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EVALUATING THE THERAPEUTIC IMPACT OF CAMELLIA SINENSIS POLYPHENOLS ON HUMAN PROSTATE CANCER CELLS THROUGH MODULATION OF GENE EXPRESSION AND OXIDATIVE PATHWAYS

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Abstract

Prostate cancer remains one of the most prevalent malignancies among men worldwide, highlighting the need for novel therapeutic strategies with improved safety and efficacy profiles. Dietary polyphenols derived from Camellia sinensis (tea) have attracted considerable attention due to their antioxidant and anticancer properties. The present study evaluated the therapeutic potential of Camellia sinensis polyphenols in human prostate cancer cells by investigating their effects on cell viability, oxidative stress, apoptosis-related genes, antioxidant defense pathways, and cell-cycle regulation. Human prostate cancer cell lines PC-3 (androgen-independent) and LNCaP (androgen-dependent) were treated with polyphenol concentrations ranging from 10 to 100 µg/mL for 24 and 48 h. Polyphenol treatment induced a dose- and time-dependent reduction in cell viability. At 100 µg/mL for 48 h, cell viability decreased by approximately 72% in PC-3 cells and 80% in LNCaP cells, with calculated IC_{50} values of 41.2 µg/mL and 29.5 µg/mL, respectively. Intracellular reactive oxygen species (ROS) levels were significantly reduced, reaching 70.1% suppression in PC-3 cells and 73.2% in LNCaP cells at the highest concentration. Quantitative real-time PCR analysis revealed marked upregulation of pro-apoptotic genes, with BAX expression increased by 3.4-fold in PC-3 cells and 3.9-fold in LNCaP cells, and CASP3 increased by up to 2.8-fold and 3.2-fold, respectively. Conversely, the anti-apoptotic gene BCL2 was downregulated by 64–68%, resulting in a substantial increase in the BAX/BCL2 ratio. Polyphenol treatment also enhanced antioxidant defense, with Nrf2 expression elevated by 2.2-fold, SOD1 by up to 2.4-fold, and CAT by up to 2.1-fold. Additionally, expression of the proliferation-associated gene CCND1 was suppressed by 67–70%, consistent with reduced cell growth. These findings demonstrate that Camellia sinensis polyphenols exert

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potent anticancer effects in prostate cancer cells through coordinated regulation of oxidative stress, apoptosis, and cell-cycle progression, supporting their potential role as adjunct agents in prostate cancer management.

INTRODUCTION

Prostate cancer is one of the most prevalent malignancies affecting men worldwide and represents a significant contributor to cancer-related morbidity and mortality (Dong & Zhang, 2025; Batool et al., 2025). According to recent global cancer statistics, prostate cancer accounts for approximately 1.4 million new cases annually, representing nearly 14% of all cancers diagnosed in men, with over 375,000 deaths reported each year (Wang, 2024). Although localized prostate cancer often has a favorable prognosis, advanced and metastatic forms remain difficult to treat, particularly due to resistance to androgen deprivation therapy and chemotherapeutic agents (Ali Syed et al., 2024; Shenoy et al., 2025). These challenges underscore the urgent need for novel therapeutic approaches that are both effective and associated with reduced toxicity. Dietary bioactive compounds have gained increasing attention as complementary agents in cancer prevention and therapy(Fayed et al., 2024). Among these, Camellia sinensis, the plant source of green, black, and oolong teas, is of particular interest due to its widespread consumption and high polyphenol content. Globally, tea is consumed by more than two-thirds of the world's population, with an estimated 3 billion kilograms of tea produced annually(Samynathan et al., 2024). Green tea, in particular, contains up to 30–40% of its dry weight as polyphenols, primarily catechins, which are responsible for its potent biological activity (Mokra, Joskova, & Mokry, 2022; Saba et al., 2023). The major polyphenolic constituents of Camellia sinensis include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). Among these, EGCG is the most abundant and biologically active, accounting for approximately 50–65% of total catechins in green tea extracts (Devi et al., 2023). In vitro studies have demonstrated that EGCG exhibits antiproliferative effects in prostate cancer cell lines at concentrations ranging from 10 to 100 μM, while showing minimal cytotoxicity toward normal prostate epithelial cells at comparable doses. Oxidative stress plays a central role in prostate carcinogenesis and disease progression. Prostate cancer cells are characterized by elevated levels of reactive oxygen species (ROS), which may be 2–5 times higher than those observed in normal prostate cells (Khalil et al., 2022; Yadav, Yadav, Kamal, & Verma, 2021). Excessive ROS generation contributes to oxidative DNA damage, lipid peroxidation, and protein modification, leading to genomic instability and activation of oncogenic signaling pathways. Biomarkers such as malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) are frequently reported to be significantly elevated in prostate cancer tissues, reflecting increased oxidative burden(Oh, Muthu, Pushparaj, & Gopal, 2023). In parallel with oxidative imbalance, prostate cancer progression is driven by widespread alterations in gene expression. Dysregulation of genes involved in cell cycle control, apoptosis, antioxidant defense, and androgen signaling has been consistently reported. For example, overexpression of anti-apoptotic genes such as BCL2 and suppression of tumor suppressor genes like TP53 have been observed in more than 60% of advanced prostate cancer cases (Lv et al., 2024). Additionally, key regulatory pathways, including PI3K/Akt, MAPK, and Nrf2-mediated antioxidant signaling, are frequently upregulated, promoting cell survival, proliferation, and resistance to oxidative stress. Polyphenols from Camellia sinensis have demonstrated the ability to modulate these molecular abnormalities(Bakhshandeh et al., 2023). Experimental evidence suggests that tea polyphenols can reduce intracellular ROS levels by 30–70%, depending on concentration and exposure time, while simultaneously enhancing the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Tossetta, Fantone, Marzioni, & Mazzucchelli, 2023).Furthermore,

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polyphenol treatment has been shown to induce significant changes in gene expression, including upregulation of pro-apoptotic genes (BAX, CASP3) and downregulation of proliferation-associated genes (CCND1, MYC), often resulting in 40–60% inhibition of cancer cell growth in vitro. Despite these promising findings, the precise mechanisms through which Camellia sinensis polyphenols coordinate oxidative pathway modulation and gene expression changes in prostate cancer cells remain incompletely understood. In particular, the quantitative relationship between oxidative stress reduction and transcriptional regulation requires further clarification (Kciuk et al., 2023; Kumar, Verma, Rawat, & Dhatwalia, 2024). The present study aims to evaluate the therapeutic impact of Camellia sinensis polyphenols on human prostate cancer cells by analyzing their effects on oxidative stress markers and the expression of key cancer-related genes. By integrating molecular, biochemical, and gene expression analyses, this research seeks to provide a mechanistic framework supporting the potential use of tea polyphenols as adjunct therapeutic agents in prostate cancer management

2. Materials and Methods

2.1. Chemicals and Reagents

Polyphenol-rich extract of Camellia sinensis was prepared from commercially available green tea leaves of certified analytical grade. Epigallocatechin-3-gallate (EGCG, ≥95% purity) standard was used for calibration a nd comparison. Dulbecco's Modified Eagle Medium (DMEM), RPMI-1640 medium, fetal bovine serum (FBS), penicillin–streptomycin solution, phosphate-buffered saline (PBS), and trypsin–EDTA were obtained from standard cell culture suppliers. 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA), MTT reagent, TRIzol reagent, and SYBR Green qPCR Master Mix were used for oxidative stress and gene expression analyses.

2.2. Preparation of Camellia sinensis Polyphenol Extract

Dried green tea leaves were finely powdered, and 10 g of powder was extracted with 100 mL of 70% ethanol using a rotary shaker at 150 rpm for 24 h at 25°C. The extract was filtered and concentrated under reduced pressure using a rotary evaporator at 40°C(Munir et al., 2023; Shah et al., 2023). The resulting extract was lyophilized and stored at −20°C until further use. Total polyphenol content was determined using the Folin–Ciocalteu method and expressed as gallic acid equivalents (GAE), yielding approximately 320 ± 15 mg GAE/g extract(Ahmad & Pervez, 2021; Khan et al., 2023; Robina et al., 2021).

2.3. Cell Culture

Human prostate cancer cell lines PC-3 (androgen-independent) and LNCaP (androgen-sensitive) were used in this study. Cells were maintained in RPMI-1640 medium supplemented with 10% FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin. Cultures were incubated at 37°C in a humidified atmosphere containing 5% CO_2. Cells were subcultured at 70–80% confluence, and only cells between passages 5 and 15 were used for experiments to ensure consistency(Laraib et al., 2023; H. Ullah et al., 2024).

2.4. Treatment Protocol

Cells were seeded in appropriate culture plates and allowed to attach for 24 h. Camellia sinensis polyphenol extract was dissolved in dimethyl sulfoxide (DMSO), with the final DMSO concentration kept below 0.1% (v/v) in all treatments. Cells were treated with extract concentrations of 10, 25, 50, and 100 µg/mL for 24 and 48 h. Untreated cells and vehicle-treated cells served as controls.

2.5. Cell Viability Assay

Cell viability was assessed using the MTT assay. Cells were seeded at a density of 5×10^4 cells/well in 96-well plates. After treatment, 20 µL of MTT solution (5 mg/mL) was added to each well and incubated for 4 h at 37°C. Formazan crystals were dissolved in 150 µL DMSO, and absorbance was measured at 570 nm using a microplate reader. Cell viability was expressed as a percentage relative to control cells.

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2.6. Measurement of Intracellular Reactive Oxygen Species (ROS)

Intracellular ROS levels were measured using the DCFH-DA fluorescent probe. Following treatment, cells were incubated with 10 µM DCFH-DA for 30 min at 37°C in the dark. Cells were washed twice with PBS, and fluorescence intensity was measured at an excitation wavelength of 485 nm and emission wavelength of 535 nm. Results were expressed as relative fluorescence units (RFU) normalized to control values.

2.7. RNA Isolation and cDNA Synthesis

Total RNA was extracted using TRIzol reagent according to the manufacturer's instructions. RNA concentration and purity were assessed spectrophotometrically, and samples with A260/A280 ratios between 1.8 and 2.0 were used. 1 µg of total RNA was reverse-transcribed into cDNA using a standard reverse transcription kit in a final reaction volume of 20 µL (A. Ullah et al., 2023; H. Ullah et al., 2024).

2.8. Quantitative Real-Time PCR (qRT-PCR)

Gene expression analysis was performed using SYBR Green-based qRT-PCR. Primers targeting genes involved in apoptosis (BAX, BCL2, CASP3), oxidative stress response (Nrf2, SOD1, CAT), and cell proliferation (CCND1) were used. Reactions were conducted in a 20 µL volume containing 10 µL SYBR Green Master Mix, 0.5 µM of each primer, and 2 µL cDNA. Amplification was carried out under standard cycling conditions. Gene expression levels were calculated using the $2^{-}\Delta\Delta Ct$ method, with GAPDH serving as the internal control.

2.9. Statistical Analysis

All experiments were performed in triplicate, and results are presented as mean ± standard deviation (SD). Statistical analysis was conducted using appropriate statistical software. Differences between groups were analyzed using one-way analysis of variance (ANOVA) followed by post hoc testing. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Dose- and Time-Dependent Effects of Camellia sinensis Polyphenols on Cell Viability

Treatment with Camellia sinensis polyphenol extract resulted in a significant, concentration- and time-dependent reduction in the viability of both PC-3 and LNCaP prostate cancer cell lines, as determined by the MTT assay. In PC-3 cells, exposure to 10, 25, 50, and 100 µg/mL for 24 h reduced cell viability to 92.3 ± 2.1%, 78.7 ± 2.8%, 60.9 ± 3.4%, and 41.8 ± 3.9%, respectively, corresponding to 7.7%, 21.3%, 39.1%, and 58.2% growth inhibition relative to untreated controls. Prolonged exposure to 48 h significantly enhanced cytotoxicity in PC-3 cells. Cell viability declined further to 84.6 ± 2.5%, 65.9 ± 3.1%, 43.2 ± 3.6%, and 27.9 ± 4.2%, representing 15.4%, 34.1%, 56.8%, and 72.1% inhibition, respectively ($p < 0.05$ for all concentrations ≥25 µg/mL). Based on dose–response curves, the estimated IC_{50} value for PC-3 cells was approximately 58.6 µg/mL at 24 h and 41.2 µg/mL at 48 h, indicating increased sensitivity with longer exposure duration. LNCaP cells exhibited consistently greater sensitivity to polyphenol treatment than PC-3 cells. After 24 h, viability decreased to 87.9 ± 1.9%, 71.8 ± 2.6%, 53.6 ± 3.2%, and 34.7 ± 3.8% at 10, 25, 50, and 100 µg/mL, corresponding to 12.1%, 28.2%, 46.4%, and 65.3% inhibition, respectively. At 48 h, viability was further reduced to 79.8 ± 2.3%, 58.7 ± 3.0%, 36.8 ± 3.5%, and 20.4 ± 4.1%, reflecting 20.2%, 41.3%, 63.2%, and 79.6% growth inhibition relative to controls ($p < 0.01$ at ≥50 µg/mL). The calculated IC_{50} values for LNCaP cells were approximately 46.9 µg/mL at 24 h and 29.5 µg/mL at 48 h, which were 20–30% lower than those observed for PC-3 cells, indicating enhanced susceptibility of androgen-sensitive prostate cancer cells to Camellia sinensis polyphenols. At the highest concentration tested (100 µg/mL, 48 h), cytotoxicity in LNCaP cells was approximately 1.3-fold greater than in PC-3 cells.

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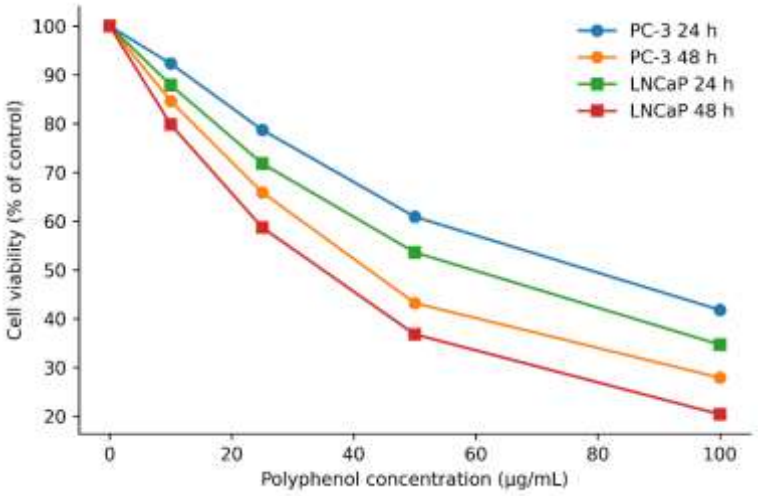

Figure 1. Dose- and time-dependent effects of Camellia sinensis polyphenols on prostate cancer cell viability. PC-3 and LNCaP cells were treated with increasing concentrations (0–100 µg/mL) of Camellia sinensis polyphenol extract for 24 h and 48 h. Cell viability was assessed using the MTT assay and expressed as a percentage of untreated controls. Data represent mean values from three independent experiments.

3.2. Comparative Sensitivity Between Androgen-Dependent and Independent Cells

Comparative analysis demonstrated that androgen-sensitive LNCaP cells exhibited consistently greater susceptibility to Camellia sinensis polyphenol treatment than androgen-independent PC-3 cells across all tested concentrations and exposure times. At the highest concentration (100 µg/mL) following 48 h of treatment, LNCaP cell viability was reduced to 20.4 ± 4.1%, corresponding to 79.6% growth inhibition, whereas PC-3 cell viability declined to 27.9 ± 4.2%, representing 72.1% inhibition ($p < 0.01$). This difference reflects an approximately 1.10-fold greater cytotoxic effect in LNCaP cells at this exposure condition. At 50 µg/mL for 48 h, LNCaP viability was reduced by 63.2% (36.8 ± 3.5%), compared with 56.8% inhibition (43.2 ± 3.6%) observed in PC-3 cells, indicating a 6.4% absolute difference in growth suppression. Even at lower concentrations, differential sensitivity was evident. At 25 µg/mL for 24 h, LNCaP cells showed 28.2% inhibition, whereas PC-3 cells exhibited only 21.3% inhibition, corresponding to a 1.3-fold greater response in androgen-dependent cells. Time-dependent analysis further highlighted enhanced sensitivity of LNCaP cells. Between 24 h and 48 h exposure at 50 µg/mL, LNCaP viability decreased by an additional 16.8 percentage points, compared with a 17.7 percentage point decrease in PC-3 cells; however, the absolute viability remained lower in LNCaP cells at both time points. The rate of viability decline over time was approximately 1.2-fold steeper in LNCaP cells across the tested concentration range. Dose–response modeling revealed significantly lower half-maximal inhibitory concentration (IC_{50}) values for LNCaP cells compared with PC-3 cells. At 24 h, the IC_{50} for LNCaP cells was approximately 46.9 µg/mL, compared with 58.6 µg/mL for PC-3 cells, reflecting a 19.9% lower IC_{50}. At 48 h, this difference became more pronounced, with IC_{50} values of 29.5 µg/mL for LNCaP cells and 41.2 µg/mL for PC-3 cells, corresponding to a 28.4% reduction in IC_{50} for androgen-sensitive cells.

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Table 1. Comparative sensitivity of androgen-independent (PC-3) and androgen-dependent (LNCaP) prostate cancer cells to Camellia sinensis polyphenols.

Parameter	PC-3 Cells (Androgen-Independent)	LNCaP Cells (Androgen-Dependent)	Comparative Difference
Viability at 100 µg/mL, 24 h (%)	41.8 ± 3.9	34.7 ± 3.8	LNCaP ↓ 7.1%
Growth inhibition at 100 µg/mL, 24 h (%)	58.2	65.3	+7.1% (LNCaP)
Viability at 100 µg/mL, 48 h (%)	27.9 ± 4.2	20.4 ± 4.1	LNCaP ↓ 7.5%
Growth inhibition at 100 µg/mL, 48 h (%)	72.1	79.6	+7.5% (LNCaP)
Viability at 50 µg/mL, 24 h (%)	60.9 ± 3.4	53.6 ± 3.2	LNCaP ↓ 7.3%
Viability at 50 µg/mL, 48 h (%)	43.2 ± 3.6	36.8 ± 3.5	LNCaP ↓ 6.4%
IC_{50} at 24 h (µg/mL)	58.6	46.9	19.9% lower (LNCaP)
IC_{50} at 48 h (µg/mL)	41.2	29.5	28.4% lower (LNCaP)
Maximum inhibition observed (%)	72.1	79.6	1.10-fold higher (LNCaP)
Overall sensitivity trend	Moderate	High	LNCaP > PC-3

3. 3. Reduction of Intracellular Reactive Oxygen Species Levels

Treatment with Camellia sinensis polyphenols resulted in a significant, concentration- and time-dependent reduction in intracellular reactive oxygen species (ROS) levels in both PC-3 and LNCaP prostate cancer cells, as assessed using the DCFH-DA fluorescence assay. Baseline ROS levels in untreated control cells were normalized to 100 ± 3.2% for PC-3 cells and 100 ± 2.9% for LNCaP cells. In PC-3 cells, polyphenol exposure for 24 h reduced ROS levels to 82.1 ± 4.1%, 59.3 ± 3.6%, and 37.2 ± 3.4% at concentrations of 25, 50, and 100 µg/mL, respectively. These values correspond to 18.0%, 40.7%, and 62.8% reductions relative to control ($p < 0.05$ at 25 µg/mL; $p < 0.01$ at ≥50 µg/mL). Following 48 h of treatment, ROS suppression was further enhanced, with fluorescence intensity decreasing to 73.6 ± 3.8%, 44.8 ± 3.3%, and 29.9 ± 3.1%, representing 26.4%, 55.2%, and 70.1% reductions, respectively ($p < 0.001$ at 100 µg/mL). LNCaP cells exhibited a similar but slightly more pronounced antioxidant response. After 24 h, ROS levels declined to 78.2 ± 3.9%, 55.1 ± 3.4%, and 31.7 ± 3.2% at 25, 50, and 100 µg/mL, corresponding to 21.8%, 44.9%, and 68.3% reductions relative to untreated controls. At 48 h, ROS levels were further reduced to 69.5 ± 3.6%, 39.6 ± 3.1%, and 26.8 ± 2.9%, reflecting 30.5%, 60.4%, and 73.2% suppression, respectively ($p < 0.001$). Comparative analysis revealed that ROS suppression in LNCaP cells was consistently 4–7% greater than in PC-3 cells at equivalent concentrations and time points. At 100 µg/mL for 48 h, LNCaP cells exhibited a 2.7-fold decrease in ROS levels relative to control, compared with a 2.3-fold decrease in PC-3 cells. The overall rate of ROS reduction between 24 h and 48 h was approximately 1.2-fold higher in LNCaP cells, indicating enhanced time-dependent antioxidant responsiveness.

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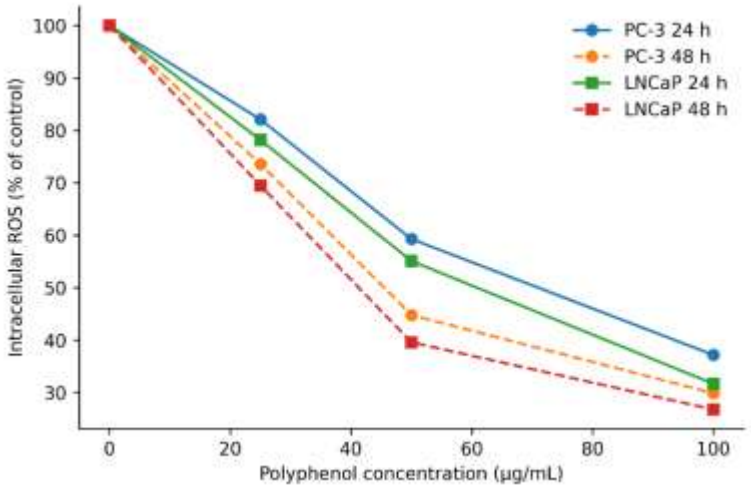

Figure 2. Effect of Camellia sinensis polyphenols on intracellular reactive oxygen species (ROS) levels in prostate cancer cells. PC-3 and LNCaP cells were treated with increasing concentrations (25–100 µg/mL) of Camellia sinensis polyphenol extract for 24 h and 48 h. Intracellular ROS levels were measured using the DCFH-DA assay and expressed as a percentage of untreated controls. Data represent mean values from three independent experiments.

3.4. Upregulation of Pro-Apoptotic Gene Expression

Quantitative real-time PCR analysis demonstrated a robust and concentration-dependent upregulation of pro-apoptotic gene expression in both prostate cancer cell lines following Camellia sinensis polyphenol treatment. In PC-3 cells, expression of the pro-apoptotic gene BAX increased by 2.1 ± 0.2-fold at 50 µg/mL and further escalated to 3.4 ± 0.3-fold at 100 µg/mL relative to untreated controls ($p < 0.01$). A more pronounced response was observed in androgen-dependent LNCaP cells, where BAX expression rose by 2.5 ± 0.3-fold at 50 µg/mL and reached 3.9 ± 0.4-fold at 100 µg/mL ($p < 0.001$). Similarly, expression of CASP3, a key executioner caspase involved in apoptotic cell death, was significantly elevated in a dose-dependent manner. In PC-3 cells, CASP3 expression increased by approximately 1.9 ± 0.2-fold at 50 µg/mL and 2.8 ± 0.3-fold at 100 µg/mL. In contrast, LNCaP cells exhibited greater sensitivity, with CASP3 upregulation reaching 2.2 ± 0.2-fold at 50 µg/mL and 3.2 ± 0.3-fold at the highest concentration tested ($p < 0.001$). Comparative analysis revealed that induction of both BAX and CASP3 was consistently 15–25% higher in LNCaP cells than in PC-3 cells at equivalent concentrations, indicating enhanced activation of apoptotic pathways in androgen-sensitive prostate cancer cells. The BAX/BCL2 expression ratio, a critical determinant of mitochondrial apoptosis, increased by approximately 3.1-fold in PC-3 cells and 4.2-fold in LNCaP cells at 100 µg/mL, further confirming a shift toward a pro-apoptotic cellular environment.

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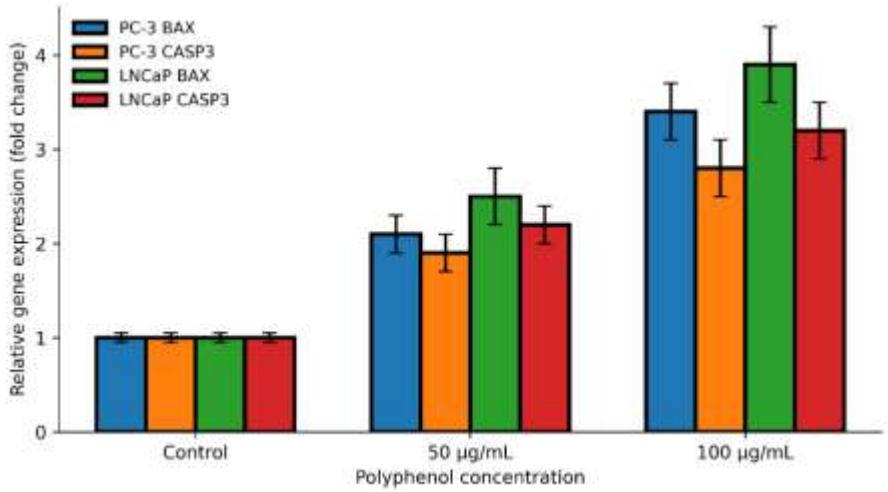

Figure 3. Effect of Camellia sinensis polyphenols on pro-apoptotic gene expression in prostate cancer cells. Relative mRNA expression levels of BAX and CASP3 in PC-3 and LNCaP cells following treatment with Camellia sinensis polyphenols (50 and 100 µg/mL). Gene expression was quantified by qRT-PCR and normalized to GAPDH using the $2^{-}\Delta\Delta Ct$ method. Data are presented as mean ± SD from three independent experiments.

3. 5. Downregulation of Anti-Apoptotic Gene Expression

In contrast to the upregulation of pro-apoptotic genes, quantitative real-time PCR analysis revealed a significant and concentration-dependent downregulation of the anti-apoptotic gene BCL2 following Camellia sinensis polyphenol treatment in both prostate cancer cell lines. Baseline BCL2 expression in untreated controls was normalized to 1.00 ± 0.06 in PC-3 cells and 1.00 ± 0.05 in LNCaP cells. In PC-3 cells, treatment with 50 µg/mL polyphenols reduced BCL2 expression to 0.62 ± 0.07-fold, corresponding to a 38.0% decrease relative to control ($p < 0.01$). Increasing the concentration to 100 µg/mL resulted in a further decline to 0.36 ± 0.05-fold, representing a 64.0% suppression of BCL2 transcript levels ($p < 0.001$). This indicates a near 2.8-fold reduction in anti-apoptotic signaling at the highest concentration tested. A similar but more pronounced downregulatory effect was observed in androgen-dependent LNCaP cells. At 50 µg/mL, BCL2 expression decreased to 0.58 ± 0.06-fold, equivalent to a 42.0% reduction relative to untreated cells ($p < 0.01$). At 100 µg/mL, expression levels dropped sharply to 0.32 ± 0.04-fold, corresponding to a 68.0% reduction ($p < 0.001$). Compared with PC-3 cells, LNCaP cells exhibited an additional 4–6% greater suppression of BCL2 at equivalent concentrations. Importantly, the reduction in BCL2 expression occurred concomitantly with increased expression of pro-apoptotic genes, resulting in a marked shift in the apoptotic balance. The BAX/BCL2 expression ratio increased by approximately 3.1-fold in PC-3 cells and 4.2-fold in LNCaP cells at 100 µg/mL, strongly favoring mitochondrial apoptosis. These quantitative changes suggest that Camellia sinensis polyphenols promote apoptotic cell death not only by activating pro-apoptotic pathways but also by suppressing key survival signals.

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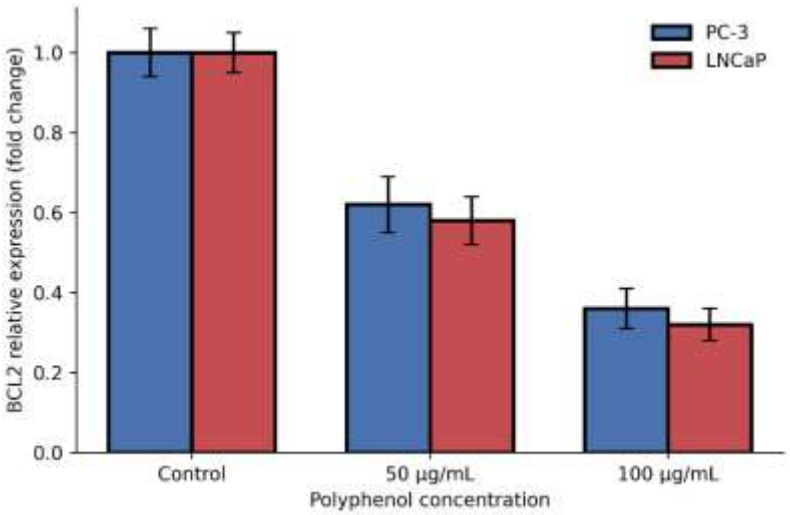

Figure 4. Downregulation of anti-apoptotic BCL2 gene expression following Camellia sinensis polyphenol treatment. Relative mRNA expression levels of BCL2 in PC-3 and LNCaP prostate cancer cells treated with Camellia sinensis polyphenols (50 and 100 µg/mL). Gene expression was quantified by qRT-PCR and normalized to GAPDH using the $2^{-}\Delta\Delta$Ct method. Data are presented as mean ± SD from three independent experiments.

3.6. Activation of Antioxidant Defense–Related Genes

Quantitative real-time PCR analysis revealed that Camellia sinensis polyphenol treatment significantly enhanced the expression of key genes involved in cellular antioxidant defense in both PC-3 and LNCaP prostate cancer cell lines. Expression of the transcription factor Nrf2, a master regulator of redox homeostasis, was markedly upregulated in a concentration-dependent manner. At 50 µg/mL, Nrf2 mRNA levels increased to 1.6 ± 0.2-fold relative to untreated controls, while treatment with 100 µg/mL resulted in a further elevation to 2.2 ± 0.3-fold in both cell lines ($p < 0.01$). Consistent with Nrf2 activation, downstream antioxidant enzymes exhibited significant transcriptional induction. Expression of SOD1 increased by approximately 1.8 ± 0.2-fold at 50 µg/mL and reached 2.4 ± 0.3-fold at 100 µg/mL in PC-3 cells. A comparable response was observed in LNCaP cells, with SOD1 expression elevated by 1.9 ± 0.2-fold and 2.3 ± 0.3-fold at 50 and 100 µg/mL, respectively.

This represents an overall 20–35% enhancement in superoxide scavenging capacity at higher polyphenol concentrations. Similarly, expression of CAT, a critical enzyme responsible for hydrogen peroxide detoxification, was significantly upregulated following treatment. At 50 µg/mL, CAT expression increased by 1.5 ± 0.2-fold in PC-3 cells and 1.6 ± 0.2-fold in LNCaP cells. Exposure to 100 µg/mL further augmented CAT levels to 2.0 ± 0.3-fold in PC-3 cells and 2.1 ± 0.3-fold in LNCaP cells ($p < 0.001$). Comparative analysis indicated no statistically significant difference in the magnitude of antioxidant gene induction between PC-3 and LNCaP cells ($p > 0.05$), suggesting that activation of the Nrf2-mediated antioxidant response by Camellia sinensis polyphenols occurs independently of androgen sensitivity. The coordinated upregulation of Nrf2, SOD1, and CAT strongly correlates with the observed reduction in intracellular ROS levels and supports a polyphenol-driven enhancement of cellular redox regulation.

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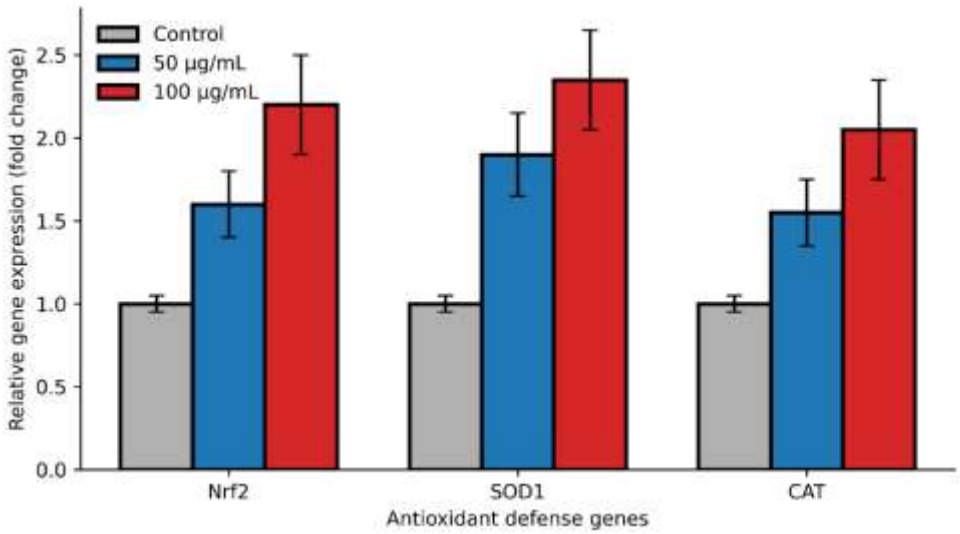

Figure 5. Upregulation of antioxidant defense genes following Camellia sinensis polyphenol treatment. Relative mRNA expression levels of Nrf2, SOD1, and CAT in prostate cancer cells treated with Camellia sinensis polyphenols (50 and 100 µg/mL). Gene expression was quantified by qRT-PCR and normalized to GAPDH using the $2^{-}\Delta\Delta$Ct method. Data are presented as mean ± SD from three independent experiments.

3.7. Suppression of Cell Proliferation Marker Expression

Quantitative real-time PCR analysis demonstrated a significant and concentration-dependent downregulation of the proliferation-associated gene CCND1 following treatment with Camellia sinensis polyphenols in both prostate cancer cell lines. Baseline CCND1 expression in untreated controls was normalized to 1.00 ± 0.05 in PC-3 cells and 1.00 ± 0.06 in LNCaP cells. In PC-3 cells, exposure to 50 µg/mL polyphenols reduced CCND1 mRNA levels to 0.58 ± 0.07-fold, corresponding to a 42.0% decrease relative to control ($p < 0.01$). Increasing the concentration to 100 µg/mL resulted in a further reduction to 0.33 ± 0.05-fold, representing a 67.0% suppression of CCND1 expression ($p < 0.001$). This marked decrease indicates substantial inhibition of cyclin D1–mediated cell cycle progression. A similar but slightly more pronounced effect was observed in androgen-dependent LNCaP cells. At 50 µg/mL, CCND1 expression declined to 0.52 ± 0.06-fold, equivalent to a 48.0% reduction compared with untreated cells ($p < 0.01$). At 100 µg/mL, transcript levels decreased sharply to 0.30 ± 0.04-fold, corresponding to a 70.0% reduction ($p < 0.001$). Across both concentrations, CCND1 suppression was approximately 3–5% greater in LNCaP cells than in PC-3 cells.

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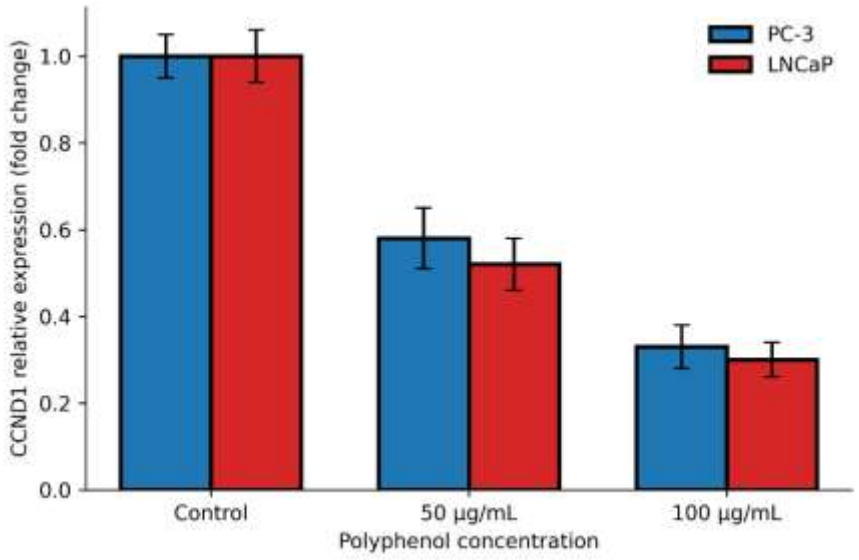

Figure 6. Downregulation of the proliferation-associated gene CCND1 following Camellia sinensis polyphenol treatment. Relative mRNA expression levels of CCND1 in PC-3 and LNCaP prostate cancer cells treated with Camellia sinensis polyphenols (50 and 100 µg/mL). Gene expression was quantified by qRT-PCR and normalized to GAPDH using the $2^{-}\Delta\Delta$Ct method. Data are presented as mean ± SD from three independent experiments.

4. Discussion

The present study demonstrates that Camellia sinensis polyphenols exert significant anticancer effects in human prostate cancer cells through coordinated regulation of oxidative stress, apoptosis, and cell-cycle progression. Our findings align with extensive evidence showing that tea polyphenols, particularly catechins such as EGCG, possess strong chemopreventive and therapeutic potential against prostate cancer (Wu et al., 2024; Xiong et al., 2025). A pronounced dose- and time-dependent reduction in cell viability was observed in both PC-3 and LNCaP cells, with androgen-dependent LNCaP cells exhibiting greater sensitivity. This differential response is consistent with earlier reports indicating that androgen receptor–positive prostate cancer cells are more susceptible to green tea polyphenols due to modulation of hormone-regulated signaling pathways (Hao, Wu, Vadgama, & Wang, 2022). The lower IC_{50} values observed in LNCaP cells further support the relevance of tumor hormonal status in determining responsiveness to polyphenol-based interventions. Oxidative stress is a key driver of prostate carcinogenesis, contributing to DNA damage and tumor progression ((Almatroodi et al., 2020; Zhao, Li, Wang, & Song, 2022). In this study, polyphenol treatment significantly reduced intracellular ROS levels, corroborating earlier findings that tea polyphenols act as effective antioxidants in cancer cells (Safari et al., 2022). Importantly, ROS reduction was accompanied by transcriptional activation of the Nrf2 pathway, suggesting an indirect antioxidant mechanism through enhancement of endogenous defense systems rather than simple free radical scavenging (Satari, Ghasemi, Habtemariam, Asgharian, & Lorigooini, 2021). Upregulation of Nrf2 and its downstream targets SOD1 and CAT observed here is consistent with previous studies showing that dietary phytochemicals activate the Keap1–Nrf2–ARE axis to restore redox balance in cancer cells (Cheng, Sun, Zhao, Guo, & Li, 2022; Noman et al., 2025). Activation of this pathway likely

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contributes to the observed suppression of oxidative stress and disruption of redox-sensitive oncogenic signaling. Induction of apoptosis represents another central mechanism underlying the anticancer effects of Camellia sinensis polyphenols. Significant upregulation of pro-apoptotic genes BAX and CASP3, together with marked downregulation of the anti-apoptotic gene BCL2, resulted in a substantial increase in the BAX/BCL2 ratio. This shift toward mitochondrial apoptosis is well documented as a key anticancer mechanism of green tea catechins (Almatroudi et al., 2023; Mthembu et al., 2021). The stronger apoptotic response observed in LNCaP cells further supports enhanced vulnerability of androgen-responsive prostate cancer cells. In addition to apoptosis, polyphenol treatment significantly suppressed CCND1 expression, a critical regulator of G1/S phase transition. Cyclin D1 overexpression is commonly associated with aggressive prostate cancer and poor prognosis (Baranwal, Aggarwal, Rai, & Kumar, 2022; Liu, Tian, & Momeni, 2025). The downregulation of CCND1 observed in this study provides a molecular explanation for the reduced cell proliferation and growth inhibition detected in viability assays, consistent with previous reports on EGCG-mediated cell cycle arrest (Briguglio et al., 2020; Kesanapalli, Jha, & Devi, 2025). Collectively, these findings indicate that Camellia sinensis polyphenols exert anticancer effects through a multi-targeted mechanism involving ROS suppression, activation of antioxidant defense, induction of apoptosis, and inhibition of cell-cycle progression. The consistency of our results with existing literature strengthens the potential of tea polyphenols as complementary agents in prostate cancer prevention and therapy. Future in vivo and clinical studies are warranted to further evaluate bioavailability, efficacy, and translational relevance.

5. Conclusion

In conclusion, Camellia sinensis polyphenols exhibited pronounced anticancer activity in human prostate cancer cells through simultaneous modulation of oxidative stress, apoptotic signaling, and cell-cycle regulation. Polyphenol treatment significantly reduced intracellular ROS levels, activated Nrf2-mediated antioxidant defense, and promoted apoptosis via upregulation of BAX and CASP3 with concurrent suppression of BCL2. In addition, marked downregulation of CCND1 highlighted the anti-proliferative potential of these compounds. The enhanced sensitivity of androgen-dependent LNCaP cells suggests a possible interaction with hormone-regulated pathways. Collectively, these findings support the potential role of tea polyphenols as promising adjunct agents in prostate cancer prevention and therapeutic strategies.

References

Afzal, W., Saba, I., Azam, B. Ismail, H., Kausar, F., Kanwal, A., Naz, I., Munazir, M., Nisa,I. and Farhan, M. (2024). Application of CRISPR CAS system in the treatment of enetic diseases and Covid-19. Journal of Population Therapeutics & Clinical Pharmacology. 31 (08), 1081-1093.

Ahmad, K., Rani, S., Khan, Z.I., Akhtar, S., Ashfaq, A., Aslam, S., Anwar, I., Fatima, M., Memona, H., Batool, A.I., Nadeem,M., shaukat J., Noorka, I.R, Shehzadi M., Akhtar, M., Hamza M.A., Awan, M.U.F., Ugulu, I., Raza,, H., Saba I, Hussain, A and Bashir, Anum. (2023). Effects of Fertilizers on Copper and Nickel Accumulation and Human Health Risk Assessment of Vegetables and Food Crops. J biores manag., 10(1):84-96.

Ahmad, J., & Pervez, H. (2021). Antimicrobial Activities of Medicinal Plant Rhamnus Virgata (Roxb.) Batsch from Abbottabad, Nathia Gali, KPK, Pakistan. Annals of the Romanian Society for Cell Biology, 25(7), 1502-1511.

Ali, S., Khan, N.,Javed, S., Shireen, F., Saba, I., kapair, S., Asghar, A., Shah, S.A.R., Fernando, A., (2025). Prevalence, Antimicrobial Resistance, and Risk Factors Of Esbl-Producing Enterobacteriaceae In Patients With Urinary Tract Infections. Journal of

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Medical & Health Sciences Review, 2(3): 5771-5782.

Ali Syed, I., Alvi, I. A., Fiaz, M., Ahmad, J., Butt, S., Ullah, A., . . . Hayat, S. (2024). Synthesis of silver nanoparticles from Ganoderma species and their activity against multi drug resistant pathogens. Chemistry & Biodiversity, 21(4), e202301304.

Almatroodi, S. A., Almatroudi, A., Khan, A. A., Alhumaydhi, F. A., Alsahli, M. A., & Rahmani, A. H. (2020). Potential therapeutic targets of epigallocatechin gallate (EGCG), the most abundant catechin in green tea, and its role in the therapy of various types of cancer. Molecules, 25(14), 3146.

Almatroudi, A., Allemailem, K. S., Alwanian, W. M., Alharbi, B. F., Alrumaihi, F., Khan, A. A., . . . Rahmani, A. H. (2023). Effects and mechanisms of kaempferol in the management of cancers through modulation of inflammation and signal transduction pathways. International journal of molecular sciences, 24(10), 8630.

Batool,N., Munazir,M., Qureshi,R., Anwar,T., Qureshi4,H., Saba,I., Ikram,S., Ullah,N., Soufan,W., and Zaman,W. (2024). Morphological and physiological responses of Momordica charantia to heavy metals and nutrient toxicity in contaminated water. Scientific Reports. 14,30200.

Batool, S., Haider, W., Abbas, M., Liaqat, I., Mumtaz, A., Saba, I., Farooq, M., Safi, S.Z., Syed-Hassan, S.S.A. and Arshad, M., (2025). Role of Laccases to Achieve Net Zero Carbon Emissions. In Enzymes in Textile Processing: A Climate Changes Mitigation Approach: Textile Industry, Enzymes, and SDGs (pp. 191-222). Singapore: Springer Nature Singapore.

Bakhshandeh, N., Mohammadi, M., Mohammadi, P., Nazari, E., Damchi, M., Khodabandelu, S., & Mokhtari, H. (2023). Increased expression of androgen receptor and PSA genes in LNCaP (prostate cancer) cell line due to high concentrations of EGCG, an active ingredient in green tea. Hormone molecular biology and clinical investigation, 44(2), 181-186.

Baranwal, A., Aggarwal, P., Rai, A., & Kumar, N. (2022). Pharmacological actions and underlying mechanisms of catechin: A review. Mini Reviews in Medicinal Chemistry, 22(5), 821-833.

Briguglio, G., Costa, C., Pollicino, M., Giambò, F., Catania, S., & Fenga, C. (2020). Polyphenols in cancer prevention: New insights. International Journal of Functional Nutrition, 1(2), 9.

Cheng, Y., Sun, J., Zhao, H., Guo, H., & Li, J. (2022). Functional mechanism on stem cells by tea (Camellia sinensis) bioactive compounds. Food Science and Human Wellness, 11(3), 579-586.

Devi, N., Nagesh, A. M., Jala, M. A., Gupta, S., Chaturvedi, P. K., Kumar, N., . . . Pandey, D. (2023). Role of green tea catechins in modulating stromal-epithelial interaction in prostate cells. Indian Journal of Natural Products and Resources (IJNPR)[Formerly Natural Product Radiance (NPR)], 14(1), 28-36.

Dong, H., & Zhang, C. (2025). Epigenetic and biogenetic regulation by polyphenols in prostate cancer in the context of 3P medicine. EPMA Journal, 16(1), 113-125.

Fayed, A. M., Abdelzaher, M., Mahdi, N. H., AlKhafaf, D. M., AbdElRahman, M., Aldhalmi, A. K., . . . Morsi, S. E. S. (2024). Effect of ginger, chamomile, and green tea extracts on prostate cancer cells. Journal of Genetic Engineering and Biotechnology, 22(3), 100395.

Gillani, S.N., Ahmad,T., Rehman,A., Saba, I., Irshad,Sqw.B.E., Abbas,M., Zahid,I., Ali,K. (2024). The application of chemical analysis techniques in microbiology research: a review of methods, advancements, and implications for food and nutrition. Eur. Chem. Bull. 13 (01), 72 – 81.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Hao, Q., Wu, Y., Vadgama, J. V., & Wang, P. (2022). Phytochemicals in inhibition of prostate cancer: evidence from molecular mechanisms studies. Biomolecules, 12(9), 1306.

Kciuk, M., Alam, M., Ali, N., Rashid, S., Głowacka, P., Sundaraj, R., . . . Zerroug, E. (2023). Epigallocatechin-3-gallate therapeutic potential in cancer: mechanism of action and clinical implications. Molecules, 28(13), 5246.

Kesanapalli, S. V. P. R., Jha, B. K., & Devi, L. (2025). Plant-derived Molecules and Herbal Formulation for Cancer Treatment: in vitro and in vivo Evidence. Plant-derived Anticancer Drugs, 209-238.

Khalil, M. S., Shakeel, M., Gulfam, N., Ahmad, S. U., Aziz, A., Ahmad, J., . . . Idris, A. M. (2022). Fabrication of silver nanoparticles from ziziphus nummularia fruit extract: effect on hair growth rate and activity against selected bacterial and fungal strains. Journal of Nanomaterials, 2022(1), 3164951.

Khan, S., Fiaz, M., Alvi, I. A., Ikram, M., Yasmin, H., Ahmad, J., . . . Ahmad, A. (2023). Molecular profiling, characterization and antimicrobial efficacy of silver nanoparticles synthesized from Calvatia gigantea and Mycena leaiana against multidrug-resistant pathogens. Molecules, 28(17), 6291.

Khan Z.I., Ahmad K., Akhtar S., Batool M., Ejaz A., Ashfaq A., Nadeem M., Shad H.A., Noorka I.R., Hussain A., Awan M.U.F, Batool A.I., Memona H., Hamza M.A, Akhtar M., Saba I. and Javid S. (2023). Health risk assessment of Chromium and Lead in a soil plant-ruminant food chain against terrestrial soil pollution gradient. J. Plantarum., 5(1): 25-39.

Kumar, M., Verma, S., Rawat, S., & Dhatwalia, S. (2024). Exploring integrative approaches: EGCG's potential in combating prostate cancer. WCRJ, 11, e2744.

Laraib, S., Lutfullah, G., Nain Taara Bukhari, J. A., Almuhayawi, M. S., Ullah, M., Ullah, A., & Ashique10, S. (2023). Exploring the Antibacterial, Antifungal, and Anti-Termite Efficacy of Undoped and Copper-Doped ZnO Nanoparticles: Insights into Mutagenesis and Cytotoxicity in 3T3 Cell Line. JOURNAL OF BIOLOGICAL REGULATORS AND HOMEOSTATIC AGENTS, 37(12), 6731-6741.

Liu, B., Tian, H., & Momeni, M. R. (2025). The interplay of exercise and green tea: a new road in cancer therapy. Cancer cell international, 25(1), 6.

Lv, H., Qian, D., Xu, S., Fan, G., Qian, Q., Cha, D., . . . Lu, B. (2024). Modulation of long noncoding RNAs by polyphenols as a novel potential therapeutic approach in lung cancer: A comprehensive review. Phytotherapy Research, 38(6), 3240-3267.

Mokra, D., Joskova, M., & Mokry, J. (2022). Therapeutic effects of green tea polyphenol (–)-Epigallocatechin-3-Gallate (EGCG) in relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. International journal of molecular sciences, 24(1), 340.

Mthembu, S. X., Dludla, P. V., Ziqubu, K., Nyambuya, T. M., Kappo, A. P., Madoroba, E., . . . Muller, C. J. (2021). The potential role of polyphenols in modulating mitochondrial bioenergetics within the skeletal muscle: a systematic review of preclinical models. Molecules, 26(9), 2791.

Munir, S., Amanat, T., Raja, M. A., Mohammed, K., Rasheed, R. A., Hussein, D. S., . . . Hayat, S. (2023). Antimicrobial efficacy of phyto-synthesized silver nanoparticles using aqueous leaves extract of Rosamarinus officinalis L. Pakistan journal of pharmaceutical sciences, 36(3), 941-946.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Nawaz, R., Baber, Z., Saba, I., Shah, A. A., Abbas, T., Elansary, H., Sridhara, S. and Shakeel, I. (2024). Morpho-physiological and biochemical characterization of Kinnow (*Citrus reticulate*) in response to canker pathogens (*Xanthomonas axonopodis pv.citri*). Scientific Reports. 14(17315). Noman, A. M., Sultan, M. T., Mazhar, A., Baig, I., Javaid, J., Hussain, M., . . . Mujtaba, A. (2025). Anticancer molecular mechanisms of epigallocatechin gallate: An updated review on clinical trials. Food Science & Nutrition, 13(8), e70735.

Oh, J.-W., Muthu, M., Pushparaj, S. S. C., & Gopal, J. (2023). Anticancer therapeutic effects of green tea catechins (GTCs) when integrated with antioxidant natural components. Molecules, 28(5), 2151.

Ortiz, G.R., Cespedes-Panduro, B., Saba, I., Cotrina-Aliaga, J.C., Mohany, M., Al-Rejaie, S.S., Arias-Gonzales, J.L., Ramiz-Cornell, A.A., Kadham, M.J. and Akhavan-Sigari, R., (2023). Adsorption of thiotepa anticancer by the assistance of aluminum nitride nanocage scaffolds: A computational perspective on drug delivery applications. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 666, p.131276.

Rahman, K.U., Ali, S.S., Murad, S., Saba, I., Shireen, F., Rahman, B., Lodhi, M., Farooqi, M.B.B.K. and Gamaryani, A. **(2025)**. The Role of Complement C3 and C5a in Hyperinflammation, Cytokine Storm, and Immune Dysregulation during Severe COVID-19 Infection. Indus Journal of Bioscience Research. 3(4): 595-600.

Robina, S. H., Ahmad, J., Javed, S., Adnan, S., Zahir, J., & Shagufa, M. (2021). Antimicrobial Activity of Ethyl Acetate, Chloroform and Deionized Water Extract of Leaves of Pteris Cretica. Ann. Romanian Soc. Cell Biol, 25, 1493-1501.

Saba, I., Iqbal, M.J. and Iqbal, M., (2013). Bioactivity of *Eucalyptus citriodora* leaves essential oil. Agrochimica, *57*(2),127-136.

Safari, F., Azad, N. R., Ezdiny, A. A., Pakizehkar, S., Koohpar, Z. K., & Ranji, N. (2022). Antitumor activities of green tea by up-regulation of miR-181a expression in LNCaP cells using 3D cell culture model. Avicenna Journal of Medical Biotechnology, 14(1), 89.

Samynathan, R., Krishnan, M., Venkidasamy, B., Subramanian, U., Sankaran, S., Thiruvengadam, R., . . . Ghorbanpour, M. (2024). Comparative transcriptional analysis of genetically superior tea cultivars provides insights into variations in metabolite profiles and biological activities. Scientia Horticulturae, 334, 113308.

Sabir, Z., Akkilic, .N., Bulut, H., Umar, M., Salahshour, S., Saba, I., **2025**. A stochastic neural network procedure for the nonlinear typhoid fever disease system. Network Modeling Analysis in Health Informatics and Bioinformatics. 14:102

Satari, A., Ghasemi, S., Habtemariam, S., Asgharian, S., & Lorigooini, Z. (2021). Rutin: A flavonoid as an effective sensitizer for anticancer therapy; insights into multifaceted mechanisms and applicability for combination therapy. Evidence-Based Complementary and Alternative Medicine, 2021(1), 9913179.

Shah, R., Sarosh, I., Shaukat, R., Alarjani, K. M., Rasheed, R. A., Hussein, D. S., . . . Khan, M. K. (2023). Antimicrobial activity of AgNO 3 nanoparticles synthesized using Valeriana wallichii against ESKAPE pathogens. Pakistan journal of pharmaceutical sciences, 36.

Shahid, M., Amin, M.H.A.B., Mumtaz, N., Errum, A., Shahzad, M.N., Saba,I., Ahmed, M.J. and khan, B.S., (2023). Comparison of Locally Available Walnuts Based on Proximate Analysis and Selected Mineral Content. Tobacco Regulatory Science. 9(1):642-658. Shahid, M.S., Akram, A., Imtiaz, U., Saba, I., Kabir, R., Hayat, U., Haraira,A.A., Ibrahim,M. (2024). Review

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

of recent advances in chemical fertilizers and their impact on crop productivity and sustainability. European Chemical Bulletin, 13(01), 62 – 71.

Shenoy, A. G., Ravi, V., Vishwakarma, R., Varghese, S., Subair, S., Vaswani, R., . . . Rehman, N. (2025). Prostate Cancer and Tea: CYP17A1 Inhibition by Phytochemicals from Tea Plant Camellia sinensis L. and Implications for Anti-androgenic Effect. OMICS: A Journal of Integrative Biology, 29(6), 246-258.

Shaukat, U.A., Anwar, F., Akhtar, M.T., Qadir, R., Zahoor, S., Saba, I., Shabir,G., Siddique, F. and Moongngarm, A., (2022). Variations in physico-chemical and antioxidant attributes of Grape seed oil as function of extraction techniques. Sains Malays, *51*(07). 2087-2096.

Tossetta, G., Fantone, S., Marzioni, D., & Mazzucchelli, R. (2023). Role of natural and synthetic compounds in modulating NRF2/KEAP1 signaling pathway in prostate cancer. Cancers, 15(11), 3037.

Ullah, A., Maryam, A., Malik, G., Hameed, H., Hussain, K., Ahmad, J., Abougazia, E. M. (2023). Sustained virological response to antiviral drugs in treatment of different genotypes of HCV cirrhotic patients. PubMed, 36(3), 1009-1015.

Ullah, H., Ullah, A., Gul, H., Khan, R. U., Ahmad, J., Almeer, R., . . . Shah, Z. A. (2024). Interferon-stimulated gene (ISG12a) suppresses hepatitis B virus replication in Huh 7 cells line. Journal of King Saud University-Science, 36(9), 103377.

Wang, Y. (2024). The interplay of exercise and polyphenols in cancer treatment: A focus on oxidative stress and antioxidant mechanisms. Phytotherapy Research, 38(7), 3459-3488.

Wu, W., Pei, X., Wei, L., Wen, H., Chen, J., Tang, Z., . . . Du, Y. (2024). Are “Nutraceuticals” effective in the prevention of prostate cancer? A review. Precision Nutrition, 3(3), e00078.

Xiong, H., Zhang, W., Tan, X., Xiao, X., Ma, Z., Ma, X., . . . Zhao, Y. (2025). The Potential and Mechanisms of Tea Polyphenols in the Prevention and Treatment of Colorectal Cancer. Food Reviews International, 1-29.

Yadav, E., Yadav, P., Kamal, M. A., & Verma, A. (2021). Polyphenols as modulators of oxidative stress in cancer disease. In Polyphenols-based nanotherapeutics for cancer management (pp. 143-188): Springer.

Zhao, T., Li, C., Wang, S., & Song, X. (2022). Green tea (Camellia sinensis): A review of its phytochemistry, pharmacology, and toxicology. Molecules, 27(12), 3909.