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Original Article

Enhancing Radiosensitivity in Prostate Adenocarcinoma by 7-Geranyloxycoumarin: The Potential Roles of β-Catenin, c-MYC, and PSMD10

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Abstract

Introduction: Prostate adenocarcinoma is commonly treated with radiation and chemotherapy, but resistance and toxicity limit their success, highlighting the need for novel radiosensitizers. We investigated the effects of 7-Geranyloxycoumarin, alone and in combination with radiation, on the expression of β-catenin (*CTNNB1*), *c-MYC*, and Gankyrin (*PSMD10*), key mediators of Wnt signaling pathway associated with radioresistance in prostate adenocarcinoma cells.

Methods: STRING and GEPIA2 were used for interactome mapping, pathway enrichment, and expression/survival validation in prostate adenocarcinoma. Human prostate adenocarcinoma (PC-3) cells were pretreated with 40 μM 7-Geranyloxycoumarin and subsequently irradiated with 4 Gy. Gene expression was assessed by real-time PCR after 72 h.

Results: In silico analyses confirmed interactions among *CTNNB1*, c-MYC, and *PSMD10*, their involvement in the Wnt pathway, and the overexpression and prognostic trends of *c-MYC* and *PSMD10*. In PC-3 cells, 7-Geranyloxycoumarin treatment significantly decreased *c-MYC* expression ($P<0.0001$), while the combined treatment increased *CTNNB1* ($P<0.01$) but decreased *PSMD10* and *c-MYC*, indicating disruption of Wnt pathway.

Conclusion: 7-Geranyloxycoumarin modulates the Wnt signaling pathway by suppressing the expression of *CTNNB1*, c-MYC, and *PSMD10*, key mediators of this pathway, thereby enhancing radiosensitivity and highlighting its potential as an adjuvant therapy in prostate adenocarcinoma.

Introduction

Prostate adenocarcinoma is the second most prevalent cancer in men worldwide, [1,2] and it has just been identified as the third most prevalent cancer in Iranian men.[3,4]The treatment of prostate cancer includes surgery, chemotherapy, radiotherapy, hormone therapy and their combination.[5-8] Simultaneous chemoradiotherapy is superior to radiotherapy alone or to alternating radiotherapy and chemotherapy.[9,10]

Natural products represent a promising frontier in cancer therapy, enhancing tumor cell sensitivity to radiation and significantly improving the outcomes of simultaneous chemoradiotherapy. [10-12] Radiosensitizers increase the sensitivity of tumor cells to radiation, allowing for lower doses while maintaining therapeutic efficacy.[13,14]

7- Geranyloxycoumarin (also known as auraptene) is a natural coumarin derivative found in citrus plant extracts that can be synthesized under laboratory conditions. This coumarin has various biological activities, such as antibacterial, antifungal, anti-inflammatory, and antioxidant properties, and its anti-cancer and cancer-prevention effects have been demonstrated in numerous studies.[15-19] Its synergistic effects with chemotherapy drugs have also been reported in skin, esophageal, and colon cancer cells.[9,20,21]

The Wnt/β-catenin pathway, a key regulator of proliferation, differentiation, and metastasis, can be modulated by coumarins.[22] Wnt pathway genes can drive radioresistance by modulating other genes or pathways.[23] For example, β-catenin regulates LIG4 expression, while WISP1 directly phosphorylates histone 2 (γ-H2AX). The β-catenin/TCF transcriptional complex also regulates the expression of ALDH. Together, LIG4, γ-H2AX, and ALDH enhance DNA damage repair capacity, contributing to radioresistance.[24,25]

c-MYC is one of the most frequently activated oncogenes, estimated to be involved in ~20% of all

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human cancers. As a transcription factor, it regulates genes controlling proliferation, apoptosis, and DNA repair.[26] In breast cancer, c-MYC activates Wnt signaling by suppressing the inhibitors DKK1 and SFRP1, although the detailed mechanisms and biological significance remain unclear.[27]

PSMD10 (Gankyrin), a proteasome assembly chaperone, is an oncoprotein that is upregulated in a variety of cancers.[28] Gankyrin also promotes Wnt/β-catenin signaling by stabilizing and enhancing both the β-catenin protein expression and transcriptional activity which drives transcription of Wnt target genes like c-MYC. In turn, β-catenin and c-MYC can transcriptionally upregulate *PSMD10*, forming a positive feedback loop that amplifies Wnt pathway activation and tumor progression.[28,29] Building on our previous study that demonstrated the radiosensitizing effects of 7-Geranyloxycoumarin in prostate adenocarcinoma cells, we aimed to investigate the underlying molecular mechanisms. To our knowledge, no previous study has examined how 7-Geranyloxycoumarin modulates key Wnt/β-catenin signaling components (*CTNNB1*, *c-MYC*, and *PSMD10*) in prostate adenocarcinoma. Therefore, we analyzed the effects of 7-Geranyloxycoumarin, alone and in combination with radiation, on their expression in PC-3 cells, a cell line derived from androgen-independent metastatic prostate adenocarcinoma. This model replicates aggressive, radioresistant disease and exhibits high Wnt activity, making it an ideal model for evaluating radiosensitizers using real-time PCR.

Materials and Methods

Computational Analyses

For interactome mapping of *CTNNB1*, *c-MYC*, and *PSMD10*, the STRING database (https://string-db.org/) was used, and gene set enrichment analysis was performed using Reactome pathways, with results reported as false discovery rate (FDR). To validate the expression of *CTNNB1*, *c-MYC*, and *PSMD10* in prostate adenocarcinoma samples compared to normal specimens, GEPIA 2.0 (http://gepia2.cancer-pku.cn/) was utilized; this tool leverages data from the TCGA and GTEx databases.

Survival analysis was conducted using GEPIA2 with default settings (median cutoff for high/low expression groups) on TCGA-PRAD data. STRING was selected for its comprehensive protein-protein interaction database, integrating experimental and predicted interactions. GEPIA2 was chosen for its seamless integration of TCGA and GTEx data, enabling robust expression and survival comparisons.

In Vitro Gene Expression Analysis

To determine the effects of 7-Geranyloxycoumarin, both alone and in combination with radiation on PC-3 cells, RNA samples previously generated and reported in our earlier study Abolhassani et al., 2023 were used. Briefly, PC-3 cells were pretreated with 40 μM 7-Geranyloxycoumarin and irradiated with 4 Gy X-ray (Elekta Compact™ linear accelerator, Crawley). After 72 h recovery, total RNA was extracted from treated cells and their relevant controls using the RiboEx Total RNA kit (GeneAll). The extracted RNAs were eluted using diethyl pyrocarbonate-treated water. The concentration and purity (260/280 and 260/230 ratios) were measured in duplicate using a NanoDrop™ 2000c spectrophotometer (Thermo Scientific). To confirm RNA integrity, aliquots of RNA samples were electrophoresed on 1.5% agarose gel. Bands of 28S, 18S, and 5S rRNAs were observed, indicating RNA integrity. Reverse transcription of total RNA to cDNA was then performed according to the manufacturer's protocol (Yekta Tajhiz Azma). Using specific primers listed in Table 1, real-time PCR was performed with SYBR Green master mix (Pars Tous) following the manufacturer's instructions. The PCR cycling conditions were as follows: 95 °C for 5 min to activate the polymerase and perform initial denaturation, followed by 40 cycles of 95 °C for 5 s and 60 °C for 30 s. The melting curves of the PCR products were monitored at the end of each reaction to evaluate PCR specificity. Gene expression was normalized to GAPDH using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

The results were statistically analyzed using GraphPad Prism version 9.0. One-way ANOVA tests followed by Tukey's post-hoc test was used for multiple comparisons. Real-time PCR experiments were conducted in triplicate across three independent experiments. The data are presented as mean ± SEM, and statistically significant differences were defined as a p-value less than 0.05.

Results

In Silico Analysis of CTNNB1, c-MYC, and PSMD10 in Prostate Cancer

In silico analysis using STRING revealed an interaction network among *CTNNB1*, *c-MYC*, and *PSMD10*, consisting of 23 nodes and 79 edges, with a highly significant enrichment score ($P < 1.0e-16$) (Figure 1A). Reactome pathway enrichment identified several significant terms, including "Deactivation of the β-catenin transactivating complex" (FDR = 1.65e-17) and "TCF-dependent signaling in response to WNT" (FDR = 2.38e-17) (Figure 1B). Moreover, validation of

Table 1. The primer sequences used for real-time PCR

Gene name	Amplicon length (bp)	Primer sequence (5′ → 3′)
GAPDH	205	Forward: 5′- GGA TTT GGT CGT ATT GGG-3′ Reverse: 5′- GGA AGA TGG TGA TGG GATT-3′
c-MYC	159	Forward: 5′- ACTCTGAGGAGGAACAAGAA -3′ Reverse: 5′- TGGAGACGTGGCACCTCTT -3′
CTNNB1	76	Forward: 5′- GCTTTCAGTTGAGCTGACCA -3′ Reverse: 5′- AAGTCCAAGATCAGCAGTCTCA -3′
PSMD10	155	Forward: 5′- AGCAGCCAAGGGTAACTTGA -3′ Reverse:5′- TACTTGCTCCTTGGGACACC -3′

expression profiles using GEPIA2 showed that *c-MYC* and *PSMD10* were significantly overexpressed in prostate adenocarcinoma tissues (n = 492) compared with normal samples (n = 154) (Figure 2).

To further validate the clinical relevance, survival correlations were assessed using TCGA prostate adenocarcinoma data via GEPIA2 (Figure 3). High *c-MYC* expression was associated with poorer overall survival (HR = 1.902, 95% CI: 0.962-3.76, $P = 0.0645$), whereas *PSMD10* showed a trend toward a worse prognosis (HR = 6.265, 95% CI: 0.735-53.409, $P = 0.0933$). In contrast, *CTNNB1* expression exhibited a protective trend (HR = 0.257, 95% CI: 0.059-1.121, $P = 0.0707$). These findings support the oncogenic roles of *c-MYC* and *PSMD10* in prostate adenocarcinoma progression.

Effect of 7-Geranyloxycoumarin on Gene Expression Level

As shown in Figure 4, real-time PCR analysis revealed that treatment with 7-Geranyloxycoumarin significantly reduced *c-MYC* expression in PC-3 cells compared to the control group ($P < 0.0001$). A significant decrease in *c-MYC* expression was also observed following radiation treatment alone ($P < 0.0001$). Similarly, DMSO-treated cells exposed to radiation showed a significant reduction in *c-MYC* expression ($P < 0.001$).

In contrast, combined treatment with 7-Geranyloxycoumarin and radiation significantly increased *CTNNB1* expression compared with the control ($P < 0.01$), whereas no significant changes were observed in the other treatment groups. Moreover, *PSMD10* expression was markedly reduced in both the radiation-

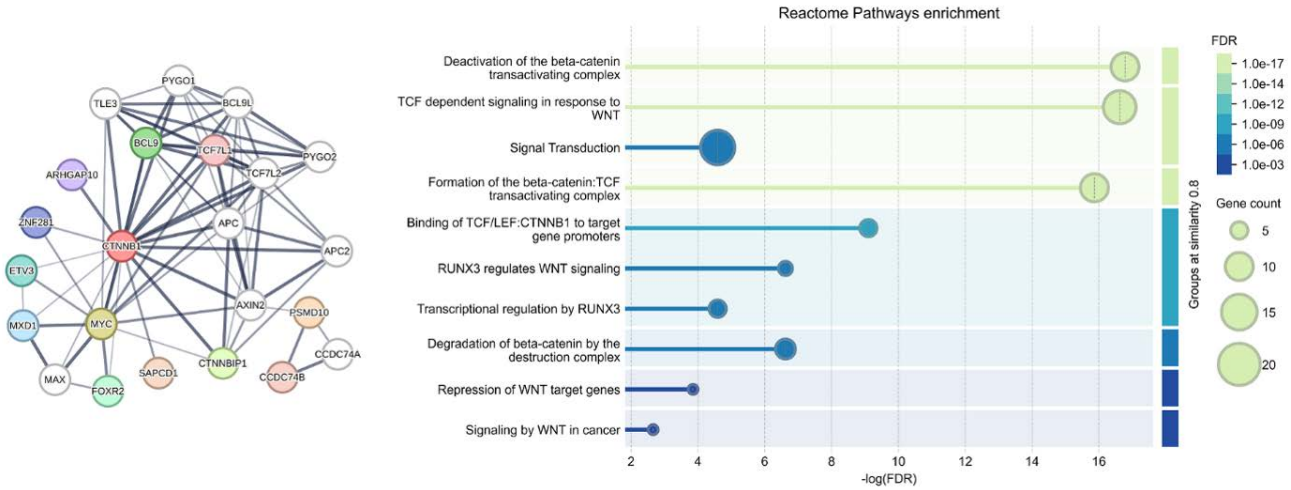

Figure 1. In silico interactome and pathway enrichment analysis. (A) Protein–protein interaction networks for *CTNNB1*, *c-MYC*, and *PSMD10* and their related partners were constructed using STRING. (B) Reactome pathway enrichment analysis highlighting significant terms, including "Deactivation of the β-catenin transactivating complex" and "TCF-dependent signaling in response to WNT

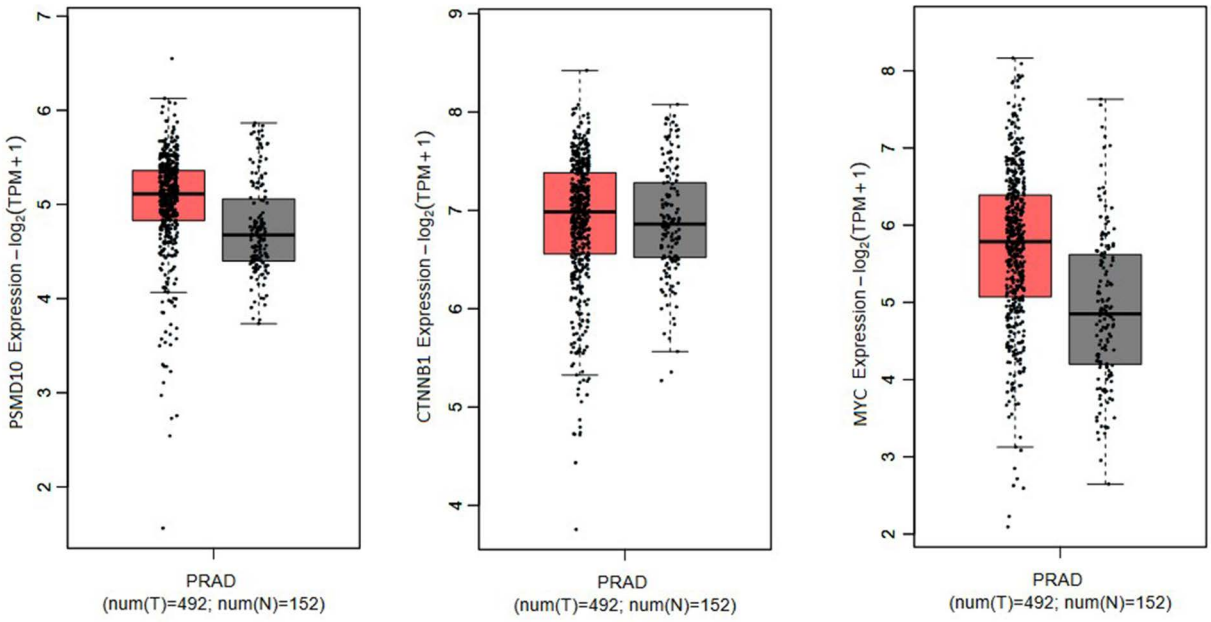

Figure 2. Validation of *CTNNB1*, *c-MYC*, and *PSMD10* expression in prostate adenocarcinoma using GEPIA2. Box plots represent transcript levels in tumor tissues (n = 492) compared with normal prostate samples (n = 154). Results indicate significant overexpression of *c-MYC* and *PSMD10* in tumor tissues, while *CTNNB1* showed no marked difference between the two groups. Data are presented as mean ± SEM.

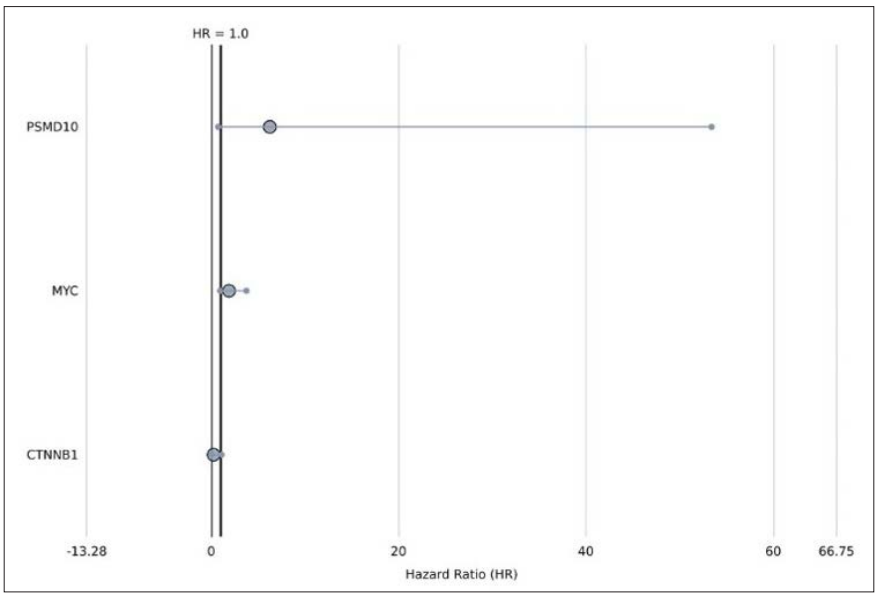

Figure 3. Survival correlations of *CTNNB1*, *c-MYC*, and *PSMD10* in prostate adenocarcinoma, analyzed using TCGA data via GEPIA2.

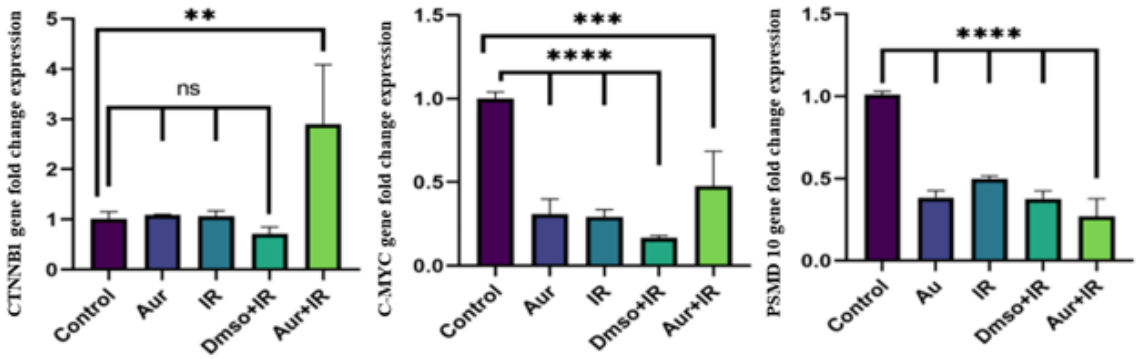

Figure 4. Relative expression of *CTNNB1*, *c-MYC*, and *PSMD10* in PC-3 cells across five treatment groups, as determined by real-time PCR (n = 3 biological replicates, each performed in technical triplicates). Gene expression levels were normalized to GAPDH as the internal control. Data are presented as mean ± SEM. Statistical significance compared with the untreated control group (one-way ANOVA with Tukey's post-hoc test): $^{**}P < 0.01$ for *CTNNB1* increase in combined treatment; $^{****}P < 0.0001$ for *c-MYC* decrease in 7-Geranyloxycoumarin alone, radiation alone, and combined treatment; $^{***}P < 0.001$ for *c-MYC* decrease in DMSO-treated irradiated cells; $^{****}P < 0.0001$ for *PSMD10* decrease in radiation and combined treatment groups.

only and the combined treatment groups ($P < 0.0001$). This upregulation of *CTNNB1*, although seemingly counterintuitive given its role in Wnt activation, coincided with the downregulation of downstream oncogenes *c-MYC* and *PSMD10*, potentially indicating a disruption of canonical Wnt signaling.

Discussion

Prostate adenocarcinoma is one of the most prevalent and lethal cancers affecting men globally, with treatment often involving radiotherapy following chemotherapy or surgery. Since development of radioresistance in cancer cells considerably reduces the clinical response to radiotherapy, there is an urgent need to identify new compounds that enhance the radiosensitivity of prostate adenocarcinoma cells, thereby improving therapeutic outcomes.[30-32] Previous research has shown that 7-Geranyloxycoumarin has anticancer and antiproliferative properties in various cancer types, including skin, breast, and colon cancers. However, the specific effects of 7-Geranyloxycoumarin on the radiation response in prostate adenocarcinoma cells, as well as the underlying molecular mechanisms, have not been adequately explored.[15] In our previous study, we investigated the effects of 7-Geranyloxycoumarin on enhancing radiosensitivity of prostate adenocarcinoma cells. The focus of this study was to further elucidate the underlying molecular mechanisms responsible for this effect. Computational analyses in the current study revealed functional and physical associations between *CTNNB1*, *c-MYC*, and *PSMD10* in the protein-protein interaction network. Pathway enrichment analysis further confirmed their involvement in Wnt signaling, a pathway crucial for tumor growth and therapy resistance. Additionally, *c-MYC* and *PSMD10* were upregulated in prostate adenocarcinoma tissue samples. The inclusion of survival correlations further supports the in silico findings, suggesting that *c-MYC* and *PSMD10* may serve as potential prognostic markers, consistent with their overexpression and involvement in radioresistance.

Findings from real-time PCR indicate that in prostate adenocarcinoma cells exposed to radiation,

7-Geranyloxycoumarin changed the expression of *c-MYC*, *CTNNB1* and *PSMD10*. These genes are key components of the Wnt signaling pathway, which regulates cell proliferation, survival, invasion, metastasis, and radiation resistance in prostate adenocarcinoma.[33,34]

We also found that the expression of *c-MYC* and *PSMD10* genes in PC-3 cells was significantly reduced by 7-Geranyloxycoumarin, both when used alone and in combination with radiation. In contrast, the expression of *CTNNB1* was notably increased. These results suggest that 7-Geranyloxycoumarin enhances the radiosensitivity of prostate adenocarcinoma cells by suppressing the *c-MYC* and *PSMD10* genes, thereby altering Wnt signaling, highlighting its potential as a novel radiosensitizer for prostate cancer therapy.

Oncogenes such as *c-MYC* and *PSMD10* are known to promote cell proliferation, invasion, and metastasis in prostate adenocarcinoma. They also play critical roles in regulating DNA damage repair, the cell cycle, and apoptosis processes essential for radioresistance. Stabilized *c-MYC* promotes resistance to chemotherapy and radiation by accelerating cell cycle progression and preventing apoptosis. Furthermore, the stabilization and activation of β-catenin have been shown to enhance the growth and survival of prostate adenocarcinoma cells under androgen-deprived conditions. Interestingly, stabilized β-catenin also appears to reduce *c-MYC* activity, a key transcription factor involved in cell growth and proliferation, as well as the motility of prostate adenocarcinoma cells.[34-36]

The PI3K/Akt and Wnt/β-catenin pathways are both essential for cell survival and radioresistance, and they can be regulated by *PSMD10*.[24,37] In line with this, our data showed that 7-Geranyloxycoumarin increased *CTNNB1* expression but simultaneously reduced *c-MYC* and *PSMD10*, two oncogenic downstream targets of β-catenin. The observed increase in *CTNNB1* expression following combined treatment appears paradoxical, as elevated β-catenin is typically associated with enhanced radioresistance through Wnt pathway activation.[23,24] However, this may reflect context-dependent regulation, where β-catenin stabilization could inhibit downstream effectors like *c-MYC* under certain conditions, as seen in androgen-deprived prostate cells.[38] In our study, the concurrent downregulation of *c-MYC* and *PSMD10*, both oncogenic targets of β-catenin, supports a potential disruption of the positive feedback loop,[16,29] contributing to radiosensitization. This hypothesis aligns with our previous functional data showing reduced cell survival,[16] but lacks direct evidence of β-catenin's altered activity.

Rigorous follow-up studies, including β-catenin knockdown experiments, are needed to clarify the molecular mechanisms by which 7-Geranyloxycoumarin regulates β-catenin expression and function in prostate adenocarcinoma cells, and to reconcile these findings with established mechanisms.

Deeper analysis of the Wnt pathway reveals that *PSMD10* enhances β-catenin stability by inhibiting its degradation, while *c-MYC* amplifies the loop through transcriptional activation.[33,35] Our findings suggest 7-Geranyloxycoumarin may interrupt this at the *PSMD10*-β-catenin interface, possibly via non-canonical mechanisms, as evidenced by *CTNNB1* upregulation without proportional oncogene activation.[33,35] This could involve crosstalk with PI3K/Akt, where *PSMD10* inhibition reduces Akt-mediated β-catenin phosphorylation.

Our research indicates that 7-Geranyloxycoumarin reduced the expression of *c-MYC* and *PSMD10*, modulating the Wnt signaling pathway and enhancing the radiosensitivity of prostate adenocarcinoma cells. These findings suggest its potential use in combination with radiation therapy to improve clinical outcomes for patients with prostate adenocarcinoma. Future studies should investigate protein expressions, employ pathway inhibitors, and utilize in vivo models to validate radiosensitization and clarify the roles of non-canonical Wnt signaling. Taken together, these results provide a rationale for considering 7-Geranyloxycoumarin as an adjuvant radiosensitizer in prostate adenocarcinoma, which could ultimately improve therapeutic efficacy in clinical practice.

Conclusion

This study demonstrated that 7-Geranyloxycoumarin significantly reduced the expression of *c-MYC* and *PSMD10*, thereby modulating the Wnt signaling pathway and enhancing the radiosensitivity of prostate adenocarcinoma cells. These findings highlight its potential as an adjuvant radiosensitizer in prostate cancer treatment. Although *CTNNB1* upregulation warrants cautious interpretation, the overall effect appears to favor radiosensitization through suppression of downstream oncogenes. Further validation in additional cell lines and preclinical models is warranted to confirm the therapeutic applicability of 7-Geranyloxycoumarin.

Authors' Contribution

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Writing–Review & Editing: Fatemeh B. Rassouli, Khadijeh Jamialahmadi.

Competing Interests

There is no conflict of interest.

Data Availability Statement

Not applicable.

Ethical Approval

This study was approved by the Research Council of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1401.674).

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Informed Consent
Not applicable.

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