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# Effects of Trans-Cinnamaldehyde on Epithelial-Mesenchymal Markers in Prostate Cancer

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***Abstract***
Advanced-stage prostate cancer is associated with low survival rates and high metastatic potential, often driven by epithelial–mesenchymal transition (EMT)**.** Current therapeutic options remain limited, encouraging the exploration of natural compounds with anticancer potential. Cinnamaldehyde (CA)**,** a bioactive compound derived from *Cinnamomum* bark, was investigated for its effects on EMT markers in LNCaP prostate cancer cells**.** Cells were treated with 10–40 µM CA for 24 and 48 hours, and cell viability was assessed using the MTT assay to identify effective concentrations. Expression levels of EMT-related genes such as *E-cadherin, Claudin, ZEB-1, Vimentin* and *MMP-2* were analyzed via RT-PCR**.** CA reduced prostate cancer cell viability at 20–30 µM and modulated EMT, as evidenced by decreased mesenchymal markers (*ZEB-1, MMP-2, Vimentin*) and increased epithelial markers (*E-cadherin, Claudin*). These results underscore its therapeutic potential, warranting further in vivo and clinical investigations to fully assess efficacy and safety.

***Keywords:*** Prostate Cancer, LNCaP, Cinnamaldehyde, EMT

## 1. Introduction

Prostate cancer (PCa) arises in approximately 80% of cases from the peripheral zone, and more than 95% of these cancers are adenocarcinomas [1]. Of the diagnosed cases, 80% are organ-confined, 15% present with regional metastasis, and 5% with distant metastasis [2]. While the 10-year survival probability of patients diagnosed at an early stage is 99%, this rate drops to 30% in cases with distant metastasis [1].

The primary metastatic sites of prostate cancer are the regional lymph nodes and, via hematogenous spread, the bone marrow stroma of the axial skeleton. In most patients with distant metastasis, castration-resistant prostate cancer (CRPC) develops after androgen deprivation therapy. This condition, seen as the most important cause of mortality and morbidity, ultimately progresses to treatment- and castration-resistant prostate cancer (t-CRPC), which represents the terminal stage of the disease with no available curative treatment [3].

Treatment options include active surveillance, chemotherapy (mainly cabazitaxel and docetaxel), radiotherapy, hormonal therapy, surgery, and cryotherapy [4]. These approaches may be used individually or in combination. For example, in low-risk PCa, a patient who has undergone prostatectomy with removal of the prostate and surrounding tissues may also receive radiotherapy [5]. Despite the variety of treatment options, metastatic PCa remains an incurable disease due to the resistance mechanisms it develops over time against different therapies [4]. Additionally, side effects of chemotherapeutic agents complicate treatment and impair patient compliance. The most common adverse effects include cardiovascular complications, sexual dysfunction, rectal toxicity, cognitive impairment, and chemotherapy-related neuropathy, neutropenia, diarrhea, fatigue, and hematologic problems [6–12].

Because of these side effects, researchers have sought agents that not only treat prostate cancer but also exert minimal toxicity. These agents are predominantly derived from plants. Looking at plant-based agents previously studied in prostate cancer: PC-SPES, a herbal compound, inhibited cell growth [13]. Polyphenon E, a green tea catechin, showed mild inhibitory effects on high-grade intraepithelial prostate neoplasia in placebo-controlled studies [14]. In prostate cancer patients with biochemical recurrence, pomegranate juice consumption significantly prolonged PSA doubling time, although it did not completely halt disease progression [15]. In a placebo-controlled trial, six months of oral curcumin supplementation did not induce cancer regression but suppressed PSA elevation [16]. Lycopene, found in tomatoes, exhibited inhibitory effects on prostate cancer as a monotherapy, and its combination with docetaxel enhanced docetaxel's efficacy by approximately 38% [17]. Sulforaphane, abundant in broccoli sprouts, was observed to modulate PSA doubling time [18]. Indole-3-carbinol, found in cruciferous vegetables, demonstrated anti-androgenic and anti-carcinogenic properties [19]. Flaxseed supplementation reduced tumor proliferation, as shown by Ki-67 index analysis [20]. These studies on prostate cancer highlight the importance of natural herbal products not only as complementary agents in the treatment of prostate cancer but also as potential alternatives to conventional treatments. Their ability to target multiple oncogenic pathways while maintaining a relatively favorable safety profile highlights their importance in the ongoing search for novel, well-tolerated anticancer strategies.

Cinnamaldehyde, which makes up about 65% of cinnamon extract and gives cinnamon its characteristic aroma and flavor, has also been investigated in various cancers. Findings from numerous experimental studies indicate that cinnamaldehyde displays multifunctional pharmacological properties, notably by promoting apoptotic pathways, suppressing angiogenic responses, restricting cell viability, and attenuating inflammatory signaling, in addition to providing antioxidant protection [21–26]. Despite extensive research on the anticancer properties of cinnamaldehyde in different tumor models, limited studies have examined its potential role in regulating epithelial–mesenchymal transition (EMT) in prostate cancer. In particular, the effects of cinnamaldehyde on EMT-associated gene expression in androgen-dependent prostate cancer cells remain insufficiently characterized. Therefore, the present study aimed to investigate the effects of cinnamaldehyde on EMT-related gene expression in the androgen-dependent prostate cancer cell line LNCaP. It should be noted that the findings of this study are limited to an in vitro experimental model using a single androgen-dependent prostate cancer cell line.

## 2. Material and Method

### *2.1. Culturing of LNCaP Cells*

For all cell culture procedures involving the LNCaP cell line (ATCC # CRL-1740), such as thawing, passaging, and cryopreservation, RPMI-1640 (Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS) (Cegrogen Biotech, Stadtallendorf, GERMANY) and 1% penicillin/streptomycin (Invitrogen, Carlsbad, CA, USA) was used. Cells were subcultured under standard culture conditions of 37 ℃, 95% humidity, and 5% $CO_2$. Cells were washed with 1X PBS (phosphate-buffered saline) (Cegrogen Biotech, Stadtallendorf, GERMANY) and passaged in the presence of 1X 0.25% trypsin-EDTA (+0.1% EDTA, ethylenediaminetetraacetic acid) (Thermo Scientific, Waltham, MA, USA).

### *2.2. Experimental Preparation of Cinnamaldehyde:*

Trans-cinnamaldehyde (CA) (Sigma-Aldrich, USA) was prepared under sterile conditions as a stock solution in sterile DMSO at a final concentration of 100 μM. Intermediate stock solutions were freshly prepared by diluting the main stock with culture medium just before experiments.

### *2.3. Cell Viability/Cytotoxicity Assay:*

The Cistron Biologics MTT Assay Kit (Cistron Biologics, Turkey), was used for the detection of cell viability. LNCaP cells were added to 96-well plate at 4.000 per well and incubated overnight to allow for adherence and then treated with 7 different concentrations (10, 15, 20, 25, 30, 35, 40 μM) of CA for 24 and 48 hours. Following treatments, 100 μL of the MTT: RPMI solution prepared according to the kit protocol was added to each well. The resulting changes in cell viability after CA exposure were measured using a spectrophotometer (Thermo Scientific Multiskan GO Microplate Spectrophotometer) at an absorbance of 590 nm. Results were expressed as the mean ± standard error of mean (SEM) of three independent experiments and reported as percentages relative to control conditions.

### *2.4. Gene Expression Analysis by RT-PCR:*

Total RNA was isolated using TRIzol™ reagent (Invitrogen, Carlsbad, CA, USA). Complementary DNA (cDNA) was synthesized using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Vilnius, LTU). Genes (*E-Cadherin,* F: 5′-TTAGAGGTCAGCGTGTGTGA-3′, R: 5′-CTT CTC CGC CTC CTT CTT CA-3′, *Vimentin,* F: 5′-CTG CCA ACC GGA ACA ATG AC-3′; R: 5′-TAG TTA GCA GCT TCA ACG GC-3′, *ZEB-1,* F: 5′-AGG AGC CAC AAA AGG ACA GT-3′; R: 5′-TGG GGA ATC AGA ATC GTT TGC-3′, *Claudin,* F: 5′-TGC TTG GAA GAC GAT GAG GT-3′; R: 5′-GAG CCT GAC CAA ATT CGT ACC-3′, *MMP-2,* F: 5′-TTC ATT TGG CGG ACT GTG AC-3′; R: 5′-GTG CTG GCT GAG TAG ATC CA-3′ and *GAPDH* F: 5′-GTC TCC TCT GAC TTC AAC AGC G-3′; R: 5′-ACC ACC CTG TTG CTG TAG CCA A-3′) were analyzed using Platinum® Taq DNA Polymerase kits. PCR was conducted with an initial denaturation at 94 °C for 2 min, followed by 35 cycles comprising denaturation, annealing, and extension steps (94 °C for 30 s, 55 °C for 45 s, and 72 °C for 1 min, respectively), and completed with a final 5 min extension at 72 °C. The PCR products were mixed with 10X BlueJuice™ Gel Loading Buffer (Invitrogen, Carlsbad, CA, USA) and resolved on 1.2% agarose gels in 1X TBE buffer containing 1X SYBR Green fluorescent dye. Relative band intensities of specific mRNA products were quantified using Microsoft Excel (version 16.84, 2024 Microsoft Corporation, Redmond, WA, USA) software. Expression values were normalized against GAPDH and reported as fold change compared with control conditions.

### *2.5. Statistical Analyses*

Data from three independent experiments are expressed as mean ± SEM. PCR band intensities were quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA). Relative expression levels were calculated after normalization to GAPDH and analyzed using Microsoft Excel (v16.84; Microsoft Corporation, Redmond, WA, USA). Statistical comparisons were performed using Student's t-test and one-way ANOVA, with *p < 0.05 considered statistically significant.

## 3. Results

### *3.1. Cinnamaldehyde Reduces Prostate Cancer Cell Viability*

LNCaP cells were incubated with 10, 15, 20, 25, 30, 35, and 40 µM CA for 24 and 48 hours. Compared to nontreated (NT) conditions, 20, 25, and 30 µM CA treatments for 24 hours inhibited LNCaP cell viability by 37%, 49%, and 57%, respectively. At 48 hours, these inhibitions were observed as 30%, 45%, and 53%, respectively (Figure 1). Based on these results, 20, 25, and 30 µM CA concentrations were selected for subsequent gene expression analysis due to their significant inhibitory effects on LNCaP cell viability.

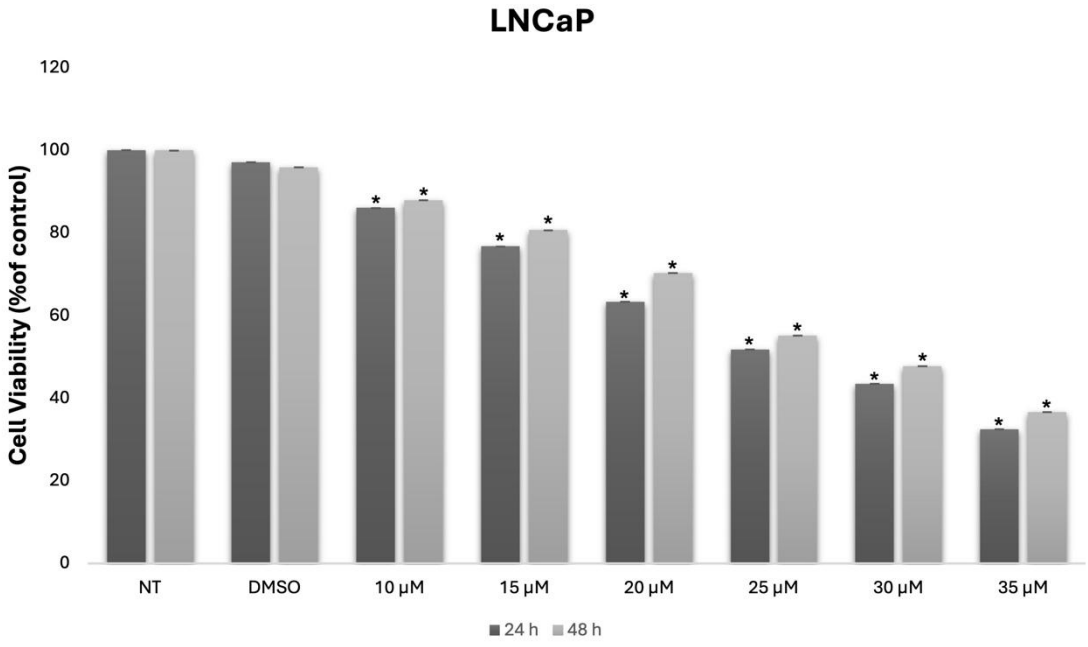



**Figure 1.** Cinnamaldehyde inhibited the cell viability of LNCaP cells. Cell viability was assessed using the MTT assay, and the mean absorbance at 590 nm was measured at 24 and 48 hours. Results are presented as mean ± SEM of three independent experiments. Statistical significance was determined by comparison to the NT control, with *p <0.05 indicating a significant difference.

### *3.2. Regulation of EMT Markers by Cinnamaldehyde in Prostate Cancer*

Based on the results from cell viability assays, the effects of 20, 25, and 30 µM cinnamaldehyde (CA) on the gene expression of EMT key mediators in LNCaP prostate cancer cell line was further analyzed by RT-PCR, relative to NT condition. Among mesenchymal markers, *ZEB-1* expression was significantly reduced by 15% and 14% following 20 and 25 µM CA treatment for 24 hours, respectively. Interestingly, a modest increase of 9% in *ZEB-1* expression was observed with 30 µM CA. However, after 48 hours, all three doses of CA significantly diminished *ZEB-1* expression, with reductions

of 23%, 36%, and 55% at 20, 25, and 30 µM, respectively (Figure 2). These findings revealed the potent regulatory effect of CA on mesenchymal mediators and suggested its potential role in promoting a more epithelial-like phenotype in androgen-dependent prostate cancer cells.

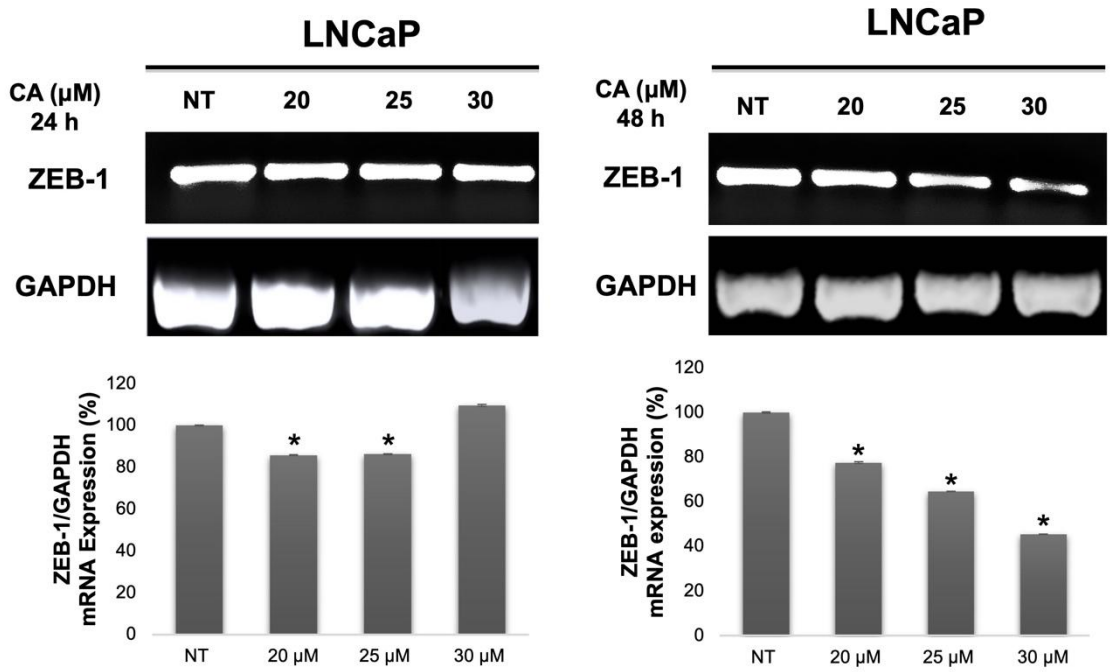



**Figure 2**. Cinnamaldehyde suppresses the expression of *ZEB-1* gene expression in LNCaP cells. *GAPDH* served as the internal control for RT-PCR analysis. Gene expression levels were normalized to the loading control and are presented as mean ± SEM of three independent experiments. *ZEB-1* expression was quantified relative to NT controls, with *p <0.05 indicating statistical significance.

Upon 24-hour treatment, CA elicited a concentration-dependent modulation of *Vimentin* expression, with slight upregulation at 20 µM (6%) and a more pronounced induction at 25 µM (25%), followed by a moderate increase at 30 µM (18%). However, this increase was reversed after 48 hours of treatment, wherein *Vimentin* expression was markedly attenuated, showing reductions of 11%, 9%, and 33% at 20, 25, and 30 µM, respectively (Figure 3). These findings suggest a biphasic and time-dependent regulatory effect of CA on *Vimentin*, characterized by transient induction at earlier stages and subsequent suppression with prolonged exposure.

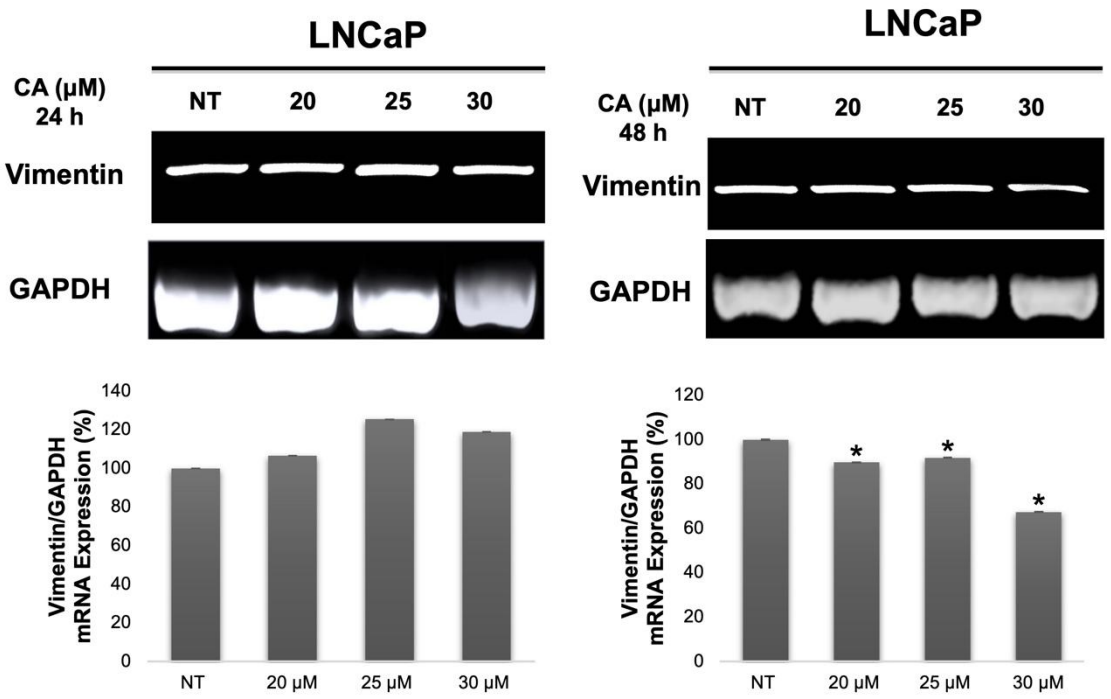



**Figure 3.** Cinnamaldehyde suppresses the expression of *Vimentin* gene expression in LNCaP cells. *GAPDH* served as the internal control for RT-PCR analysis. Gene expression levels were normalized to the loading control and are presented as mean ± SEM of three independent experiments. *Vimentin* expression was quantified relative to NT controls, with *p <0.05 indicating statistical significance.

Treatment with CA markedly affected *MMP-2* expression in an especially time-dependent manner. After 24 hours, *MMP-2* levels were substantially diminished at 20 μM (85% reduction), while only modest decreases were observed at 25 μM (12%) and 30 μM (19%). When prolonged exposure for 48 hours, this decrease was deeper at higher concentrations, as 85% and 93% at 25 and 30 μM, respectively (Figure 4). These results highlight the potent suppressive capacity of CA on *MMP-2* expression, particularly evident under extended treatment conditions.

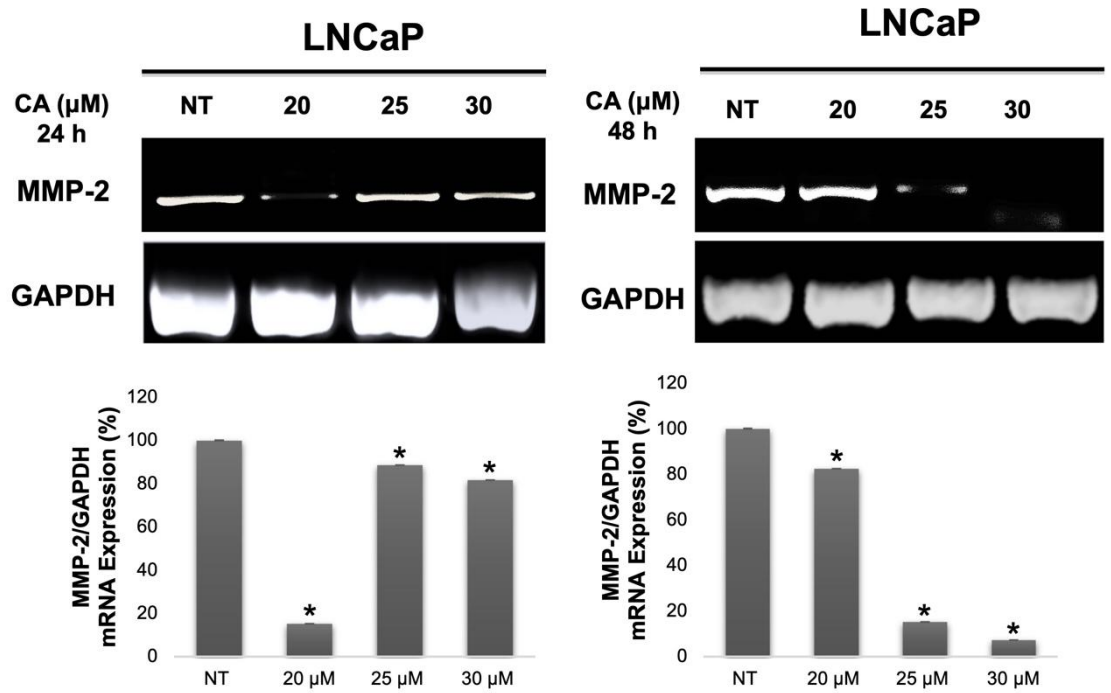


**Figure 4.** Cinnamaldehyde suppresses the expression of *MMP-2* gene expression in LNCaP cells. *GAPDH* served as the internal control for RT-PCR analysis. Gene expression levels were normalized to the loading control and are presented as mean ± SEM of three independent experiments. *MMP-2* expression was quantified relative to NT controls, with *p <0.05 indicating statistical significance.

Among epithelial mediators, *Claudin* expression exhibited a significant increase only in 20 µM CA treatment for 48 hours, as 79% (Figure 5). In contrast, *E-Cadherin* displayed a distinct expression pattern: after 24 hours, treatment with 20, 25, and 30 µM CA induced marked increases of 7.9-, 3.9-, and 1.1-fold, respectively. At 48 hours, *E-Cadherin* remained elevated only with 20 µM CA (2.2-fold increase), while higher concentrations (25 and 30 µM) produced significant reductions of 26% and 32%, respectively (Figure 6).

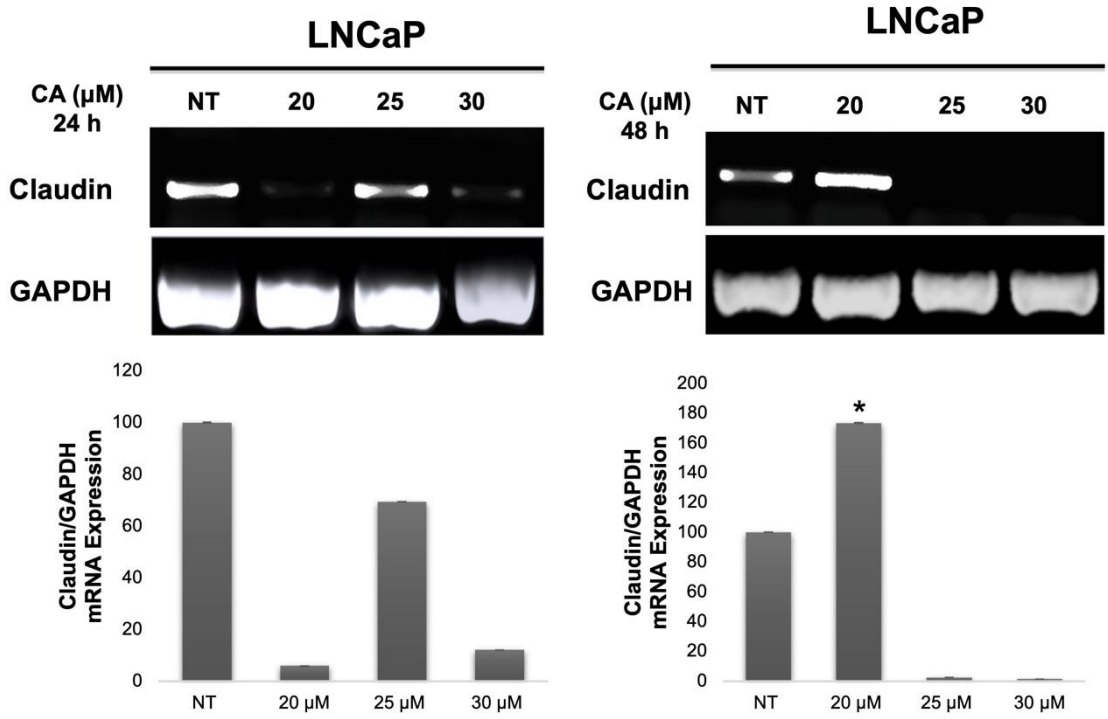



**Figure 5.** Treatment with 20 µM cinnamaldehyde for 48 hours led to an increase in *Claudin* gene expression in LNCaP cells. *GAPDH* served as the internal control for RT-PCR analysis. Gene expression levels were normalized to the loading control and are presented as mean ± SEM of three independent experiments. *Claudin* expression was quantified relative to NT controls, with *p <0.05 indicating statistical significance.

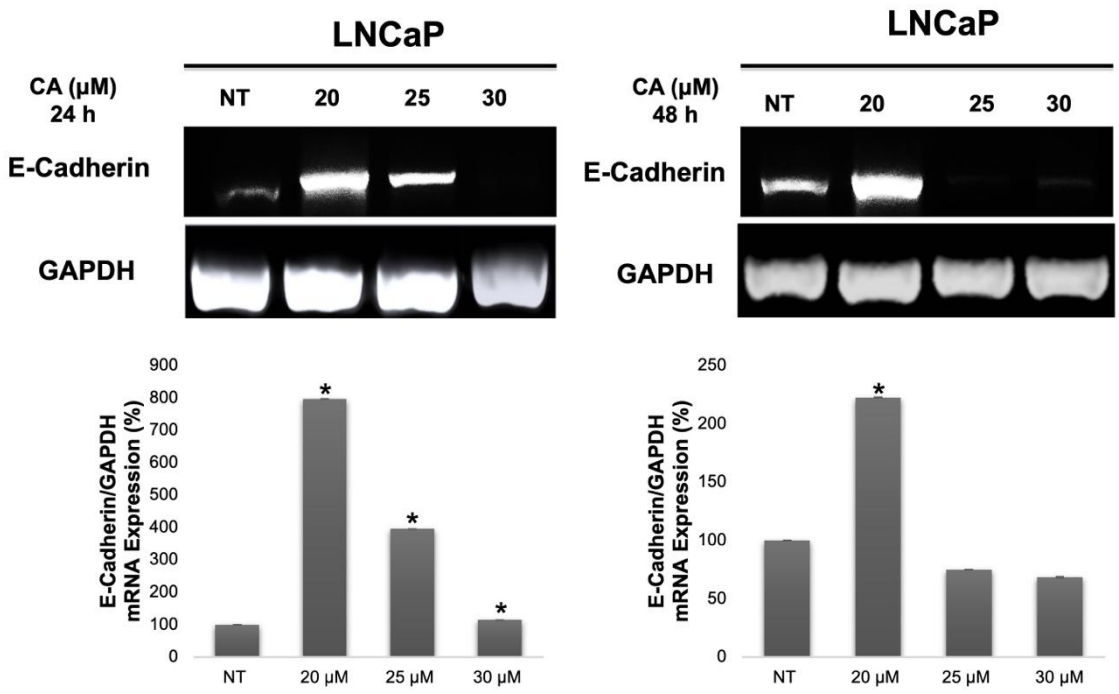



**Figure 6.** In LNCaP cells, cinnamaldehyde upregulates *E-Cadherin* expression. *GAPDH* served as the internal control for RT-PCR analysis. Gene expression levels were normalized to the loading control and are presented as mean ± SEM of three independent experiments. *E-Cadherin* expression was quantified relative to NT controls, with *p <0.05 indicating statistical significance.

## 4. Conclusion

CA exerted profound, dose- and time-dependent effects on LNCaP prostate cancer cells, regulating both cellular viability and the expression of key EMT mediators. Cell viability assays revealed that CA significantly suppressed cell viability at concentrations of 20–30 μM, with inhibitory effects evident at both 24 and 48 hours, thereby establishing a cytotoxic window that guided subsequent analyses.

Studies have demonstrated that CA exerts a broad spectrum of biological activities, including the induction of apoptosis and the inhibition of angiogenesis, cellular viability, and inflammatory processes, while also conferring significant antioxidant effects [21–26]. According to studies investigating the anticancer effects of CA in different cancer cell lines, the effective doses and mechanistic effects have been reported as follows [27]: In breast cancer, it demonstrated anti-cancer activity by inducing autophagy, inhibiting migration and metastasis, and suppressing angiogenesis. In the MDA-MB-231 cell line, following 24 and 48 hours of cinnamaldehyde treatment, the IC50 doses were determined as 16.9-12.23 μg/ml, respectively [28]. In liver cancer cells HepG2, the IC50 dose was reported as 9.76 μM [29]. For human metastatic skin cancer cell lines A375, G361, and LOX, the IC50 doses were 6.3-8.1-3.4 μM, respectively [30]. In leukemia L1210 cells, the ED50 value was 4.8 μg/ml [31]. In colon cancer cells LoVo and HT-29, the IC50 doses of CA were 9.48-9.12 μg/ml, respectively [32], and also it inhibited cell viability by inducing programmed cell death [21,32,33]. In non-small cell lung cancer mouse models, it suppressed tumor growth through the inhibition of the cell cycle and induced apoptosis [21,34,35]. In human colorectal cancer cells HCT116, it exerted a synergistic effect in apoptosis by inhibiting genes responsible for drug metabolism [21,32,33]. In gastric cancer, it enhanced apoptosis and reduced migration [25]. In bladder cancer, it inhibited HER2/neu, an oncogene [26]. In cervical cancer, it inhibited the PI3K/AKT pathway and promoted degradation of the E6 and E7 proteins [36]. In ovarian cancer cell

lines SKOV3 and A2780, it induced cell cycle arrest at the G2/M phase [21,24], while in fibroblast-associated prostate cancer mouse models (PF179T cell lines), it inhibited the cell cycle and triggered apoptosis. In renal adenocarcinoma mouse models, cinnamaldehyde was shown to suppress tumor angiogenesis [21,37,38].

Consistent with its cell viability activity, CA treatment markedly influenced mesenchymal regulators. *ZEB-1* expression was modestly reduced at lower concentrations after 24 hours, whereas prolonged exposure resulted in a pronounced downregulation across all tested doses, highlighting a strong inhibitory action on EMT transcriptional programs. Similarly, *Vimentin* exhibited a biphasic response, with transient induction at 24 hours followed by substantial suppression at 48 hours, suggesting early adaptive changes preceding a longer-term attenuation of mesenchymal phenotype. In alignment with these findings, *MMP-2* expression was potently inhibited, particularly after 48 hours at higher concentrations, underscoring CA's ability to impair extracellular matrix remodeling and invasive potential. In contrast, epithelial mediators responded in a more nuanced manner. *Claudin* expression was enhanced only under 20 μM CA at 48 hours, whereas all other conditions led to downregulation, indicating a concentration-specific reinforcement of tight junctions. *E-Cadherin*, a central adhesion molecule, was robustly induced at 24 hours—most prominently at 20 μM—but declined at higher doses upon extended exposure, reflecting a biphasic regulation that may balance epithelial stability with cytotoxic stress.

Research examining the influence of cinnamaldehyde on the EMT mechanism has shown that, in 4T1 breast cancer cells, cinnamaldehyde suppressed EMT via MMP-9 when applied at a concentration of 25 μg/ml [39]. In the ovarian cancer cell lines IOSE80, A2780 and SKOV3, the IC50 values were calculated as 19.18, 11.82, and 23.00 μg/ml at 24 hours, and 5.956, 8.651 and 5.792 μg/ml at 48 hours. At these concentrations, cinnamaldehyde was reported to inhibit the EMT process through modulation of the PI3K/AKT signaling pathway [21]. In colorectal cancer cell lines HCT116 and SW480, it exhibited a reverse effect on the EMT process under hypoxic conditions [40]. In the non-small cell lung cancer cell lines A549, YTMLC-90, and NCI-H1299, the IC50 values were calculated as 41.02, 32.30, and 10.50 μg/ml, respectively. At these concentrations, cinnamaldehyde was found to suppress EMT by targeting the Wnt/β-catenin signaling pathway [41].

In summary, the findings provide evidence that CA orchestrates a dynamic, context-dependent modulation of EMT-associated pathways in prostate cancer cells. By simultaneously suppressing mesenchymal markers and selectively enhancing epithelial traits, CA appears to promote a shift toward a less invasive phenotype, while its cytotoxic effects further limit tumor cell viability. This dual action highlights the therapeutic potential of CA in suppressing both the growth-related and migratory capacities of prostate cancer cells, emphasizing the need for further investigation into its underlying molecular mechanisms and possible translational applications. However, the present findings should be interpreted with caution, as the experiments were conducted using only a single androgen-dependent prostate cancer cell line (LNCaP). Therefore, the results cannot be directly generalized to other prostate cancer subtypes, particularly androgen-independent or castration-resistant models. Future studies including additional prostate cancer cell lines and in vivo models are required to validate these observations.

Our findings suggest that CA may influence metabolic activity and EMT-associated gene expression in androgen-dependent prostate cancer cells. While these results indicate a potential role of cinnamaldehyde in modulating EMT-related pathways, further studies

using additional prostate cancer models and in vivo systems are required to confirm its therapeutic relevance. A limitation of this study is the use of a single androgen-dependent prostate cancer cell line, which restricts the generalizability of the findings.

## *Authorship contribution statement*

**M. Balaban** contributed 35% to Data Curation, Formal Analysis, and Original Draft Writing. **Z. Akpınar** contributed 30% to Conceptualization, Investigation, Formal Analysis, Methodology, and Visualization. **N. Gurbuz** contributed 35% to Conceptualization, Formal Analysis, Resource/Material/Instrument Supply, Review and Editing, Project Administration, and Supervision/Observation/Advice

## *Declaration of competing interest*

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## *Ethics Committee Approval and/or Informed Consent Information*

As the authors of this study, we declare that we do not have any ethics committee approval and/or informed consent statement.

**References**

[1] S. Wasim, S. Y. Lee and J. Kim, "Complexities of Prostate Cancer", *International Journal of Molecular Sciences*, 23(22), 14257, 2022.
[2] R. L. Siegel, K. D. Miller and A. Jemal, "Cancer Statistics, 2018", *CA Cancer Journal for Clinicians*, 68(1), 7–30, 2018.
[3] R. B. Berish, A. N. Ali, P.G. Telmer, J. A. Ronald and H. S. Leong, "Translational Models of Prostate Cancer Bone Metastasis", *Nature Reviews Urology*, 15(7), 403–421, 2018.
[4] M. Sekhoacha, K. Riet, P. Motloung, L. Gumenku, A. Adegoke and S. Mashele, "Prostate Cancer Review: Genetics, Diagnosis, Treatment Options, and Alternative Approaches", *Molecules*, 27(17), 5730, 2022.
[5] A. W. Lambert, D. R. Pattabiraman and R. A. Weinberg, "Emerging Biological Principles of Metastasis", *Cell*, 168(4), 670–691, 2017.
[6] C. Bach, S. Pisipati, D. Daneshwar, M. Wright, E. Rowe and D. Gillatt, "The Status of Surgery in the Management of High-Risk Prostate Cancer", *Nature Reviews Urology*, 11(6), 342–351, 2014.
[7] K. Desai, J. M. McManus, N. Sharifi, "Hormonal Therapy for Prostate Cancer", *Endocrine Reviews*, 42(3), 354–373, 2021.
[8] S. Kakkat, P. Pramanik, S. Singh, A. P. Singh, C. Sarkar and D. Chakroborty, "Cardiovascular Complications in Patients with Prostate Cancer: Potential Molecular Connections", *International Journal of Molecular Sciences*, 24(8), 6984, 2023.
[9] I. M. da Fonseca Pedroso, M. L. S. Siqueira, T. A. B. P. de Sousa Santos, K. de Paula Barbosa, E. A. N. de Lima and A. C. R. I. Sampaio, "Conservative Treatment of Sexual Dysfunction among Men Undergoing Prostate Cancer Treatment: A Systematic Review", *Sexual Medicine Reviews*, 12(4), 710–719, 2024.
[10] K. Fukata, H. Kawamura, N. Kubo, T. Kanai, M. Torikoshi, T. Nakano, "Retrospective Comparison of Rectal Toxicity Between Carbon-Ion Radiotherapy and Intensity-Modulated Radiation Therapy Based on Treatment Plan, Normal Tissue Complication Probability Model, and Clinical Outcomes in Prostate Cancer", *Physica Medica*, 90, 6–12, 2021.
[11] B.A. Cowan, K. Olivier, B. Tombal and J. S. Wefel, "Treatment-Related Cognitive Impairment in Patients with Prostate Cancer: Patients' Real-World Insights for Optimizing Outcomes", *Advances in Therapy*, 41(2), 476–491, 2024.

[12] T. Kulasegaran and N. Oliveira, "Metastatic Castration-Resistant Prostate Cancer: Advances in Treatment and Symptom Management", *Current Treatment Options in Oncology*, 25(7), 914–931, 2024.
[13] W. K. Oh, P. W. Kantoff, V. Weinberg, G. Jones, B. I. Rini and M. K. Derynck, "Prospective, Multicenter, Randomized Phase II Trial of the Herbal Supplement, PC-SPES, and Diethylstilbestrol in Patients With Androgen-Independent Prostate Cancer", *Journal of Clinical Oncology*, 22(18), 3705–3712, 2004.
[14] N. B. Kumar, J. Pow-Sang, K. M. Egan, P. E. Spiess, S. Dickinson and R. Salup, "Randomized, Placebo-Controlled Trial of Green Tea Catechins for Prostate Cancer Prevention", *Cancer Prevention Research*, 8(10), 879–887, 2015.
[15] C. J. Paller, A. Pantuck and M. A. Carducci, "A Review of Pomegranate in Prostate Cancer", *Prostate Cancer and Prostatic Diseases*, 20(3), 265–270, 2017.
[16] Y. H. Choi, D. H. Han, S. Kim, M. Kim, H. H. Sung and H. G. Jeon, "A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Role of Curcumin in Prostate Cancer Patients with Intermittent Androgen Deprivation", *Prostate*, 79(6), 614–621, 2019.
[17] E. Zhuang, E. Uchio, M. Lilly, X. Zi and J. P. Fruehauf, "A Phase II Study of Docetaxel plus Lycopene in Metastatic Castrate Resistant Prostate Cancer", *Biomedicine and Pharmacotherapy*, 143, 112226, 2021.
[18] J. J. Alumkal, R. Slottke, J. Schwartzman, G. Cherala, M Munar and J. N. Graff, "A Phase II Study of Sulforaphane-Rich Broccoli Sprout Extracts in Men with Recurrent Prostate Cancer", *Investigational New Drugs*, 33(2), 480–489, 2015.
[19] F. H. Sarkar and Y. Li, "Indole-3-Carbinol and Prostate Cancer", *Journal of Nutrition*, 134(12), 3493S–3498S, 2004.
[20] W. Demark-Wahnefried, T. J. Polascik, S. L. George, B. R. Switzer, J F. Madden and M.T. Ruffin, "Flaxseed Supplementation (Not Dietary Fat Restriction) Reduces Prostate Cancer Proliferation Rates in Men Presurgery", *Cancer Epidemiology, Biomarkers and Prevention*, 17(12), 3577–3587, 2008.
[21] J. Peng, X. Song, W. Yu, Y. Pan, Y. Zhang and H. Jian, "The Role and Mechanism of Cinnamaldehyde in Cancer", *Journal of Food and Drug Analysis*, 32(2), 146–160, 2024.
[22] Y. Olayiwola and L. Gollahon, "Natural Compounds and Breast Cancer: Chemo-Preventive and Therapeutic Capabilities of Chlorogenic Acid and Cinnamaldehyde", *Pharmaceuticals*, 17(3), 361, 2024.
[23] A. Nile, J. Shin, J. Shin, G. S. Park, S. Lee and J. H. Lee, "Cinnamaldehyde-Rich Cinnamon Extract Induces Cell Death in Colon Cancer Cell Lines HCT 116 and HT-29", *International Journal of Molecular Sciences*, 24(9), 8191, 2023.
[24] Y. Wang, Y. Li, L. Wang, B. Chen, M. Zhu and C. Ma, "Cinnamaldehyde Suppressed EGF-Induced EMT Process and Inhibits Ovarian Cancer Progression Through PI3K/AKT Pathway", *Frontiers in Pharmacology*, 13, 2022.
[25] Y. Geng, S. Yang, Z. Liu, S. Wang and P. Ge, "Cinnamaldehyde Regulates the Migration and Apoptosis of Gastric Cancer Cells by Inhibiting the Jak2/Stat3 Pathway", *Digestive Diseases and Sciences*, 69(8), 2875–2882, 2024.
[26] Z. Aminzadeh, N. Ziamajidi and R. Abbasalipourkabir, "Anticancer Effects of Cinnamaldehyde Through Inhibition of ErbB2/HSF1/LDHA Pathway in 5637 Cell Line of Bladder Cancer", *Anticancer Agents in Medicinal Chemistry*, 22(6), 1139–1148, 2022.
[27] S. Banerjee and S. Banerjee, "Anticancer Potential and Molecular Mechanisms of Cinnamaldehyde and Its Congeners Present in the Cinnamon Plant", *Physiologia*, 3(2), 173–207, 2023.
[28] Y. Liu, T. An, D. Wan, B. Yu, Y. Fan and X. Pei, "Targets and Mechanism Used by Cinnamaldehyde, the Main Active Ingredient in Cinnamon, in the Treatment of Breast Cancer", *Frontiers in Pharmacology*, 11, 2020.
[29] L. T. Ng and S.J. Wu, "Antiproliferative Activity of Cinnamomum cassia Constituents and Effects of Pifithrin-Alpha on Their Apoptotic Signaling Pathways in Hep G2 Cells", *Evidence-Based Complementary and Alternative Medicine*, 2011(1), 2011.
[30] C. M. Cabello, W. B. Bair, S. D. Lamore, S. Ley, A. S. Bause and S. Azimian, "The Cinnamon-Derived Michael Acceptor Cinnamic Aldehyde Impairs Melanoma Cell Proliferation, Invasiveness, and Tumor Growth", *Free Radical Biology and Medicine*, 46(2), 220–231, 2009.
[31] K. H. Moon and M. Y. Pack, "Cytotoxicity of Cinnamic Aldehyde on Leukemia L1210 Cells", *Drug and Chemical Toxicology*, 6(6), 521–535, 1983.
[32] C. Yu, S. L. Liu, M. H. Qi and X. Zou, "Cinnamaldehyde/Chemotherapeutic Agents Interaction and Drug-Metabolizing Genes in Colorectal Cancer", *Molecular Medicine Reports*, 9(2), 669–676, 2014.
[33] M. Long, S. Tao, M. Rojo de la Vega, T. Jiang, Q. Wen, S. L. Park, D. D. Zhang and G. T. Wondrak. "Nrf2-dependent suppression of azoxymethane/dextran sulfate sodium-induced colon carcinogenesis by the cinnamon-derived dietary factor cinnamaldehyde. *Cancer Prevention Research (Phila)*, 8(5), 444–454, 2015
[34] J. Park and S. H. Baek. "Combination Therapy with Cinnamaldehyde and Hyperthermia Induces Apoptosis of A549 Non-Small Cell Lung Carcinoma Cells via Regulation of Reactive Oxygen Species and

Mitogen-Activated Protein Kinase Family." *International Journal of Molecular Sciences*, 21(17), 6229, 2020.
[35] R. Chen, J. Wu, C. Lu, T. Yan, Y. Qian, H. Shen, Y. Zhao, J. Wang, P. Kong and X. Zhang, "Systematic Transcriptome Analysis Reveals the Inhibitory Function of Cinnamaldehyde in Non-Small Cell Lung Cancer." *Frontiers in Pharmacology*, 11, 2021.
[36] S. Mulati, F. Shen, Z. Talihati, Y. Zhang, H. Huang and W. Zhang, "Targeting RPS16 with Cinnamaldehyde to Suppress Cervical Cancer: Inhibition of the PI3K/AKT Pathway and Degradation of HPV E6 and E7 Proteins", *Biochemical Pharmacology*, 242, 117225, 2025.
[37] J. Mei, J. Ma, Y. Xu, Y. Wang, M. Hu, F. Ma, Z. Qin, R. Xue, and N. Tao "Cinnamaldehyde Treatment of Prostate Cancer-Associated Fibroblasts Prevents Their Inhibitory Effect on T Cells Through Toll-Like Receptor 4." *Drug Design, Development and Therapy*, 14, 3363-3372, 2020.
[38] L. Han, J. Mei, J. Ma, F. Wang, Z. Gu, J. Li, Z. Zhang, Y. Zeng, X. Lou, X. Yao, N. Tao and Z. Qin, "Cinnamaldehyde induces endogenous apoptosis of the prostate cancer-associated fibroblasts via interfering the Glutathione-associated mitochondria function." *Medical Oncology*, 37(10), 91, 2020.
[39] A. N. Aliyah, G. Lintangsari, G. G. Maran, A. Hermawan and E. Meiyanto, "Cinnamon Oil as a Co-Chemotherapy Agent Through Inhibition of Cell Migration and MMP-9 Expression on 4T1 Cells", *Journal of Complementary and Integrative Medicine*, 19(4), 921–928, 2022.
[40] C. Wu en, Y. wen Zhuang, Y. yong Zhou, S. lin Liu, R. ping Wang and P. Shu, "Cinnamaldehyde Enhances Apoptotic Effect of Oxaliplatin and Reverses Epithelial-Mesenchymal Transition and Stemness in Hypoxic Colorectal Cancer Cells", *Experimental Cell Research*, 383(1), 111500, 2019.
[41] C. Wu, Y. Zhuang, S. Jiang, F. Tian, Y. Teng and X. Chen, "Cinnamaldehyde Induces Apoptosis and Reverses Epithelial-Mesenchymal Transition Through Inhibition of Wnt/β-Catenin Pathway in Non-Small Cell Lung Cancer", *International Journal of Biochemistry and Cell Biology*, 84, 58–74, 2017.