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Review Paper

Pro-Oxidant Therapy in Prostate Cancer Treatment: A Review of Mechanisms, Delivery Systems, And Future Directions

Dr. Karthika Jawahar*, B. Aravind, R. Dhinesh Kumar

Department of Pharmacy Practice, JKKN College of Pharmacy, Kumarapalayam, Namakkal, India.

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ABSTRACT

Pro-oxidant therapy has emerged as a promising approach for treating prostate cancer by utilizing the increased sensitivity of cancer cells to oxidative stress. This narrative review evaluates recent advancements in pro-oxidant therapy and highlights key compounds such as piperlongumine (PL) and menadione sodium bisulfite (MSB), which exhibit selective cytotoxicity toward cancer cells through reactive oxygen species (ROS)-mediated pathways. A systematic search was conducted across PubMed, Scopus, and Google Scholar to identify relevant studies. Articles were selected based on predefined inclusion criteria, including experimental studies, clinical trials, and comprehensive reviews that examined the mechanisms, efficacy, and clinical applications of pro-oxidant therapies in prostate cancer. Data were extracted using a standardized method, concentrating on treatment modalities, bioavailability, innovative drug delivery systems, and biomarker-driven therapeutic strategies. The review synthesized data to identify trends in pro-oxidant therapy, particularly advanced delivery systems such as chitosan-fucoidan nanoparticles, which have enhanced the bioavailability and targeting efficiency of therapies, addressing previous limitations in solubility and distribution. Integrating personalized medicine approaches, such as genetic profiling and biomarker monitoring, has further improved treatment outcomes, with biomarker-driven strategies showing success rates between 1.6% and 10.7%. Emerging combination approaches, including the integration of conventional treatments with CAR-T cell therapy, hold promise for therapeutic synergy. Despite challenges like optimizing therapeutic windows and managing tumor heterogeneity, ongoing advancements in precision medicine and innovative drug delivery systems provide promising avenues for enhancing prostate cancer treatment. This review consolidates current evidence on the mechanisms of action, therapeutic potential, and future directions of pro-oxidant therapy, emphasizing its role in advancing personalized

***Corresponding Author:** Dr. Karthika Jawahar
Address: *Assistant Professor, Department of Pharmacy Practice, JKKN College of Pharmacy, Kumarapalayam, Namakkal, India.*
Email ✉: karthikajawahar475@gmail.com

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approaches for prostate cancer treatment.

INTRODUCTION

Prostate cancer treatment has advanced significantly in recent years, providing a range of effective options. Surgery and radiation remain the primary curative therapies for localized prostate cancer, while active surveillance is increasingly preferred by patients with less aggressive forms of the disease.[1] The introduction of innovative medications for managing metastatic prostate cancer, such as docetaxel chemotherapy and hormonal agents like abiraterone, enzalutamide, and apalutamide, has transformed the standard approach to androgen deprivation therapy.[2] Recent advancements, including the first oral gonadotropin-releasing hormone receptor antagonist, relugolix, and poly-ADP ribose polymerase inhibitors like olaparib and rucaparib, have created new treatment opportunities for patients with specific genetic profiles.[2] Moreover, lutetium-177-prostate-specific membrane antigen-617 has shown promise as a treatment option, improving survival rates in cases of metastatic disease.[2]

Multidisciplinary teams typically make treatment decisions by evaluating tumor characteristics, cancer stage, and individual patient factors to enhance outcomes while maintaining quality of life.[3] Prostate cancer is the most common malignancy among men worldwide and ranks as the fifth leading cause of cancer-related deaths. In 2020, there were 1,414,259 new cases and 375,304 fatalities.[4,5]. Projections suggest that the annual incidence of new cases globally will surpass 3 million by 2040, with many low- and middle-income countries encountering challenges related to late diagnoses and inadequate healthcare infrastructure.[6]

Despite advancements, current prostate cancer treatments face significant challenges including medication resistance, issues with treatment tolerance, and high recurrence costs, all of which impact patient survival and quality of life.[7] Conventional treatments such as radical prostatectomy, radiation, and brachytherapy carry ongoing risks, severe side effects, and considerable costs, especially in low-resource areas, highlighting the need for alternative approaches.[8-10]

In addition to patients, healthcare professionals face several systemic challenges. Ignorance, long wait times, and the limited availability of supportive treatments, such as outpatient therapy, are increasingly affecting individuals from low-income families.[11-15] These issues have sparked interest in complementary and alternative medicine, with 25-50% of patients seeking natural remedies to balance illness management and quality of life.[16,17] Integrative techniques that combine conventional therapy, lifestyle changes, and alternative treatments show promise.

Pro-oxidant treatment is an emerging approach for targeting cancer cells by exploiting oxidative stress. Researchers have shown that piperlongumine (PL) and menadione sodium bisulfite (MSB) effectively induce cancer cell death and inhibit tumor growth by capitalizing on the vulnerability of cancer cells to reactive oxygen species (ROS). Nanoparticles made from chitosan and fucoidan represent novel delivery methods that enhance the solubility and bioavailability of PL for more practical application. This approach is particularly significant in the context of androgen deprivation therapy, which induces oxidative stress in prostate cancer cells.

When combined with personalized treatments such as endostatin, pro-oxidant therapy shows promise for advancing disease-specific therapies in the future. These advancements are crucial components currently absent in existing therapies aimed at increasing patient effectiveness while ensuring a consistent quality of life.[19, 24]

Methods

A systematic search was performed across three major databases: PubMed, Scopus, and Google Scholar. The review methodology aimed to comprehensively analyze advancements in pro-oxidant therapy for prostate cancer treatment, focusing on advanced delivery systems and biomarker-driven approaches.

Search Strategy and Article Selection

The literature search focused on articles published between 2000 and 2024. Articles were selected based on predefined inclusion criteria:

- Experimental studies investigating pro-oxidant mechanisms
- Clinical trials evaluating therapeutic efficacy
- Comprehensive reviews of pro-oxidant therapies
- Studies examining drug delivery systems
- Research on biomarker-driven therapeutic strategies

Key search terms included:

- "pro-oxidant therapy" AND "prostate cancer"
- "oxidative stress" AND "cancer treatment"
- "reactive oxygen species" AND "cancer therapy"
- "chitosan-fucoidan nanoparticles"
- "biomarker-driven treatment"
- "drug delivery systems" AND "prostate cancer"

Data Extraction and Analysis

Data extraction was conducted using a standardized method, focusing on:

- Treatment modalities and mechanisms of action
- Drug bioavailability and distribution
- Innovative delivery systems, particularly chitosan-fucoidan nanoparticles
- Biomarker-driven therapeutic strategies
- Clinical outcomes and applications

Data Synthesis

The review synthesized data to identify:

- Trends in pro-oxidant therapy development
- Advancements in delivery systems
- Improvements in bioavailability and targeting efficiency
- Solutions to previous limitations in solubility and distribution
- Integration of biomarker-driven approaches

Special attention was given to innovative delivery systems, particularly chitosan-fucoidan nanoparticles, which have demonstrated enhanced therapeutic potential through improved bioavailability and targeting efficiency.

Understanding Pro-Oxidants and Their Mechanisms

Pro-oxidants generate reactive oxygen species (ROS) that play a complex dual role in cancer development. While these substances can induce carcinogenesis through DNA mutations and genomic disruption, they have also emerged as promising cancer therapies by exploiting cancer cells' vulnerability to oxidative stress.[25] These treatments selectively target cancer cells by elevating ROS levels beyond their tolerance threshold, leading to cell death, whereas normal cells handle the oxidative burden more effectively.[26] Cancer cells typically have higher baseline ROS levels than normal cells, making them more susceptible to additional oxidative stress. This has sparked renewed interest in pro-oxidant therapy as a targeted approach for cancer treatment.[25,26] The mechanism involves increasing oxidative stress in cancer cells by producing high levels of ROS, overwhelming cellular antioxidant

defenses, and triggering cytotoxic effects.[25,27] This heightened oxidative stress ultimately results in cancer cell death through apoptosis, as shown by compounds like piperlongumine and protocatechuic acid, which specifically target cancer cells by disrupting their redox balance and activating death pathways.[19,28] Pro-oxidants have advantages due to their ability to exploit cancer cells' inherently elevated ROS levels, pushing them beyond their survival threshold.[29] Studies involving substances such as pomegranate fruit extract have demonstrated that they induce ROS-mediated apoptosis in cancer cells while protecting normal tissues.[30,31] Pro-oxidants primarily induce oxidative stress in prostate cancer cells, leading to cell death through various pathways. For instance, green tea extract (PE) generates ROS and promotes mitochondrial dysfunction while inhibiting Akt activation, ultimately resulting in cancer cell death.[32] Likewise, pro-oxidant agents like piperlongumine, particularly when delivered using specific carriers such as chitosan-fucoidan nanoparticles, show enhanced efficacy.

Figure 1: Mechanism of Pro-Oxidant Therapy: Oxidative Stress-Induced Cytotoxicity in Prostate Cancer Cells36

Pro-Oxidant Supplements in Prostate Cancer: Current Evidence

Recent advances in pro-oxidant therapy have created opportunities for treating prostate cancer. In 2024, a vitamin K analog known as menadione sodium bisulfite was identified as an effective inhibitor of prostate cancer in rodent models by interacting with the Vacuolar Protein Sorting 34 (VPS34) pathway.[20] Researchers found that PL induces cancer cell death through targeted oxidative stress, and innovative chitosan-fucoidan nanoparticle delivery methods significantly boost its effectiveness.[19] Laboratory studies produced similar positive outcomes, with green tea extract notably decreasing cancer cell viability in PC3 cells by enhancing ROS generation and mitochondrial damage.[19,32] An intriguing discovery was made with oleuropein from olive oil, which smartly differentiates between cancerous and normal prostate cells, acting as a pro-oxidant solely in cancer cells.[37] These laboratory successes have transitioned effectively into animal studies, where Menadione Sodium Bisulfite (MSB) demonstrated a remarkable ability to suppress prostate cancer by targeting specific cellular pathways.[19,20] The SELECT trial involving 35,000 men had a significant influence on the direction of the field, as an unexpected increase in cancer risk from vitamin E supplementation prompted researchers to investigate pro-oxidant strategies.[20] Evolution has proven advantageous, with compounds like PL and MSB showing promise. However, low solubility restricts the clinical application of PL.[20,38] A recent study also suggests that drug combinations can be highly effective, with quercetin showing enhanced anticancer benefits when paired with vitamins C and K3, greatly increasing its efficacy against prostate cancer cells.[39] Nonetheless, researchers have noted considerable risks tied to common supplements such as vitamins E, selenium, and others,[40] since these compounds can sometimes shift from protective antioxidants to harmful pro-oxidants under specific conditions, even though the precise mechanisms remain unclear.[41, 42]

Mechanisms of Action in Prostate Cancer Cells

Pro-oxidants play a critical role in inducing apoptosis in prostate cancer cells by utilizing oxidative stress and targeting multiple molecular pathways. They elevate ROS levels, resulting in oxidative stress, DNA damage, and cell cycle arrest while activating caspase-dependent mechanisms and modifying the B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax) (Bcl-2/Bax)

ratio to promote apoptosis.[30,43-46] These compounds disrupt the mitochondrial membrane potential, causing mitochondrial dysfunction and the release of pro-apoptotic factors such as cytochrome c, which activates downstream caspases and initiates cell death.[30,46,48-50] Additionally, pro-oxidants inhibit Akt and mTOR phosphorylation and influence NF-κB and Nrf2-ARE pathways, further enhancing oxidative stress.[30,46] Modulating androgen receptor (AR) signaling helps counteract hormone therapy resistance and sensitizes castration-resistant prostate cancer cells to anti-androgens, disrupting androgen-mediated growth pathways.[24,52–54] Furthermore, pro-oxidants work synergistically with conventional treatments, enhancing DNA damage, cellular stress, and immunotherapy responses, ultimately improving therapeutic outcomes and overcoming resistance mechanisms.[22,54] For a detailed breakdown of these mechanisms and their interplay, refer to Table 1 below.

Table 1: Pro-oxidant Mechanisms in Prostate Cancer Cells

Biological Process	Mechanism and Effect
Induction of Oxidative Stress[19,43]	Elevated ROS levels lead to oxidative stress, DNA damage, and cell cycle arrest, initiating apoptosis in cancer cells.
Activation of Apoptosis Pathways[43,45]	Caspase activation and alterations in the Bcl-2/Bax ratio drive programmed cell death while sparing normal cells.
Mitochondrial Disruption[30,46,48,49]	Triggers mitochondrial dysfunction, cytochrome c release, and activation of caspase-9 and caspase-3, disrupting membrane potential and driving apoptosis.
Regulation of Cellular Signaling[46,48]	Suppresses Akt/mTOR signaling and modulates NF-κB and Nrf2-ARE pathways, enhancing oxidative stress and promoting cancer cell death.
AR Modulation[24,49,50]	Modifies AR signaling through oxidative stress, inhibits androgen-dependent growth, and sensitizes cells to anti-androgen therapies, counteracting hormone resistance.
Therapeutic Synergy[51,52]	Enhances efficacy of chemotherapy and radiotherapy by amplifying oxidative stress, DNA damage, and disrupting cancer cell redox balance.
Combination Strategies[22,53]	Combines ROS-inducing agents with antioxidant system inhibitors, demonstrating synergistic effects and enhancing responses to immunotherapy and chemotherapy.

Challenges and Limitations of Pro-Oxidant Therapy

Pro-oxidant therapy in cancer patients results in over 40 side effects, including nerve damage and bone marrow suppression, along with severe oxidative damage to normal tissues, especially cardiomyocytes. This damage is caused by mechanisms such as anthracycline-induced toxicity.[21]The narrow therapeutic window, stemming from indiscriminate oxidative stress, limits dosing and frequency.[21] Tumor heterogeneity, driven by genetic and metabolic

variations, diminishes treatment efficacy; cancer stem cells and slowly cycling cells show resistance to oxidative stress, which contributes to recurrence.[21,54] Transition metals increase toxicity via Fenton reactions, while mutations in TP53 and the deregulation of DNA repair processes impact treatment responses.[54,55] Variations in the tumor microenvironment and patient-specific factors complicate standardized protocols, making it challenging to find a balance between efficacy and toxicity.[21,54]

Proposed Solution: Leveraging Pro-Oxidant Therapy

Pro-oxidants can be effectively combined with chemotherapy agents like docetaxel to enhance tumor-killing activity by increasing oxidative stress and disrupting the redox balance in cancer cells.[21,56] Advanced delivery systems, such as lipid nanoemulsions and nanoparticles, improve the bioavailability and targeting of pro-oxidant therapies, while complementary strategies like aerobic exercise further amplify their therapeutic effects.[19,56] Pro-oxidants enhance anticancer effects by increasing oxidative stress and DNA damage, and they may help overcome drug resistance mechanisms in cancer cells.[19,57] Personalized treatment approaches, guided by oxidative stress biomarkers and genetic profiling, enable precise dosing and tailored interventions that optimize redox balance, improve treatment outcomes, and reduce adverse effects.[58,59] Biomarkers like ROS levels, peroxidation products, and enzymatic markers facilitate early detection of treatment efficacy or toxicity. In contrast, genetic profiling of variants such as CAT rs1001179 and genes like SOD2 and GPX1 helps identify patients most likely to benefit from therapy.[60-64] Standardized delivery systems, including chitosan-fucoidan nanoparticles and biomarker-driven clinical trials with adaptive designs, are vital for maximizing therapeutic efficacy, ensuring long-term safety, and minimizing toxicity to normal cells.[65,66] These advancements will pave the way for integrating pro-oxidants into existing cancer treatment regimens and improving patient outcomes.

Future Directions in Pro-Oxidant Therapy for Prostate Cancer

Menadione, a precursor to vitamin K, has substantial potential in prostate cancer therapy by effectively killing cancer cells through the depletion of Phosphatidylinositol 3-phosphate (PI(3)P) and demonstrating successful outcomes in mouse models.[20] PL, delivered via chitosan-fucoidan nanoparticles (CS-F NPs), offers another promising strategy by inducing cancer-specific apoptosis with minimal toxicity to normal cells.[19] Natural compounds such as parthenolide selectively enhance radiosensitivity in tumor cells while protecting normal prostate tissue, and polyphenol-rich fractions of Bergenia ligulata are effective against both androgen-dependent and androgen-refractory prostate cancer cells.[67,68] Synthetic compounds, including bardoxolone-methyl (CDDO-Me), show promise due to their anti-inflammatory and anticancer properties, while vitamin K precursors demonstrate efficacy through PI(3)P depletion mechanisms.[20,68]

Personalized medicine enhances pro-oxidant therapy by using genetic profiling and biomarker monitoring to identify individual oxidative stress profiles, antioxidant defense capacities, and drug metabolism patterns. This approach enables optimized treatment selection and dosing. Tailored delivery systems, such as nanoparticles, can adapt to patient-specific characteristics. Simultaneously, real-time monitoring of oxidative stress biomarkers allows for dynamic treatment adjustments, significantly improving success rates compared to non-biomarker-driven approaches (10.7% vs. 1.6%).[69,70] Genetic profiling identifies molecular alterations, including AR signaling

patterns and oxidative stress response genes, facilitating customized pro-oxidant therapy based on tumor characteristics and treatment responses. Comprehensive genomic analysis further refines treatment by detecting specific mutations, such as in Zinc Finger MYM-Type Containing 3 (ZMYM3) and Mitogen-Activated Protein Kinase 7 (MAP3K7), to guide personalized dosing strategies for enhanced efficacy.

Biomarker-driven approaches significantly enhance outcomes by facilitating precise patient selection and individualized therapy plans, with studies demonstrating superior results for patients receiving biomarker-guided treatments. Precision oncology identifies actionable genomic alterations in 80-90% of tested patients, while continuous biomarker monitoring during treatment enables real-time optimization of interventions. Pro-oxidants also show potential in combination therapies, such as PSMA-targeted radiation and PARP inhibitors, utilizing advanced delivery systems to improve targeting and reduce toxicity to normal cells. These strategies maximize therapeutic efficacy in prostate cancer treatment when integrated with personalized approaches like biomarker selection and molecular profiling.

Emerging therapies, such as CAR-T cell therapy, utilize ROS-responsive prodrugs like PipFcB to sensitize cancer cells to CD19 CAR-T cells without compromising T cell function or viability.[57] This approach establishes a self-amplifying ROS-inducing loop wherein antitumor T cells enhance ROS accumulation in cancer cells. Advanced delivery systems, such as chitosan-fucoidan nanoparticles, further improve targeting while reducing toxicity, making pro-oxidants a promising component of prostate cancer treatment.[19, 57]

CONCLUSION

Pro-oxidant therapy demonstrates significant therapeutic potential in the treatment of prostate cancer by leveraging the differences in redox status between cancerous and normal cells. Compounds such as PL and MSB effectively induce cancer cell death through ROS-mediated pathways while preserving the integrity of normal tissue. Chitosan-fucoidan nanoparticle delivery systems enhance bioavailability and targeting efficiency, addressing the solubility limitations of PL and the challenges faced by conventional treatments.

Integrating biomarker-driven methods with the genetic profiling of variants such as CAT rs1001179, SOD2, and GPX1 has raised success rates from 1.6% to 10.7%. Future directions focus on advanced biomarker-driven trials and combination therapy strategies, especially those involving PSMA-targeted radiation and PARP inhibitors. The development of ROS-responsive prodrugs and their incorporation with CAR-T cell therapy signifies a major advancement. This progress in pro-oxidant therapy, bolstered by precision oncology approaches, lays a foundation for improving treatment outcomes through personalized interventions.

Abbreviations

AR: Androgen Receptor
ARE: Antioxidant Response Element
Bcl-2/Bax: B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax)
CAR-T: Chimeric Antigen Receptor T-cell
CS-F NPs: Chitosan-Fucoidan Nanoparticles
DNA: Deoxyribonucleic Acid
MAP3K7: Mitogen-Activated Protein Kinase Kinase Kinase 7
MSB: Menadione Sodium Bisulfite
NF-κB: Nuclear Factor Kappa B
Nrf2-ARE: Nuclear Factor Erythroid 2-Related Factor 2-Antioxidant Response Element
PARP: Poly-ADP Ribose Polymerase
PE: Green Tea Extract
PI(3)P: Phosphatidylinositol 3-phosphate

PL: Piperlongumine
PSMA: Prostate-Specific Membrane Antigen
ROS: Reactive Oxygen Species
VPS34: Vacuolar Protein Sorting 34
ZMYM3: Zinc Finger MYM-Type Containing 3

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