoptotic cells

wound healing assay. PC3 cells were plated in 6-well cell culture plates at a density of 1×10^6 cells per well in 2 mL of serum-free medium. The following day, once the cells had fully covered the well bottom, a scratch was made in the cell monolayer using the tip of a 200 μL pipette. The cells were treated with 100 μM homoeriodictyol, 3 nM docetaxel, or a combination of both. Cell migration toward the scratch

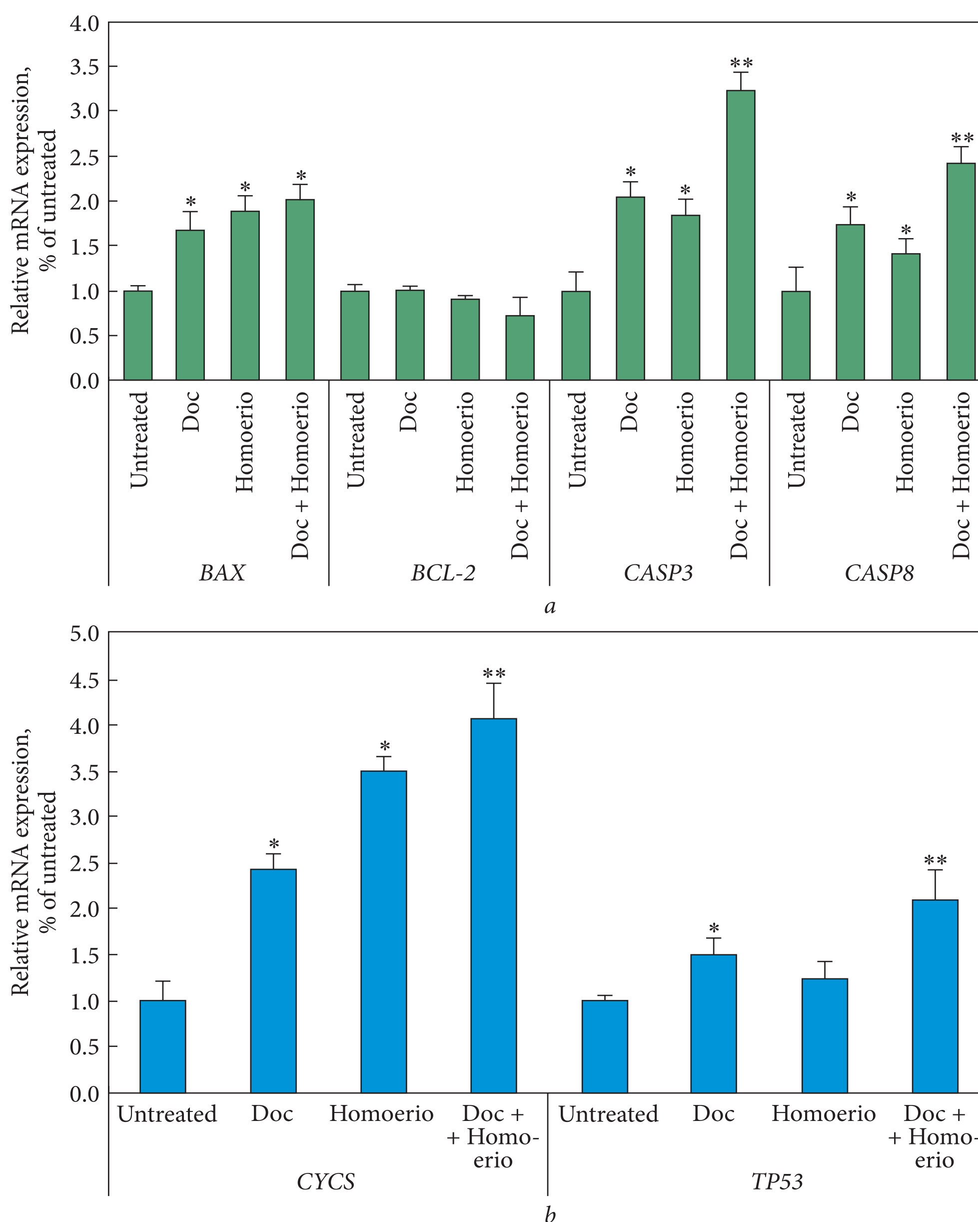


Fig. 3. Expression of genes associated with apoptosis. PC3 cells were treated with 100 μM homoeriodictyol, 3 nM docetaxel, or a combination of both for 72 h. The expression levels of the selected genes were determined by the real-time qPCR. *$p < 0.05$ compared to untreated cells; **$p < 0.05$ compared to cells treated with docetaxel

was observed by capturing images under a microscope every 24 h. This approach allowed for the performance of wound healing experiments and the calculation of cell migration percentages.

Quantification of mRNA expression. The procedure involved purifying total RNA using an RNA purification kit, followed by synthesizing cDNA with a reverse transcription cDNA synthesis kit (Thermo Fisher Scientific, Lithuania). The resulting cDNAs were then used for the real-time PCR analysis with gene-specific primer pairs. mRNA expression was analyzed using a Step One Plus real-time PCR system (Applied Biosystems, USA). The PCR cycling conditions included an initial denaturation at 95 °C for 5 min, followed by 36 cycles of 95 °C for 15 s and 60 °C for 60 s. Oligonucleotide primers (Table) were synthesized by PZR Biotech (Turkey). Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) expression was used as an internal reference. All reactions were performed in triplicate in two separate experiments with different RNA samples used in each experiment.

Statistical analysis. The data were analyzed using a one-way ANOVA test to identify significant differences. For groups with significant results, a post-hoc analysis was conducted using Duncan

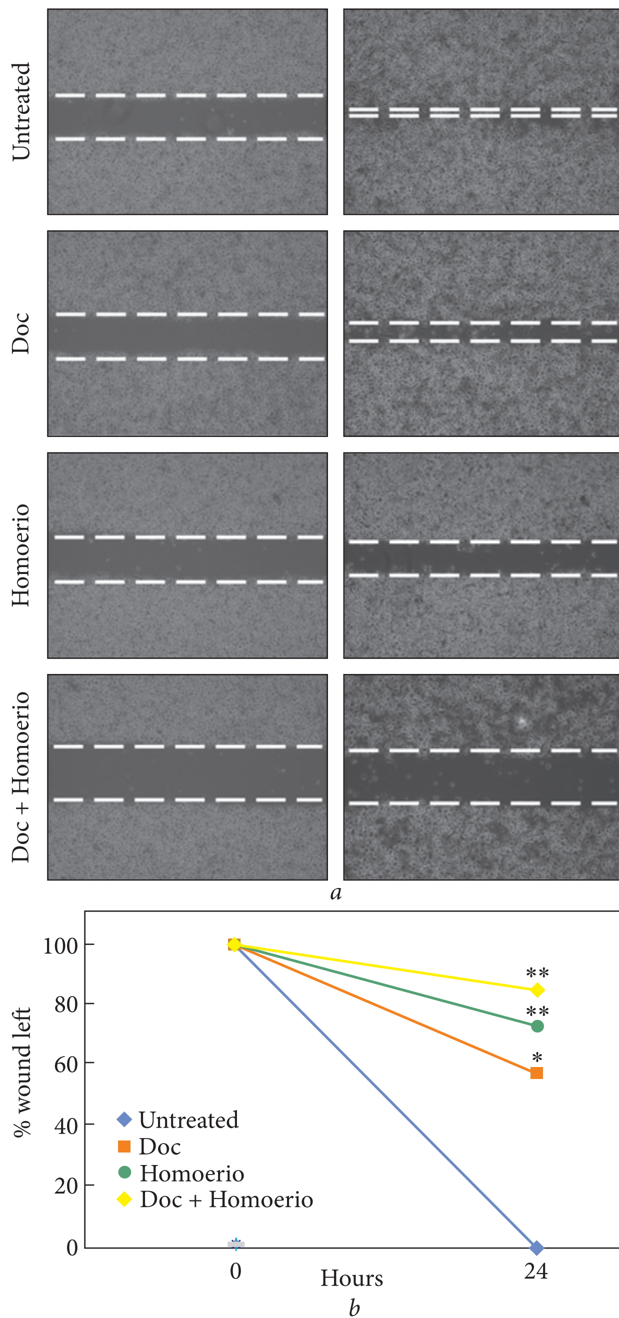


Fig. 4. Combination of homoeriodictyol with docetaxel suppresses cancer cell migration. Prostate cancer cells were incubated with 100 μM homoeriodictyol (Homoerio), 3 nM docetaxel (Doc), or a combination thereof for 24 h: (*a*) the images were taken at different time points, and the wound healing experiment was terminated when the wound gap in the control group had closed; (*b*) the wound widths were measured to determine differences between the groups. *$p < 0.05$ compared to untreated cells; **$p < 0.05$ compared to cells treated with docetaxel

tests to determine specific significance levels ($p \leq 0.05$). All statistical analyses were performed using SPSS v19 software. Additionally, half-maximum inhibitory concentration (IC_{50}) values were calculated using the IC_{50} Toolkit, available at [IC50 Toolkit](http://www.ic50.tk/index.html) [16].

Results

Homoeriodictyol inhibits cell survival. As shown in Fig. 1, *b*, homoeriodictyol reduced prostate cancer cell viability in a dose-dependent manner. For PC3 cells, IC_{50} (half maximal inhibitory concentration) of homoeriodictyol was 118.15 μM after 72 h of treatment. A concentration of 100 μM homoeriodictyol, which is close to this IC_{50} value, was used in further analyses along with docetaxel doses that had an IC_{50} value of 3 nM as established in previous studies. As shown in Fig. 1, *c*, the treatment with 3 nM docetaxel reduced cell viability to 54%, while 100 μM homoeriodictyol reduced it to 58%. Notably, the combination of homoeriodictyol and docetaxel reduced PC3 cell viability to 28%.

Homoeriodictyol induces apoptosis. The rate of apoptosis-mediated cell death of PC3 cells treated with 100 μM homoeriodictyol and 3 nM docetaxel, either separately or in combination, for 72 h was evaluated using Hoechst staining. Fluorescence and phase-contrast microscopy revealed that homoeriodictyol reduced cell density and disrupted cell morphology, and its combination with docetaxel enhanced the efficacy of this chemotherapeutic agent (Fig. 2) leading to higher apoptosis rates.

Expression of apoptosis-related genes. The molecular basis of apoptosis was investigated using RT-qPCR. Treatment of PC3 cells with homoeriodictyol significantly increased the mRNA expression of *BAX, CASP3, CASP8*, and *CYCS* (Fig. 3, *a*, *b*). Although homoeriodictyol alone did not alter the expression of *TP53*, its combination with docetaxel significantly upregulated *TP53*, along with enhanced expression of caspases (Fig. 3, *b*). The increase in *BAX/BCL2* ratio toward procaspase *BAX* expression and upregulation of caspases and cytochrome c expression, constituted the molecular evidence that the treatment modality induced apoptosis. Additionally, the increased expression of *CASP3* and *CASP8* suggests that apoptosis was initiated through both intrinsic and extrinsic pathways.

Homoeriodictyol inhibits cell migration. To assess the antimigratory effects of homoeriodictyol and combined treatment on prostate cancer cells, wound healing assays were performed. As depicted in Fig. 4, *a*, both 100 μM homoeriodictyol and

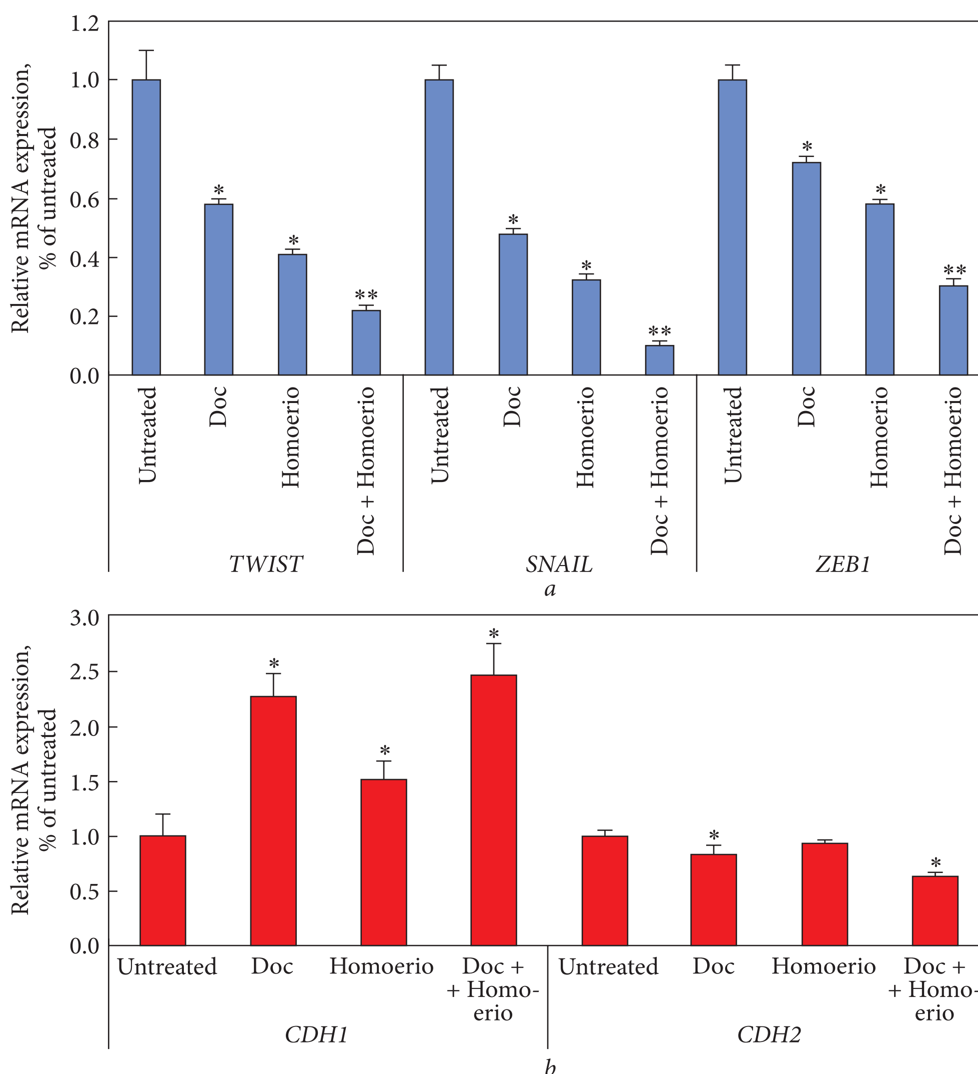


Fig. 5. Treatment with homoeriodictyol downregulates transcription factors associated with cell migration and EMT. The mRNA expression levels of transcription factors associated with cell migration and genes related to EMT were determined using RT qPCR. *$p < 0.05$ compared to untreated cells; **$p < 0.05$ compared to cells treated with docetaxel (Doc)

3 nM docetaxel significantly reduced migration of PC3 cells, with homoeriodictyol showing greater efficacy. Quantitative analysis indicated that homoeriodictyol, docetaxel, and their combination inhibited the migration by approximately 73%, 58%, and 85%, respectively (Fig. 4, *b*).

Expression of transcriptional repressors and EMT markers. The changes in the expression levels of transcriptional repressors and EMT markers in PC3 cells treated with homoeriodictyol, docetaxel, and their combination were evaluated at the level of mRNA. Homoeriodictyol reduced *TWIST, SNAIL,* and *ZEB1* mRNA expression levels by 59%, 68%, and 42%, respectively, compared to untreated cells (Fig. 5, *a*). Docetaxel treatment exerted similar suppression, while the combined treatment was significantly more effective. Homoeriodictyol increased the *CDH1* expression by 52% and did not affect the *CDH2* expression (Fig. 5, *b*). Docetaxel treatment increased *CDH1* while reducing *CDH2*. Nevertheless, the combination of docetaxel with homoeriodictyol did not alter the effects of docetaxel on the expression of these two EMT-related markers.

Discussion

The present study elucidates the anticancer potential of homoeriodictyol, used alone and in combination with docetaxel, in targeting prostate cancer cells. The results demonstrate that homoeriodictyol effectively inhibits cancer cell viability, induces apoptosis, and suppresses the migration of PC3 cells. Our findings indicate that homoeriodictyol significantly reduces the viability of prostate cancer

cells in a concentration-dependent manner, achieving an IC_{50} value of 118.15 μM after 72 h of treatment. This is consistent with the studies showing that flavonoids, including homoeriodictyol, exhibit antiproliferative effects in various cancer cell lines. In one of these studies, 500 μM homoeriodictyol caused a 51.9%, 66.7%, and 76.2% reduction in the survival of MCF-7, HeLa, and HT-29 cells, respectively [10]. Homoeriodictyol has been shown to decrease proliferation of the human lung cancer cells with the IC_{50} value of 250 μM [17]. Therefore, homoeriodictyol appears to be more effective in the treatment of prostate cancer cells compared to breast, cervical, and colon cancer cells.

The combination of 100 μM homoeriodictyol with 3 nM docetaxel resulted in a significant decrease in cell viability (up to 28%). This result evidenced that homoeriodictyol increased the effectiveness of docetaxel. This aligns with the data suggesting that combining natural compounds with chemotherapeutic agents can enhance their anticancer efficacy [7, 18—20]. Hoechst staining and phase-contrast microscopy revealed that homoeriodictyol induced apoptosis in PC3 cells more efficiently in combination with docetaxel. This is supported by molecular analyses showing the elevated mRNA expression of apoptotic markers such as *BAX*, *CASP3* (caspase-3), *CASP8* (caspase-8), and *CYCS* (cytochrome c). Notably, the combination treatment significantly upregulated *TP53* expression and enhanced caspase expression, which suggests the involvement of both intrinsic and extrinsic apoptotic pathways [21]. The *TP53* gene encodes the p53 protein, a tumor suppressor that monitors DNA integrity, aids in DNA repair, regulates the cell cycle, inhibits apoptosis, and prevents malignant transformation through autophagy control [22]. p53 inactivation due to *TP53* gene mutations is a frequent event in tumorigenesis [23]. Acting similarly to a pro-apoptotic factor and transcriptional regulator, *TP53* controls apoptosis by activating *BAX, DR-5,* and caspases. Mutations or overexpression of *TP53* are found in over 50% of human tumors and are associated with the development, progression, and prognosis of prostate cancer [24]. These findings are in line with the previous studies demonstrating that flavonoids can trigger apoptosis through the modulation of apoptotic pathways [9, 21].

The antimigratory effects of homoeriodictyol were confirmed through a wound-healing assay. Homoeriodictyol inhibited PC3 cell migration by 73%, outperforming docetaxel, which inhibited migration by 58%. The combination therapy exhibited an even higher inhibition rate of 85%. To investigate the molecular mechanisms behind the effects of homoeriodictyol on EMT, we studied how homoeriodictyol affects the transcriptional repressors *SNAIL, SLUG, TWIST,* and *ZEB-1*. The enhanced antimigratory effect is likely due to the downregulation of key EMT transcription factors, including *TWIST, SNAIL,* and *ZEB1,* and the upregulation of *CDH1* (E-Cadherin). The expression of E-cadherin, an epithelial marker protein, is reduced during EMT. Zinc finger transcription factors such as *SNAIL, SLUG, TWIST,* and *ZEB-1* are known to play a role in the down-regulation of E-cadherin expression [25]. These molecular changes are crucial for inhibiting metastasis, as EMT is a key process in cancer cell migration and invasion. It has been well documented that polyphenolic compounds can inhibit the migration of non-cancerous cells in proliferative vitreoretinopathy [26] and cancer cells [8, 27] via EMT suppression. Thus, they have the potential to prevent metastasis by inhibiting the migration of cancer cells to distant tissues, thereby preventing the formation of secondary foci.

The study highlights the potential of homoeriodictyol as a promising antiproliferation agent against prostate cancer cells. Homoeriodictyol alone or in combination with docetaxel inhibits cell viability, induces apoptosis through multiple pathways, and suppresses cell migration by modulating EMT markers. These findings provide a rationale for further preclinical investigation of homoeriodictyol as a potential adjunct treatment that enhances the efficacy of chemotherapy for prostate cancer.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship, or otherwise, that could affect the research and its results presented in this paper.

Data availability

Data will be made available on reasonable request.

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ГОМОЕРИТРОЛ ІНГІБУЄ РІСТ ТА МІГРАЦІЮ АНДРОГЕН-РЕЗИСТЕНТНИХ КЛІТИН РАКУ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ IN VITRO

Стан питання. Флавоноїди, природні метаболіти рослинного походження, досліджуються як потенційні неінвазивні засоби лікування онкологічних захворювань за їхню здатність інгібувати клітинний ріст, індукувати апоптоз та запобігати міграції злоякісних клітин. **Мета роботи.** Дослідити вплив гомоеріодиктіолу, що належить до флаванонів, на виживання, апоптоз, міграцію та проліферацію клітин раку передміхурової залози in vitro. Матеріали та методи. Андроген-резистентні клітини раку передміхурової залози лінії PC3 культивували в присутності різних концентрацій гомоеріодиктіолу, доцетакселу, а також обох речовин разом впродовж 72 год. Вплив їх на виживаність клітин, міграцію, апоптоз та експресію генів вивчали за допомогою МТТ тесту, тесту на нанесення подряпини, забарвлення за Хехстом та ПЛР в реальному часі. **Результати.** Гомоеріодиктіол індукував апоптоз клітин PC3 залежно від концентрації, при цьому більш вагомий ефект досягався за сумісного його застосування з доцетакселом. Апоптоз індукувався як рецепторним, так і мітохондріальним шляхами, що супроводжувалось підвищенням експресії генів *CASP3, CASP8, TP53, BAX* та *CYCS* і зниженням експресії *BCL2* на рівні РНК. Гомоеріодиктіол виявляв антиміграційний ефект через підвищення експресії *CDH1*, при цьому рівень експресії *CDH2* знижувався. Також гомоеріодиктіол пригнічував епітеліально-мезенхімальний перехід через зниження експресії генів *TWIST, SNAIL* та *ZEB1,* що корелювало з антиміграційним ефектом у тесті нанесення подряпини in vitro. **Висновок.** Гомоеріодиктіол інгібує проліферацію і міграцію клітин раку передміхурової залози in vitro. Ефект посилюється при сумісному застосуванні його з доцетакселом.

Ключові слова: гомоеріодиктіол, доцетаксел, клітини PC3, рак передміхурової залози, хіміотерапія.