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Cannabinoids and chemotherapy in prostate cancer: A scoping review of evidence on pain relief and quality of life

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ABSTRACT

Background: Prostate cancer remains a leading malignancy among men globally. Cannabinoids, particularly cannabidiol (CBD), have gained attention for their potential therapeutic effects, including anti-cancer properties and symptom management. However, the extent and nature of evidence supporting their use in prostate cancer care remain unclear. This scoping review aimed to map and synthesize existing preclinical and clinical evidence on the therapeutic effects of cannabinoids, either alone or in combination with chemotherapy, in prostate cancer. Specifically, the review sought to examine their potential anti-tumor properties, mechanisms of action, and any reported effects on symptom management, including pain relief and quality of life.

Methods: A scoping review was conducted following the Arksey and O'Malley framework and reported using the PRISMA-ScR guidelines. Searches were performed across PubMed, ScienceDirect, and the Cochrane Library for studies published between 2013 and 2025. Eligible studies included preclinical or clinical investigations involving cannabinoids in the context of prostate cancer. Two reviewers independently screened the articles and charted the data using the predefined eligibility criteria and third reviewer resolved the discrepancies. Data were charted and synthesised thematically.

Results: Twelve studies met the inclusion criteria, comprising ten preclinical and two clinical investigations. These included studies were conducted across various countries, including Italy, Chile, Ireland, China, the USA, South Africa, Sweden, and Australia. Most studies focused on the anti-proliferative, pro-apoptotic, and tumor-suppressive effects of CBD and other cannabinoids via mechanisms such as mitochondrial disruption and pathway modulation. Only a few studies addressed pain or quality of life, with limited and inconclusive clinical data. Variability in cannabinoid formulations and outcome measures was common.

Conclusion: While preclinical findings suggest that cannabinoids, particularly CBD, may have therapeutic potential in prostate cancer, clinical evidence remains sparse and inconclusive, especially regarding symptom relief and quality of life. High-quality clinical trials are needed to establish efficacy and guide clinical application.

Introduction

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide. In 2020, there were over 1.4 million estimated new cases globally, representing approximately 7.3 % of all male cancers [1]. The burden of prostate cancer varies considerably across regions, with the highest age-standardized incidence rates observed in Oceania (79.1 per 100,000), North America (73.7), and Europe (62.1), while lower rates are reported in Africa (26.6) and Asia (11.5) [2]. Prostate cancer is predominantly a disease of older men, with incidence increasing markedly with age from 1 in 350 men under age 50 to 1 in 52 between ages 50–59, and around 60 % of cases occurring in men over 65 years [3–5].

The etiology of prostate cancer is multifactorial. Established risk factors include age, ethnicity (with higher incidence among African-American men), family history, dietary and lifestyle factors (e.g., high-fat diets, smoking), and hormonal influences, particularly androgens such as testosterone and dihydrotestosterone (DHT) [6]. Prostate cancer typically originates in the peripheral zone of the prostate gland and is characterized by uncontrolled proliferation of prostate epithelial cells [7]. Androgen receptor (AR) signaling plays a critical role in both the initiation and progression of the disease. In the early stages, DHT binds to cytoplasmic AR, triggering conformational changes and AR dimerization [8,9]. The activated AR complex translocates to the nucleus, where it binds to androgen response elements (AREs) on DNA, regulating the transcription of genes involved in cell growth and survival [10,11]. Disruption of this pathway either by mutations in AR,

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amplification, or aberrant co-regulator activity can lead to androgen-independent prostate cancer, which is more aggressive and prone to metastasis [5].

Metastatic prostate cancer most frequently spreads to the bones, lymph nodes, liver, and lungs, and is associated with features such as osteoblastic bone lesions, elevated prostate-specific antigen (PSA) levels, and increased expression of genes associated with epithelial-to-mesenchymal transition (EMT) and angiogenesis [5,12]. Standard treatment options for localized disease include radical prostatectomy, radiation therapy, brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU), and active surveillance [13,14]. In advanced stages, androgen deprivation therapy (ADT) is the cornerstone of management. ADT can be administered via surgical castration or medical castration using luteinizing hormone-releasing hormone (LHRH) agonists/antagonists and is often combined with agents such as docetaxel, abiraterone acetate, enzalutamide, or apalutamide [15]. However, resistance to ADT manifested as castration-resistant prostate cancer (CRPC) remains a major therapeutic challenge, necessitating alternative strategies.

To address the limitations of current therapies, pharmaceutical research is exploring novel agents that can either inhibit AR signaling more effectively or bypass it altogether. This includes drugs that degrade the AR protein, block its nuclear translocation, or inhibit downstream gene expression. Additionally, attention is turning toward plant-derived and alternative therapies with fewer side effects and the potential to overcome resistance mechanisms [5].

Among these alternatives, *Cannabis sativa* (*C. sativa*) and its bioactive compounds, known as cannabinoids, are increasingly being investigated for their anti-cancer properties. *C. sativa*, also referred to as hemp, hashish, or marijuana, has a long history of use in medicine, nutrition, and industry [16]. It contains numerous pharmacologically active constituents with analgesic, anti-inflammatory, antispasmodic, antiepileptic, anxiolytic, antidepressant, and anticancer properties [17]. Since the 1990s, cannabinoids have been explored as potential treatments for a range of conditions, including epilepsy, multiple sclerosis, HIV/AIDS, and cancer [18].

Cannabinoids are broadly classified into three categories: phytocannabinoids (e.g., Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), endocannabinoids (e.g., anandamide AEA] and 2-arachidonoylglycerol (2-AG), and synthetic cannabinoids (e.g., WIN-55, JWH-133, R-methanandamide) [19,20]. *C. sativa* produces over 500 compounds, including cannabinoids, terpenes, flavonoids, and other secondary metabolites [21]. Cannabinoids are synthesized from cannabigerolic acid (CBGA), and over 150 variants have been identified to date[22]. Most phytocannabinoids are non-psychoactive and exhibit diverse biological effects. Synthetic cannabinoids, designed to mimic or enhance the effects of THC, can be up to 100 times more potent and are being actively researched for their anti-cancer, anti-inflammatory, and neuroprotective properties [23,24].

Cannabinoids interact with the endocannabinoid system (ECS), comprising CB1 and CB2 receptors, both of which are G protein-coupled receptors (GPCRs) [25,26]. CB1 receptors are primarily located in the central nervous system and peripheral tissues, while CB2 receptors are predominantly found in immune cells and the spleen [27]. The pharmacological effects of cannabinoids depend on the specific ligand–receptor interaction; for example, 2-AG is a high-efficacy agonist at both CB1 and CB2, whereas anandamide has lower efficacy, particularly at CB2 [28].

Recent research has expanded our understanding of cannabinoid pharmacodynamics by identifying orphan GPCRs (e.g., GPR18, GPR55, GPR119) and heteromeric receptor complexes, such as CB1–dopamine D2 heteromers, which may mediate unique signaling cascades in cancer cells [29,30]. These receptor interactions offer potential avenues for selective targeting of cancer-related pathways while minimizing side effects. The therapeutic relevance of such heteromers is particularly compelling in prostate cancer, where receptor expression and signaling are frequently dysregulated [31,32].

Clinical interest in cannabinoids for cancer therapy continues to grow, with a number of ongoing clinical trials evaluating their safety, tolerability, and efficacy. Notable examples include ACTRN12619001534178 and NCT04482244, which are investigating cannabinoid-based interventions in advanced cancer and anxiety among breast cancer patients, respectively [33,34]. A Phase I/Ib trial (NCT04428203) is also currently exploring the use of Epidiolex (CBD oil) in men with biochemically recurrent prostate cancer, aiming to assess its potential as a non-hormonal treatment option [33,35]. Furthermore, there is increasing interest in the role of cannabinoids for alleviating cancer-related bone pain and other symptoms in advanced prostate cancer.

While a recent meta-analysis synthesized evidence on the use of cannabinoids to improve health-related quality of life (QoL) in patients with neurological and oncological conditions, it primarily focused on general cancer populations and did not disaggregate findings by cancer type or therapeutic context [36]. As such, specific evidence pertaining to prostate cancer particularly regarding the combined use of cannabinoids and chemotherapy, and their distinct effects on pain and QoL remains unclear. Given the complex biology of prostate cancer, the evolving landscape of cannabinoid pharmacology, and the emergence of new primary studies, a scoping review is warranted to map the extent, range, and nature of the current evidence base. This scoping review, therefore, aimed to map and synthesize existing preclinical and clinical evidence on the therapeutic effects of cannabinoids, either alone or in combination with chemotherapy, in prostate cancer. Specifically, the review sought to examine their potential anti-tumor properties, mechanisms of action, and any reported effects on symptom management, including pain relief and quality of life.

Methods

This scoping review was conducted using the methodological framework proposed by Arksey and O'Malley [37], and further refined by Levac et al. [38], to systematically map the literature on cannabinoids in relation to pain relief and quality of life among individuals with prostate cancer undergoing chemotherapy. The framework consists of five compulsory stages: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) data charting, (5) collating, summarising, and reporting results. To enhance transparency and reproducibility, the review was reported in accordance with the PRISMA extension for Scoping Reviews (PRISMA-ScR) guidelines [39].

Identifying the research question

This scoping review question was developed using the Population, Concept, Context (PCC) framework to ensure a comprehensive and focused exploration of the literature. The population of interest included individuals diagnosed with prostate cancer; the concept pertains to the use of cannabinoids, either alone or in combination with chemotherapy; and the context involves the management of pain and the improvement of quality of life in this patient population.

The central question guiding this review was: What is the extent and nature of existing evidence on the use of cannabinoids, either independently or in combination with chemotherapy, for therapeutic applications in prostate cancer including anti-tumor activity, modulation of cancer-related pathways, and effects (where reported) on pain management and quality of life?

Identifying relevant studies

The aim of the literature search was to identify peer-reviewed studies that addressed the objectives of this scoping review, specifically focusing on the use of cannabinoids alone or in combination with chemotherapy for pain relief and quality of life in individuals diagnosed with prostate

cancer. To achieve this, a comprehensive search strategy was developed and implemented across three prominent biomedical and health science databases: PubMed, Cochrane Library, and ScienceDirect Web of Science. The search was limited to original articles published between 2013 and 2025 to ensure the inclusion of the most recent and relevant research reflecting advancements in cannabinoid science and prostate cancer management. The literature search was initially conducted in 2023 and updated in 2025 from 20th to 22nd March 2025.

The search strategy combined both Medical Subject Headings (MeSH) and free-text terms to optimise retrieval of pertinent literature. A combined keywords including: “Cannabinoids” “Chemotherapy” “Cancer” were utilized. Boolean operators (AND/OR) were employed to combine and refine search terms based on the databases’ unique indexing systems (Supplementary Table 1). Where applicable, syntax adjustments were made to conform to the search requirements of each database.

An information specialist was involved in the search process to ensure that the most relevant terminology and search strings were applied. In addition to the database searches, reference lists of all included studies were manually screened to identify any additional eligible publications that might have been missed in the initial search.

Restrictions on study design (e.g., observational and randomized control trials) or publication type (peer reviewed articles) was applied during the literature searches. Also, the literature search was restricted to studies published in English between 2013 and 2025. This timeframe was chosen to reflect the most up-to-date scientific evidence on the therapeutic application of cannabinoids in prostate cancer care, especially given recent increases in research output in this area. While the review initially focused on patient-centered outcomes such as pain and quality of life, preliminary scoping revealed that the majority of available studies in this domain are preclinical and center on anti-cancer mechanisms (e.g., apoptosis, proliferation, tumor suppression). As such, the review scope was expanded to include preclinical studies that investigated therapeutic effects of cannabinoids in prostate cancer models, while still highlighting instances where patient-centered outcomes were assessed. All retrieved search results were imported into EndNote Library X20 to facilitate efficient reference management, de-duplication, and screening.

Study selection and eligibility criteria

A three-stage screening process was used. In the first stage, two reviewers independently screened titles and abstracts for relevance based on predefined inclusion and exclusion criteria. In the second stage, full-text screening of potentially eligible studies was conducted independently by the same reviewers. Disagreements were resolved through with the assistance of a third reviewer.

This scoping review included studies:

- Published between 2013 and 2025;
- Focused on prostate cancer;
- Investigated the use of cannabinoids (alone or in conjunction with chemotherapy);
- Explored therapeutic outcomes, including anti-tumor effects (e.g., apoptosis, proliferation, signaling pathways), pain relief, and/or quality of life;
- Employed primary research designs (e.g., preclinical *in vitro/in vivo* models or clinical studies);
- Published in English.

Studies were excluded if they met any of the following conditions:

- Published in languages other than English
- Editorials, opinion pieces, conference abstracts, or grey literature lacking primary data
- Secondary research such as systematic reviews, meta-analyses, rapid reviews, and general literature reviews
- Not focused specifically on prostate cancer such as breast cancer

The full screening process was documented using a PRISMA flow diagram, outlining the number of records identified, screened, excluded, and included for synthesis.

Data charting

Data charting was carried out independently by two reviewers using a standardised data extraction form that was developed prior to the review and refined through pilot testing. The reviewers extracted and documented key information from each included study, ensuring consistency and completeness. Any discrepancies in the extracted data were discussed and resolved through consensus. To enhance the reliability of the process, cross-referencing was also conducted by reviewing cited references within the included studies.

The extracted data focused on the role of cannabinoids, either alone or in combination with chemotherapy, in the management of pain and the improvement of quality of life among individuals with prostate cancer. Specifically, the charted information included: author(s), year, and country of publication; study design and methodology; population characteristics; type of cannabinoid intervention (e.g., THC (delta 9-tetrahydrocannabinol), CBD (Cannabidiol), synthetic cannabinoids); the use of chemotherapy (if applicable); measured outcomes such as pain relief and quality of life; and key findings or conclusions. The synthesised data formed the basis for the analysis and interpretation of evidence presented in this review.

Collating, summarising, and reporting the results

The data were analysed descriptively and thematically. Studies were grouped according to their focus on either pain relief, quality of life, or both. Key patterns, research gaps, and emerging themes were identified. A narrative synthesis was conducted to present the range and nature of the evidence, supported by summary tables and charts.

Results

A total of 737 articles were initially identified through database searches. Following the removal of duplicates and screening against the study’s eligibility criteria including full-text review, 12 studies met the inclusion criteria and were included for data extraction and analysis (see Fig. 1).

Study selection

Characteristics of the included studies

A total of 12 studies were included in this review, comprising preclinical (n = 10) and clinical (n = 2) investigations conducted across various countries, including Italy, Chile, Ireland, China, the USA, South Africa, Sweden, and Australia. The included studies explored the therapeutic potential of cannabinoids, either as monotherapy or in combination with chemotherapy or gene-targeted interventions, in the context of prostate cancer.

Preclinical studies primarily employed *in vitro* models using androgen-sensitive and androgen-insensitive prostate cancer cell lines such as LNCaP, PC-3, DU145, and TRAMP-C2, and in some cases, *in vivo* xenograft models in immunodeficient mice [40–43]. The cannabinoid compounds investigated included Cannabidiol (CBD), Cannabis sativa extract, and synthetic cannabinoids like WIN 55,212–2 and GW-405,833, with several studies also examining botanical drug substances (BDS) enriched in specific cannabinoids [42,44]. These studies demonstrated consistent anti-proliferative, pro-apoptotic, and anti-metastatic effects, often mediated through modulation of key signaling pathways such as PI3K/Akt/mTOR, NF-κB, ROS, and mitochondrial membrane potential [43,45–47]. Notably, Mahmoud et al. [40] and Motadi et al.

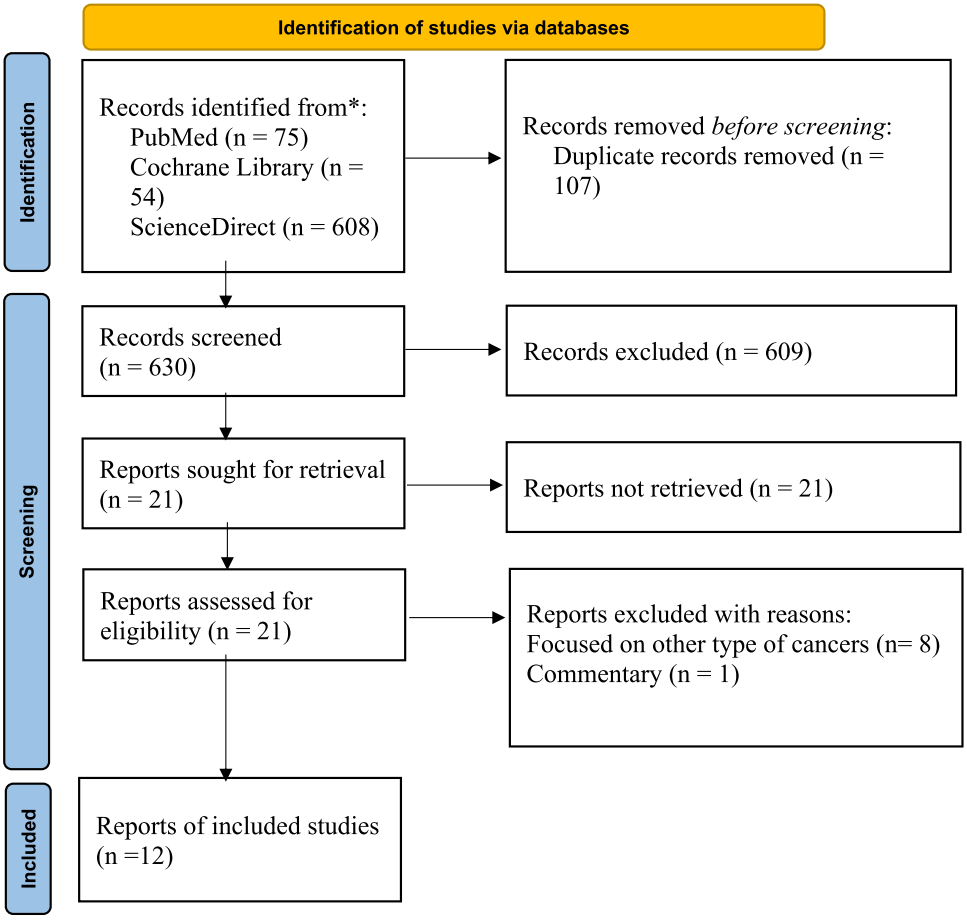

Fig. 1. Adopted PRISMA 2020 flow diagram.

[41] reported enhanced anti-cancer efficacy when cannabinoids were combined with enzalutamide or cisplatin, respectively.

Clinical studies offered important translational insights. Myint et al. conducted a Phase I trial in patients with biochemically recurrent (BCR) prostate cancer, finding that oral Epidiolex (CBD) was safe and well tolerated, with some participants achieving stable disease and reporting modest, non-significant improvements in quality of life [48]. Häggström et al. [49] and Cipriano et al. [50] while not intervention-based, used tissue microarray analysis to explore the relationship between CB1 receptor expression, tumor aggressiveness, and Akt signaling, offering important evidence of endocannabinoid system dysregulation in prostate cancer (See Table 1 for a detailed overview of the included studies.)

Cannabinoid interventions and chemotherapy use

The included studies demonstrated considerable variation in the types of cannabinoid compounds investigated and their use either as standalone interventions or alongside chemotherapy. Most studies explored non-psychoactive cannabinoids, with Cannabidiol (CBD) being the most commonly assessed compound, used either in purified form or as part of broader botanical drug substances (BDS). Other cannabinoids studied included Cannabigerol (CBG), Cannabichromene (CBC), and synthetic cannabinoids such as WIN 55,212-2 and GW-405,833 [40,42,43].

Across the preclinical studies, CBD was the principal cannabinoid investigated for its anti-proliferative, pro-apoptotic, and tumor-suppressive effects [41,45,51]. Notably, Mahmoud et al. explored both CBD and CBG, individually and in combination, and compared their efficacy to conventional chemotherapeutic agents such as docetaxel and cisplatin, though no direct combination was used [40]. Similarly, Shoeib et al. used docetaxel as a positive control but did not administer it alongside cannabinoids(46). In contrast, Motadi et al. was one of the few preclinical studies that tested CBD in combination with cisplatin, showing enhanced therapeutic outcomes [41]. Furthermore, De Petrocellis et al. reported significant tumor suppression when CBD or BDS were co-administered with docetaxel or bicalutamide, demonstrating the potential of cannabinoids as chemo-sensitizing agents [42].

Several studies also explored the role of endocannabinoids such as Anandamide (AEA) and 2-Arachidonoyl Glycerol (2-AG), or receptor-targeted analogs like Methanandamide, particularly in evaluating receptor-mediated apoptosis and signaling pathway modulation[44,47]. Synthetic cannabinoids such as WIN 55,212–2 featured prominently in studies targeting CB1 and CB2 receptor pathways, with evidence supporting their capacity to inhibit neuroendocrine differentiation and reduce tumor invasiveness [43,44].

From a clinical perspective, Myint et al. assessed the safety and tolerability of Epidiolex, a pharmaceutical-grade CBD, in patients with biochemically recurrent prostate cancer [48]. No chemotherapy was administered during the trial, although preclinical references to CBD–chemotherapy combinations were cited.

Two observational studies, Häggström et al. [49] and Cipriano et al. [50], did not involve cannabinoid administration but focused on CB1 receptor expression in prostate tissue, offering insights into the endocannabinoid system's role in tumor progression and its potential as a biomarker for treatment stratification. (Refer to Table 2 for a detailed summary of cannabinoid interventions and chemotherapy use across the included studies.)

In summary, the review highlights a predominant reliance on preclinical evidence exploring CBD and related cannabinoids as anti-cancer

Table 1
Characteristics of the included studies.

Author, year	Country	Study design and methodology	Population characteristics
Mahmoud et al. 2023 [40]	Italy	*In vitro* and in-vivo experimental study using TRAMP mouse model (hormone-refractory prostate cancer); combination of metabolomics, imaging, gene/protein expression, and Seahorse analysis.	Prostate cancer cell lines (TRAMP-C2); both naïve (non-HRPC) and hormone-refractory (HRPC); and TRAMP mouse model
Orellana-Serradell et al. 2015 [47]	Chile	*In vitro* experimental study using prostate cancer cell lines (PC3) and primary cultures from prostate cancer and benign prostatic hyperplasia (BPH); utilized immunohistochemistry, MTT assay, flow cytometry, western blot, and Annexin V assays to assess receptor presence, cell viability, apoptosis, and molecular pathways.	Human prostate cancer cell line (PC3) and primary cell cultures derived from prostate cancer and BPH patient samples.
O'Reilly et al. 2023 [51]	Ireland	In-vitro experimental study using androgen-sensitive (LNCaP) and androgen-insensitive (DU145, PC-3) prostate cancer cell lines. Employed MTT assays, clonogenic assays, flow cytometry, western blotting, fluorescence microscopy, and invasion (Transwell) assays.	Human prostate cancer cell lines: LNCaP (androgen-sensitive), DU145 and PC-3 (androgen-insensitive); and non-cancerous prostate epithelial cells: PWR-1E and RWPE-1.
Li et al. 2023 [45]	China	In-vitro experimental study using PC3 human prostate cancer cells. Assessed effects of cannabidiol (CBD) on cell viability, apoptosis, oxidative stress, mitochondrial function, and NF-κB signaling using XTT assay, Annexin V/PI flow cytometry, caspase assays, RT-qPCR, Western blotting, and fluorescent imaging.	Human prostate cancer cell line: PC3, derived from a bone metastasis of a grade IV prostate adenocarcinoma.
Pietrovito et al. 2020 [44]	Italy	In-vitro experimental study using prostate cancer cell lines (LNCaP, PC-3, DU-145), healthy prostate epithelial cells (PNT-1), and patient-derived fibroblasts (CAFs and HPFs). Cannabinoids tested: WIN 55–212.2 mesylate (synthetic agonist of CB1/CB2) and CBD. Functional assays included crystal violet staining, western blot, migration/invasion assays, gelatin zymography, and receptor antagonism.	Prostate cancer cell lines (androgen-sensitive LNCaP; androgen-insensitive PC-3 and DU-145); normal epithelial prostate cells (PNT-1); fibroblasts from patients with aggressive prostate cancer (CAFs) and adjacent non-cancerous areas (HPFs).
Shoeib et al. 2022 [46]	USA	In-vitro experimental study using human prostate cancer cell lines (PC-3 and DU-145). The study used radioligand binding, mRNA expression (qRT-PCR), functional assays (LDH release, ATP-based viability, mitochondrial membrane potential), and signal transduction profiling to evaluate cannabinoid receptor activity.	Human prostate cancer cell lines: PC-3 (low CBR density) and DU-145 (high CBR density).
Motadi et al. 2023 [41]	South Africa	*In vitro* and *in vivo* experimental study. Evaluated the anti-proliferative and pro-apoptotic effects of Cannabis sativa extract, CBD, and cisplatin, alone or in combination with RBBP6 gene silencing (siRBBP6), on PC3 prostate cancer cells. Used MTT assays, xCELLigence, caspase 3/7 assays, flow cytometry, RT-qPCR, Western blotting, and xenograft mouse models.	Human prostate cancer cell line (PC3), and *in vivo* xenograft model using immunodeficient nude mice inoculated with PC3 cells.
Myint et al. 2023 [48]	USA	Phase I open-label, single-center, dose-escalation and expansion clinical trial assessing safety, tolerability, preliminary anti-tumor activity, and quality of life of Epidiolex (pharmaceutical-grade CBD) in patients with biochemically recurrent (BCR) prostate cancer.	21 male patients with BCR prostate cancer (median age 69); prior definitive treatment with surgery and/or radiation; no metastases or recent ADT; screened for THC and psychiatric risks.
De Petrocellis et al. 2013 [42]	Italy	*In vitro* and *in vivo* experimental study using androgen receptor (AR)-positive and AR-negative prostate carcinoma cell lines (LNCaP, DU-145, PC-3, 22RV1). Evaluated pure non-THC cannabinoids and botanical drug substances (BDS) enriched in specific cannabinoids. Assays included MTT, FACS, TUNEL, caspase 3/7, qRT-PCR, immunofluorescence, xenograft tumor volume, and survival analysis in nude mice.	Human prostate cancer cell lines: LNCaP (AR-positive), DU-145, PC-3, 22RV1 (AR-negative or AR-independent). *In vivo*: athymic nude mice xenografted with LNCaP or DU-145 cells.
Häggström et al. 2014 [49]	Sweden and USA	Observational, exploratory Bayesian network analysis of prostate cancer tissue microarray data, complemented with *in vitro* experimental validation using transfected rat prostate cancer cell line (AT1). The study used directed acyclic graphs (DAGs) to infer potential upstream regulators of CB1 receptor expression in prostate cancer.	419 patients with prostate cancer diagnosed via transurethral resection (1975–1991); tissue microarrays included malignant and non-malignant prostate samples. Experimental model: R3327-AT1 rat prostate cancer cells transfected with CB1 receptor.
Cipriano et al. 2013 [50]	Sweden	Observational molecular pathology study using a prostate cancer tissue microarray (419 patient samples) to examine associations between cannabinoid receptor CB1 expression and Akt pathway activation (phosphorylated Akt immunoreactivity). CB1 immunoreactivity (CB1IR) was rescored and compared with other markers (e.g., pEGFR, ErbB2) and clinical features using statistical modeling (Spearman's correlation, ordinal regression, Cox proportional-hazards).	419 men diagnosed with prostate cancer via transurethral resection between 1975 and 1991 at a regional hospital in Västerås, Sweden. Clinical data included Gleason score, metastasis status, tumor stage, and proliferation index (Ki-67).
Morell et al. 2016 [43]	Spain	*In vitro* study using LNCaP (androgen-sensitive) and PC-3 (androgen-independent) prostate cancer cells; complemented with *in vivo* xenograft mouse model using PC-3 cells. Investigated effects of synthetic cannabinoid WIN 55,212-2 (WIN) on neuroendocrine differentiation (NED). Mechanistic analysis included Western blot, qPCR, immunofluorescence, and signaling pathway inhibitors.	Human prostate cancer cell lines (LNCaP and PC-3); nude mice xenografted with PC-3 cells.

agents, with limited but promising clinical research. While the majority of studies did not incorporate chemotherapy, those that did suggest synergistic or additive effects when cannabinoids are combined with agents such as docetaxel or cisplatin [41,44]. Clinical studies remain scarce, and future research should prioritize rigorous clinical trials assessing cannabinoids both as primary and adjunctive therapies in prostate cancer, particularly focusing on quality of life and symptom control outcomes.

Outcome measures

The included studies utilized a range of outcome measures to evaluate the effects of cannabinoids in prostate cancer models, focusing predominantly on cellular and molecular endpoints related to tumor suppression. However, few studies assessed pain relief or quality of life (QoL) outcomes, indicating a gap in the translation of findings to patient-centered endpoints.

Table 2
Type of cannabinoid intervention, and chemotherapy use across the included studies.

Author, year	Intervention	Use of chemotherapy
Mahmoud et al. 2023 [40]	CBD (Cannabidiol), CBG (Cannabigerol); tested individually and in 1:1 combination; purity ≥98 %.	No traditional chemotherapy used; comparison made with chemotherapy drugs (cisplatin, docetaxel, temozolomide); enzalutamide used to induce resistance
Orellana-Serradell et al. 2015 [47]	Endocannabinoids: Anandamide (Ana), 2-Arachidonoyl Glycerol (2-AG), and synthetic analog Methanandamide (Me).	No standard chemotherapy used. A CB1 receptor antagonist (SR141716) was used to determine receptor-mediated effects.
O'Reilly et al. 2023 [51]	Cannabidiol (CBD), >99.7 % purity, supplied by GreenLight Pharmaceuticals.	No conventional chemotherapy used; the study focused solely on CBD's effects.
Li et al. 2023 [45]	CBD, a non-psychoactive compound sourced from Cannabis sativa, applied in various concentrations (0.1–10 μM)	No conventional chemotherapy used; the study focused solely on the effects of CBD.
Pietrovito et al. 2020 [44]	WIN 55–212.2 mesylate (synthetic cannabinoid agonist for CB1 and CB2); CBD (Cannabidiol); endocannabinoids: Anandamide (AEA) and 2-Arachidonoyl glycerol (2-AG).	No standard chemotherapy used; the study evaluated cannabinoid effects and cannabinoid receptor-specific antagonists (AM281 for CB1, JTE-907 for CB2).
Shoeib et al. 2022 [46]	Synthetic cannabinoids: WIN-55,212–2 (CB1/CB2 agonist), GW-405,833 (CB2-selective agonist), rimonabant and AM-251 (CB1-selective inverse agonists), AM-630 (CB2 inverse agonist), among others.	Docetaxel was used as a positive control in cytotoxicity assays. No direct combination with cannabinoids was tested.
Motadi et al. 2023 [41]	Cannabidiol (CBD) at 10 μM; Cannabis sativa extract at 30 μM. CBD was also combined with siRBBP6 and cisplatin in some groups.	es – cisplatin (3 μM *in vitro*; 50 mg/kg/day *in vivo*) used alone and in combination with CBD and siRBBP6.
Myint et al. 2023 [48]	Epidiolex, an FDA-approved purified Cannabidiol (CBD) oral solution (>95% CBD, <0.5% THC); dose escalated from 600 mg to 800 mg daily.	No concurrent chemotherapy used; some preclinical comparisons cited use of CBD with docetaxel or bicalutamide, but this trial focused solely on CBD monotherapy.
De Petrocellis et al. 2013 [42]	Non-THC cannabinoids: Cannabidiol (CBD), Cannabichromene (CBC), Cannabigerol (CBG), CBD acid (CBDA), THC acid (THCA), Cannabidivarin (CBDV), and corresponding BDS.	Yes – tested CBD/BDS alone and in combination with docetaxel and bicalutamide in both *in vitro* and *in vivo* xenograft models.
Häggström et al. 2014 [49]	CB1 receptor agonist CP55,940 used in functional assays; CB1 receptor overexpression through transfection in AT1 cells. No phytocannabinoids (CBD, THC) were tested	Not applied. Study focused on receptor expression and regulation, not therapeutic chemotherapy.
Cipriano et al. 2013 [50]	No exogenous cannabinoids (e.g., THC, CBD) were administered. The study focused on endogenous CB1 receptor expression levels in tumor tissues.	No chemotherapy used; this was a biomarker-based observational study.
Morell et al. 2016 [43]	Synthetic cannabinoid: WIN 55,212–2 (a CB1/CB2 receptor agonist); dose: 3 μM *in vitro*, 0.5 mg/kg/day *in vivo*.	No conventional chemotherapy used; the study focused on cannabinoid monotherapy.

Across the preclinical studies, the most commonly measured outcomes included cell viability, apoptosis, gene and protein expression, and tumor suppression in animal models. For instance, Mahmoud et al. demonstrated that cannabidiol (CBD) and cannabigerol (CBG) affected mitochondrial function, triggered apoptosis, and reduced tumor volume in hormone-refractory prostate cancer models [40]. Similarly, Orellana-Serradell et al. [47]. and Li et al. [45] reported increased apoptotic activity and oxidative stress following cannabinoid treatment in PC3 cells, with involvement of key markers such as caspase-3, Bcl-2, and ROS. These molecular changes suggest a potential mechanism by which cannabinoids exert anti-cancer effects.

Studies like O'Reilly et al. [51] and Pietrovito et al. [44] further examined the impact of cannabinoids on cell proliferation, invasion, and fibroblast activation, providing insight into their potential to inhibit metastatic behavior. Shoeib et al. added to this by evaluating receptor dynamics and mitochondrial membrane potential following synthetic cannabinoid exposure[46], while Motadi et al. uniquely demonstrated *in vivo* tumor regression with minimal toxicity to healthy cells[41]. Collectively, these findings reinforce the anti-tumor potential of cannabinoids, although pain relief and QoL were not directly assessed in these studies.

In contrast, clinical research included more patient-centered outcome measures. Myint et al. assessed pain and QoL using validated tools (EORTC QLQ-C30 and PR25) in patients with biochemically recurrent prostate cancer treated with Epidiolex [48]. While pain was formally assessed through the QoL pain subscale, no statistically significant changes were observed. Minor, non-significant improvements were reported in domains such as emotional functioning and insomnia, with small deteriorations in fatigue and constipation.

On the other hand, observational studies such as those by Häggström et al. [49] and Cipriano et al. [50] did not assess pain or QoL but focused on the expression and regulation of CB1 receptors in prostate cancer tissue. These studies contributed valuable mechanistic insights but lacked direct clinical relevance to symptom or wellbeing outcomes (Refer to Table 3 for a summary of outcome measures across the included studies.)

In summary, the current evidence base shows that most cannabinoid-related prostate cancer studies focus on tumor-suppressive molecular mechanisms, with few directly assessing pain relief or quality of life, particularly in human subjects. The clinical studies that did assess QoL indicated some positive trends, but findings were often not statistically significant. These observations underscore the need for future research to adopt comprehensive, patient-centered outcomes that capture both biological efficacy and clinical benefit, especially in the context of advanced prostate cancer where pain and QoL are critical endpoints.

Summary of key findings of the included studies

The included studies collectively highlight several overarching themes regarding the therapeutic and mechanistic potential of cannabinoids in prostate cancer. These themes include tumor growth suppression, apoptosis induction, modulation of cancer-related signaling pathways, impact on the tumor microenvironment, potential synergy with conventional therapies, and emerging clinical relevance.

1. Anti-Proliferative and pro-apoptotic activity

Across the included studies, one of the most consistent findings was the anti-proliferative and pro-apoptotic effect of cannabinoids particularly Cannabidiol (CBD) in prostate cancer models. Cannabinoids inhibited cell viability and induced apoptosis through mitochondrial dysfunction, oxidative stress, p53 activation, and caspase-mediated pathways [40,42,45]. These effects were observed across both androgen-sensitive and hormone-refractory cell lines, suggesting relevance for advanced disease settings.

2. Modulation of the tumor microenvironment

Beyond their direct cytotoxic effects, cannabinoids also modulated the tumor microenvironment. Specifically, WIN 55-212.2 mesylate and

Table 3
Outcome measures by the included studies.

Author, year	General measures	Pain relief assessment	Quality of life assessment
Mahmoud et al. 2023 [40]	Mitochondrial dysfunction, apoptosis, glycolytic and OXPHOS activity, gene and protein expression (e.g., PTEN, pAkt, HIF-1α), autophagy markers, tumor volume reduction *in vivo*	Not assessed directly	Not assessed directly, though tumor suppression and progression metrics were measured *in vivo*.
Orellana-Serradell et al. 2015 [47]	CB1/CB2 receptor expression, cell viability (via MTT assay), apoptosis (Annexin V, caspase-3, Bcl-2), and involvement of ERK and AKT signaling pathways.	Not directly assessed.	Not directly measured, though anti-tumor effects were explored through mechanisms related to cell viability and apoptosis.
O'Reilly et al. 2023 [51]	Cell viability, proliferation, apoptosis, expression of CDK1, CDK2, CDK4, Cyclin D3, AKT phosphorylation, invasion potential, and E-cadherin expression.	Not assessed	Not directly measured; however, tumor-related properties such as proliferation and invasiveness were investigated
Li et al. 2023 [45]	Cell viability (XTT assay), apoptosis (caspase-3/7 activation, DNA fragmentation, Annexin V/PI), gene expression of pro-apoptotic and oxidative stress markers (Bax, Caspase-3, Caspase-9, gp91phox, iNOS, CYP2E1, Gpx1), intracellular ROS and GSH levels, mitochondrial membrane potential, ATP production, and NF-κB activation and nuclear localization	Not assessed	Not directly assessed, though tumor cell viability and death pathways were evaluated
Pietrovito et al. 2020 [44]	Cell viability, receptor expression (CB1, CB2, TRPV1), CAF activation markers (α-SMA, MMP-2), cancer cell migration/invasion, and CAF-induced epithelial-to-mesenchymal transition in PC-3 cells. Also assessed autocrine effects of endocannabinoids on CAF and cancer cell migration.	Not assessed	Not directly assessed; inferred through tumor cell invasiveness and fibroblast activation
Shoeib et al. 2022 [46]	Receptor binding affinity and density, G protein activation, Adenylyl cyclase modulation, Receptor downregulation after chronic exposure, Cytotoxicity (LDH release), ATP-dependent viability, and Mitochondrial membrane potential (MMP)	Not assessed	Not directly assessed; tumor cell viability and death-related markers were the focus
Motadi et al. 2023 [41]	Cell viability (MTT, xCELLigence), Apoptosis (caspase 3/7 activity, Annexin V/PI flow cytometry), Gene expression (p53, Bax, Bcl2, RBBP6 mRNA and protein), and *In vivo* tumor volume and weight in mouse models	Not assessed	Not directly measured; tumor suppression, apoptosis, and reduced toxicity to healthy cells were evaluated. CBD demonstrated selective cytotoxicity to cancer cells with minimal effects on normal MRC5 and HEK-293 cells.
Myint et al. 2023 [48]	Safety and tolerability (adverse events, dose-limiting toxicities), PSA levels and biochemical response (partial response, stable disease, progression), Testosterone levels, Patient-reported outcomes (QoL via EORTC QLQ-C30 and PR25), and CB1 receptor expression via immunohistochemistry	Assessed as part of QoL (EORTC QLQ-C30 pain subscale); no significant changes observed	Minor non-significant improvements in global QoL, emotional functioning, sexual functioning, and insomnia; minor worsening in fatigue and constipation; most changes not clinically or statistically significant.
De Petrocellis et al. 2013 [42]	Cell viability (MTT), Apoptosis markers (caspase 3/7, PUMA, CHOP, ROS, intracellular Ca^{2+}, TUNEL), TRPM8/TRPV1/TRPV2 channel and AR expression, *In vivo* tumor volume, weight, and survival after treatment, and Synergistic effects with chemotherapy agents	Not assessed	Not directly measured, but *in vivo* tumor growth reduction and improved survival were used as proxies for therapeutic potential.
Häggström et al. 2014 [49]	CB1 receptor expression in prostate tissue, Expression of upstream regulators: phosphorylated EGFR (pEGFR), FAAH, ErbB2, LRIG1, Network modeling of CB1 regulation via Bayesian inference, and Functional sensitivity to CB1 activation (via CP55,940) in transfected prostate cancer cells (cell viability/proliferation)	Not assessed	Not assessed
Cipriano et al. 2013 [50]	CB1 receptor expression (immunoreactivity scores), pAkt (phosphorylated Akt) expression, Correlation with tumor severity: Gleason score, tumor stage, metastasis,% tumor area, and Ki-67 index, and Disease-specific survival	Not assessed	Not assessed
Morell et al. 2016 [43]	Neuroendocrine markers: βIII tubulin and neuron-specific enolase (NSE), PI3K/Akt/mTOR and AMPK signaling activation, Tumor growth in PC-3 xenograft model, and CB1 and CB2 receptor expression in NE differentiated cells	Not assessed	Not directly assessed; therapeutic potential was inferred through reduction in NE differentiation and tumor growth

other compounds were shown to inhibit the activation of cancer-associated fibroblasts (CAFs) and reduce epithelial-to-mesenchymal transition (EMT), which in turn suppressed cancer cell invasiveness [44]. *In vivo* studies further confirmed these findings, with cannabinoids reducing tumor growth and stromal support mechanisms [43].

3. Synergistic effects with chemotherapy

Several studies demonstrated that cannabinoids could enhance the effects of conventional prostate cancer therapies. For instance, the combination of CBD with chemotherapeutic agents such as docetaxel, cisplatin, and bicalutamide produced additive or synergistic effects on tumor suppression [41,42]. These findings suggest that cannabinoids may serve as effective adjuncts in combination regimens, especially in resistant disease.

4. Receptor-Mediated and non-canonical mechanisms

While many effects were mediated through classical cannabinoid receptors (CB1 and CB2), multiple studies highlighted non-canonical mechanisms of action. For example, receptor-independent pathways and novel cannabinoid-binding sites were implicated in apoptosis and mitochondrial disruption [46,47]. Häggström et al. identified phosphorylated EGFR as an upstream regulator of CB1, suggesting intricate signaling cross-talk involved in prostate cancer progression [49].

5. Clinical potential and supportive care applications

Clinical trials investigating cannabinoids in prostate cancer remain limited but promising. Myint et al. reported that Epidiolex (CBD) was safe and well tolerated in patients with biochemically recurrent prostate cancer, with disease stabilization in the majority of participants [48]. Meanwhile, Grimison et al. demonstrated that a THC:CBD extract improved chemotherapy-induced nausea and vomiting and was preferred by patients, indicating potential for supportive care use [52].

6. Prognostic relevance of cannabinoid receptors

CB1 receptor expression has emerged as a potential prognostic marker in prostate cancer. High CB1 expression was found to be associated with increased Akt activation, higher Gleason scores, and poorer survival outcomes, highlighting its relevance for risk stratification and therapeutic targeting [49,50].

In summary, the body of evidence underscores the multifaceted therapeutic potential of cannabinoids in prostate cancer through modulation of apoptosis, metabolism, tumor microenvironment, and drug responsiveness, with CBD emerging as the most widely studied and effective compound. However, the transition from preclinical efficacy to clinical application remains limited, and further well-designed trials are needed to evaluate safety, effectiveness, and optimal therapeutic regimens in human populations. (Refer to Supplementary Table 2 for a summary of the individual study aims and key findings/conclusions across the included studies).

Discussion

This scoping review provides a comprehensive synthesis of existing literature on the use of cannabinoids either alone or in combination with chemotherapy in managing pain and improving quality of life in prostate cancer. The findings reveal a growing body of preclinical research demonstrating that cannabinoids, particularly cannabidiol (CBD), have significant anti-cancer properties. These include inhibition of cell proliferation, induction of apoptosis, reduction in metastatic potential, and modulation of tumor-promoting pathways such as PI3K/Akt, NF-κB, and ROS. Notably, several studies reported enhanced therapeutic outcomes when cannabinoids were combined with standard chemotherapy agents such as cisplatin, docetaxel, and bicalutamide.

These findings are consistent with earlier reviews that have recognized the anti-tumor potential of cannabinoids across various cancer types. For example, Velasco et al. highlighted how cannabinoids trigger apoptosis and autophagy in glioma cells through CB receptor-dependent and independent mechanisms [53]. Similar anti-cancer effects have been documented in breast, lung, and pancreatic cancer models. However, prostate cancer presents a unique context due to its dependency on androgen receptor (AR) signaling. Our review found that CBD and related cannabinoids could disrupt AR signaling indirectly by modulating downstream survival pathways, supporting observations by Orellana-Serradell et al. [47] and De Petrocellis et al. [42], who documented AR downregulation and apoptotic activation in prostate cancer models following cannabinoid treatment.

When compared to the broader systematic review by Belgers et al., which synthesized evidence on cannabinoids improving health-related quality of life (QoL) across neurological and oncological populations [36], our findings reveal a more focused gap. Belgers et al. concluded that cannabinoids may offer modest improvements in QoL, but few included studies were specific to prostate cancer. This underscores the unique contribution of our review in highlighting the lack of prostate cancer-specific clinical trials evaluating symptom management and QoL outcomes, despite the extensive preclinical support for cannabinoids in this domain.

Furthermore, while cannabinoids are often perceived as palliative agents, several studies included in this review suggest that they may also function as disease-modifying agents. For instance, Mahmoud et al. [40] and Motadi et al. [41] reported tumor volume reduction and apoptosis induction in both androgen-sensitive and hormone-refractory models, positioning cannabinoids as possible candidates for addressing resistance to androgen deprivation therapy (ADT). This aligns with recent pharmacological interest in non-hormonal pathways to overcome treatment resistance in castration-resistant prostate cancer (CRPC).

However, despite this promising preclinical evidence, clinical translation remains limited. The only included Phase I trial (Myint et al.) evaluating Epidiolex (CBD oil) in biochemically recurrent prostate cancer demonstrated good tolerability and disease stabilization in 88 % of patients, yet did not show statistically significant improvements in QoL metrics [48]. This finding is echoed by Grimison et al., who reported patient preference for a THC:CBD combination during chemotherapy, but only modest improvements in nausea and vomiting [52]. These outcomes suggest that while cannabinoids may offer symptomatic benefits, their full therapeutic potential remains underexplored due to heterogeneity in dosing, formulation, and outcome measurement.

Additionally, several studies in this review e.g., Shoeib et al. [46], Häggström et al. [49] examined the signaling roles of both canonical cannabinoid receptors (CB1 and CB2) and non-canonical receptors such as GPR55, as well as the formation of receptor heteromers like CB1–D2 complexes implicated in cancer progression. This emerging evidence expands the pharmacological landscape of cannabinoid action and offers novel avenues for drug development [54,55]. However, without standardized receptor profiling and binding affinity studies in clinical populations, the translational potential of these mechanistic findings remains theoretical.

Implications for research and policy

The findings of this scoping review underscore the need for well-designed, adequately powered clinical trials that evaluate both the therapeutic and supportive care potential of cannabinoids in prostate cancer. Future research should prioritize patient-centered outcomes including pain, function, quality of life, and psychological wellbeing in addition to tumor progression. Standardization of cannabinoid formulations, dosing regimens, and delivery methods is critical to ensuring reproducibility and comparability across studies. Policymakers should also consider the regulatory frameworks necessary to support cannabinoid-based clinical trials and eventual integration into prostate cancer care, especially for symptom management in advanced disease stages.

Translational gap and clinical challenges

Although preclinical studies included in this review highlight the anti-tumor potential of cannabinoids, particularly CBD through mechanisms such as induction of apoptosis, inhibition of cell proliferation, and tumor microenvironment modulation, their clinical translation remains limited. This translational gap is underscored by the small number of early-phase trials, lack of consistent patient-centered outcomes, and inconclusive evidence on symptom relief and quality of life in prostate cancer patients.

Several factors contribute to this gap. First, formulation variability poses a significant challenge. Cannabinoid products differ widely in their composition (e.g., CBD:THC ratios), purity, source (plant-derived vs. synthetic), and mode of administration, making it difficult to compare outcomes across studies or develop standardized dosing protocols. Second, regulatory barriers remain a major obstacle. In many jurisdictions, cannabinoids are classified as controlled substances, resulting in complex approval processes, funding constraints, and ethical concerns that hinder the design and implementation of large-scale clinical trials.

Additionally, inconsistent outcome measures across studies, particularly the lack of standardized tools for assessing pain, functional status, or QoL limit the ability to synthesize data and draw meaningful conclusions. Many studies rely on surrogate markers such as tumor volume or

biomarker expression, which do not fully capture patient experiences or treatment benefit in real-world settings.

To address these limitations, future research should prioritize standardized protocols for cannabinoid formulation and dosing, align outcome measures with established clinical endpoints, and consider regulatory pathways that facilitate ethically sound, multi-site trials. Collaboration among academic institutions, regulatory bodies, and industry stakeholders will be essential to advancing this field. By shifting focus from mechanistic promise to clinical applicability, future studies can better assess whether cannabinoids offer meaningful therapeutic value for prostate cancer patients beyond tumor biology to include improvements in quality of life and symptom management.

Strengths and limitations

A key strength of this scoping review lies in its use of a rigorous and transparent methodological approach, guided by the Arksey and O'Malley framework and the PRISMA-ScR reporting guidelines. The review involved a comprehensive search across multiple databases, systematic screening by multiple reviewers, and detailed data charting. By including both preclinical and clinical studies, this review provides a broad overview of the current state of evidence on cannabinoids in the context of prostate cancer, with particular attention to therapeutic mechanisms and reported outcomes related to symptom management.

However, several limitations should be acknowledged. First, while scoping reviews do not typically include formal assessments of methodological quality or risk of bias, the absence of such appraisal limits our ability to draw conclusions about the robustness or reliability of individual study findings. Second, the predominance of preclinical evidence and the scarcity of high-quality clinical studies restrict the direct applicability of findings to clinical practice. Third, the variability in study designs, cannabinoid formulations, and outcome measures across included studies further complicates synthesis and interpretation.

Despite these limitations, this review highlights important knowledge gaps and provides a foundation for future research to explore the clinical utility of cannabinoids in prostate cancer more rigorously.

Conclusion

Current evidence on the use of cannabinoids in prostate cancer is largely based on preclinical studies, which suggest potential therapeutic effects, particularly tumor growth inhibition, induction of apoptosis, and possible enhancement of chemotherapy efficacy. CBD, in particular, has shown promise *in vitro* and animal models. However, clinical evidence remains limited, with few trials assessing cannabinoids in human subjects, and little to no conclusive data on their effectiveness in managing pain or improving quality of life in prostate cancer patients.

Given the growing interest in cannabinoid-based therapies, future research must prioritize well-designed clinical trials that assess not only oncologic outcomes but also patient-centered measures such as pain relief, functional improvement, and health-related quality of life. Until such data are available, cannabinoids should be regarded as experimental adjuncts with unproven clinical benefits in the context of prostate cancer care.

Declaration

Consent for publication

All authors have provided consent for publication

Availability of data and materials

All data and materials are presented as references

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Declaration of competing interest

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

CRediT authorship contribution statement

Shiksha Gallow: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. **Ashley Ross:** Supervision. **Brenda Mkhize:** Supervision, Writing – review & editing. **Pavitra Pillay:** Supervision, Writing – review & editing. **Katia Tonkin:** Writing – review & editing.

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Supplementary materials

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