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Review

Cannabinoids as Potential Therapeutic Agents in the Treatment of Pancreatic Cancer

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Abstract

Pancreatic cancer is one of the most aggressive and lethal malignancies, with limited therapeutic options and low survival rates, primarily due to late-stage diagnosis and resistance to conventional therapies. Recently, cannabinoids have gained attention for their analgesic and antiemetic properties in cancer symptom management, as well as for their potential anticancer effects. This review explores the mechanisms by which cannabinoids may impact pancreatic cancer progression, focusing on their molecular interactions and therapeutic potential.

Keywords: Pancreatic cancer, cannabinoids, cannabidiol, THC, anti-cancer effects, endocannabinoid system, apoptosis, clinical trials.

Introduction

A comprehensive literature search was conducted in PubMed, Embase, and the Cochrane Library to identify studies published from 2000 to 2024 that examined the effects of cannabinoids on pancreatic cancer. Studies involving human subjects with pancreatic cancer and preclinical *in vitro* and *in vivo* research were included. Clinical and preclinical studies focusing solely on symptom relief were excluded. The search identified 46 studies, with 19 meeting the inclusion criteria (14 preclinical and 5 clinical). Preclinical studies revealed that cannabinoids, primarily Δ9- tetrahydrocannabinol (THC) and cannabidiol (CBD), exert anti-tumor effects through mechanisms such as apoptosis induction, cell cycle arrest, inhibition of angiogenesis, immune modulation, and reduction of oxidative stress. Most clinical studies emphasize cannabinoids' role in symptom management rather than direct anti-cancer effects. A notable exception is a case series suggesting improved survival in pancreatic

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cancer patients using CBD, though its preliminary findings warrant further investigation.

Pancreatic cancer remains one of the most aggressive and lethal malignancies, with limited therapeutic options and a low survival rate, mainly due to its late-stage diagnosis and resistance to conventional treatments (1, 2). Recently, cannabinoids have garnered attention not only for their analgesic and antiemetic properties in cancer-related symptoms and cancer-related pain management but also for their potential anticancer effects (3, 4). In particular, cannabinoids have shown promise in modulating various cellular processes implicated in pancreatic cancer cells' proliferation, migration, and survival. This emerging area of research suggests that cannabinoids may have a unique role in cancer progression, with effects that extend beyond mere symptom management (5-12).

Cannabinoids, primarily derived from the Cannabis sativa plant, exert their effects through binding to specific cannabinoid receptors (CB-R1 and CB-R2) and other non-cannabinoid receptors and ion channels. The two primary receptors, CB-R1 and CB-R2, are G-protein-coupled receptors expressed predominantly in the central nervous system (CB-R1) and immune cells (CB-R2). However, both receptors are expressed to varying extents in several types of cancer cells, including pancreatic cancer. CB-R1 mediate the psychoactive effects of cannabinoids, while CB-R2 are associated with immune response modulation, which can be crucial in the tumor microenvironment. Additionally, cannabinoid compounds can activate transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs), contributing to a broad spectrum of effects on cellular pathways.

One of the primary ways cannabinoids are thought to influence pancreatic cancer progression is through their effect on apoptosis or programmed cell death. THC, the principal psychoactive cannabinoid, and CBD, a non-psychoactive counterpart, have both demonstrated pro-apoptotic properties in pancreatic cancer cells by inducing apoptosis through pathways involving caspase activation and down-regulation of anti-apoptotic proteins like B-cell lymphoma 2 (Bcl-2). This process is mediated through the activation of CB-R2, suggesting that CB-R2 agonists could serve as a target for inducing apoptosis in cancer cells while sparing healthy tissue.

Cannabinoids also inhibit pancreatic tumor cell proliferation by disrupting the cell cycle. Studies have shown that THC and CBD can induce cell cycle arrest at the G0/G1 phase, limiting cancer cell division and tumor growth. The mechanism involves the modulation of crucial cell cycle regulators, including the down-regulation of cyclins and cyclin-dependent kinases (CDKs), essential for cell cycle progression. This effect is likely mediated through CB-R2 activation, which has shown promise in reducing tumor cell viability without significantly impacting healthy pancreatic cells.

Furthermore, cannabinoids may also affect tumor angiogenesis, the process by which tumors develop new blood vessels to supply nutrients and sustain growth. By activating CB-R2, cannabinoids have been found to reduce the production of vascular endothelial growth factor (VEGF), a potent angiogenic factor, and other pro-angiogenic cytokines within the tumor microenvironment. This inhibition disrupts the vascular network necessary for tumor growth, limiting the expansion and metastatic potential of pancreatic cancer.

The tumor microenvironment (TME) of pancreatic cancer is particularly dense and immunosuppressive, often impeding immune cell infiltration and reducing the efficacy of conventional therapies. Cannabinoids may play an immunomodulatory role in altering the TME, enhancing the immune response against the tumor. CB-R2 activation by cannabinoids can alter cytokine release, promoting an anti-tumor immune response. Additionally, cannabinoids have been found to inhibit the function of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), which are immunosuppressive cells commonly found within the pancreatic TME, potentially enhancing anti-tumor immunity.

In addition to receptor-mediated effects, cannabinoids also influence oxidative stress and inflammation, which are significant contributors to pancreatic cancer

progression. CBD, in particular, has antioxidant properties that can reduce reactive oxygen species (ROS) levels within the tumor, creating an environment less conducive to cancer cell survival. This reduction in ROS, along with CBD's anti-inflammatory effects mediated through the inhibition of nuclear factor-kappa B (NF-κB), contributes to reduced cancer cell proliferation and migration, further hindering tumor progression.

Despite these promising findings, research on cannabinoids' anticancer effects in pancreatic cancer remains in the early stage, with many studies conducted *in vitro* or in animal models. Translating these effects into clinical practice requires a deeper understanding of the complex interactions between cannabinoids, cancer cell receptors, and the surrounding TME. Nonetheless, cannabinoids hold potential as adjuvant therapies that could enhance current treatments, modulate the tumor microenvironment, and directly affect cancer cell survival through multiple molecular pathways.

This review aims to present the current knowledge regarding the mechanisms of interaction between cannabis and pancreatic cancer, considering *in vitro* and *in vivo* studies on both animals and humans.

Methods

We conducted a systematic search in PubMed, Embase, and the Cochrane Library for studies published between 2000 and 2024 examining the effects of cannabinoids on pancreatic cancer. Search terms included 'pancreatic cancer', 'cannabinoids', 'THC', 'CBD', 'endocannabinoid system', and 'cannabis'. Boolean operators (AND, OR) were used to combine terms. The last search was conducted on June 1st, 2024. We also search clinicaltrial.gov and EUDRACT for clinical trials in humans. We included randomized controlled trials, preclinical studies, cohort studies and case reports that evaluated the effects of cannabinoids on pancreatic cancer. More specifically, we included studies a) involving human subjects with pancreatic cancer, regardless of age or stage of the disease; b) evaluating the effects of any form of cannabinoids, including THC, CBD, or whole-plant extracts; c) comparing cannabinoids with standard treatments or placebos, and d) reporting outcomes such as tumor regression, survival rates, biomolecular response. We excluded clinical and preclinical studies that reported pain and pain-related symptoms as outcomes. Only peer-reviewed articles published in English were included.

Results

In this review, a comprehensive literature search yielded 46 studies from database searches and three additional records from other sources. After removing duplicates, another 42 studies remained for title and abstract screening. During this screening phase, 16 studies were excluded for not meeting the inclusion criteria. The full texts of 26 studies were then assessed for eligibility, resulting in the exclusion of 5 studies due to, non-relevant outcomes, or lack of preclinical or clinical data. Consequently, 19 studies (14 preclinical and 5 clinical) were included in the qualitative synthesis. The PRISMA flow diagram presents a detailed summary of the study selection process (Figure 1).

Discussion

In preclinical and *in vitro* studies, cannabinoids have shown promising potential as therapeutic agents in pancreatic cancer by exhibiting anti-tumorigenic effects, including inhibition of cancer cell proliferation, induction of apoptosis, and reduction in tumor growth in animal models. These effects are primarily mediated through the endocannabinoid system, targeting CB-R1 and CB-R2, as well as influencing pathways like mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), and NF-κB. However, clinical evidence remains limited, with only a few small case reports and early-phase clinical trials currently exploring the safety and efficacy of cannabinoids in pancreatic cancer patients. Initial findings from these case reports indicate potential symptom relief and some degree of tumor response, but

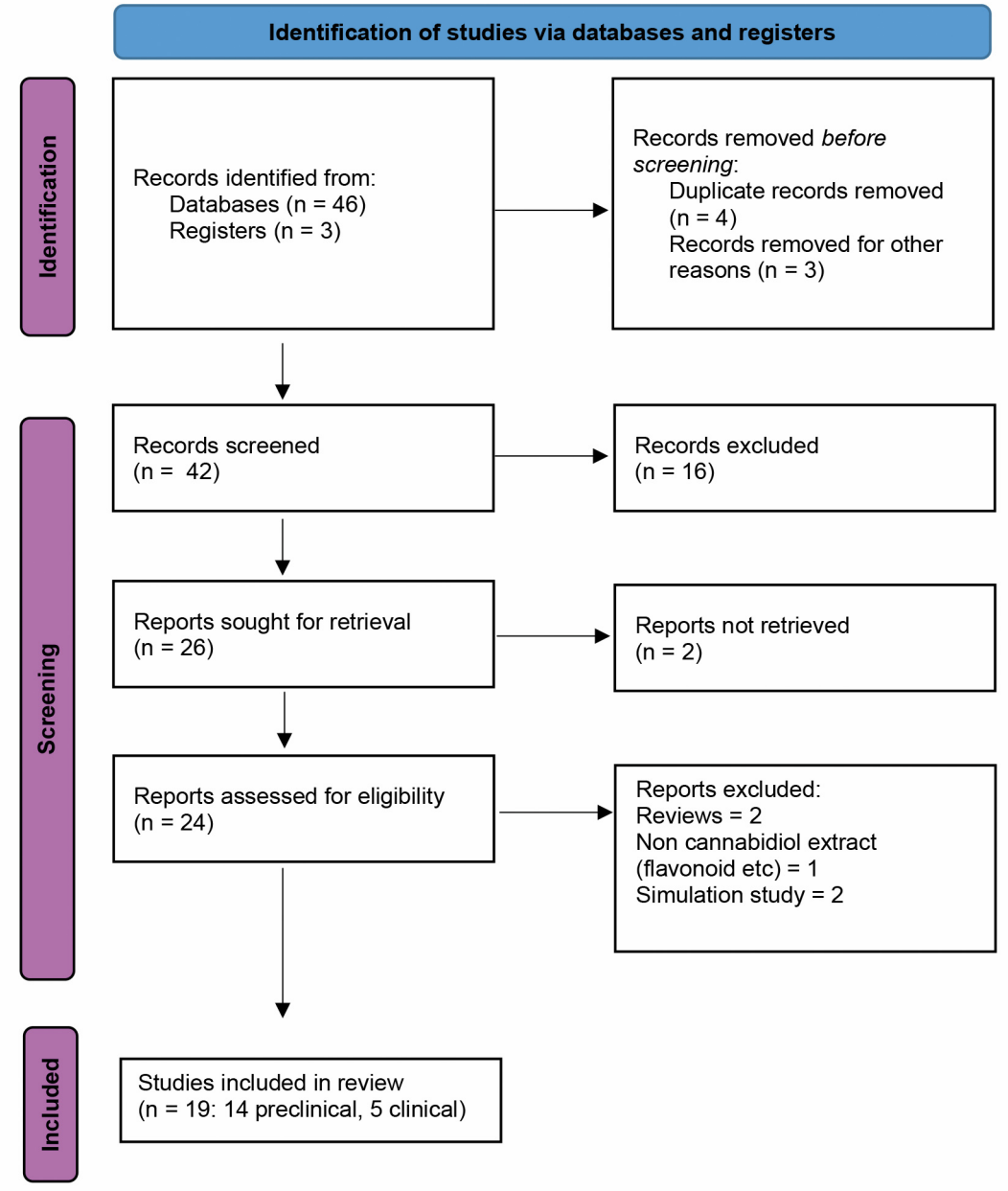

Figure 1. *PRISMA flow-chart.*

larger and more robust clinical trials are necessary to determine therapeutic efficacy, optimal dosing, and potential adverse effects in this patient population.

In vitro and in vivo studies. Shreds of preclinical *in vitro* and *in vivo* evidence highlighted that cannabinoids exert their antitumor effects on pancreatic cancer by regulating different molecular pathways (Table I). The first report was described by Fogli *et al.,* which demonstrated that cannabinoid derivatives provoked the cell death of MIA PaCa-2 cells by acting on the Janus kinase (JAK)/ Signal transducer and activator of transcription 3 (STAT) and MAPK signaling network independently from the CB-R1 (13). Subsequently,

a fascinating study demonstrated that THC induced the apoptosis of MIA PaCa-2 cells and Panc2 cells through a mechanism mediated by the CB-R2 and by the endoplasmic reticulum stress-related genes mammary expression of activating transcription factor 4 (ATF-4) and tribbles homolog 3 (TRB3) a proapoptotic protein responsible for the apoptosis induced by endoplasmic reticulum (ER) stress. Similarly, THC and the synthetic cannabinoid receptor agonists WIN55212,2 were also able to reduce the growth of tumor cells in a mouse model of pancreatic cancer (14). Donadelli *et al.*, demonstrated that the combined treatment of gemcitabine (GEM) and CB-R agonists in pancreatic cancer resulted in antiproliferative effects through a reactive oxygen species (ROS)-mediated mechanism (15). Interesting findings were reported by Dando *et al.*, which showed that cannabinoids were able to inhibit the metabolism of pancreatic cancer cells, resulting in autophagy induction and reduced proliferation of PANC1 cells through the activation of 5' AMP-activated protein kinase (AMPK) (16). Preclinical results highlighted by Yasmin-Karim *et al.* showed that the combination of cannabinoids with radiotherapy (RT) or smart biomaterials enhances the treatment efficacy in lung and pancreatic cancer. Specifically, mice with pancreatic cancer treated with CBD showed not only reduced tumor but also prolonged survival rate concerning that observed in mice treated with vehicle (17). In particular, CBD and RT enhanced the apoptosis of cancer cells and reduced tumor growth by increasing the levels of ROS. Subsequently, Ferro *et al.* (18), demonstrated that a combination of CBD and GEM inhibited tumor pancreatic cancer cell proliferation and growth, by acting on the MAPK signaling pathway. The anticancer effect of CBD on pancreatic cancer cells was also demonstrated by Luongo *et al.* (19). Authors showed that CBD and Oxygen-zone (O2/O3) attenuated the migration, induced cytotoxicity, and enhanced death of PANC-1 and MiaPaCa-2 cells by acting on NF-kB, rat sarcoma (Ras), and MAPK signaling pathways. Aizikovich tested ALAM027 and ALAM108 derivatives of tetrahydrocanna-binolic acid (THCA) in PANC1 and AsPC-1 cancer cells. These studies demonstrated that ALAM108 and ALAM027 inhibited the growth of pancreatic cancer cells through unknown mechanisms (9). Yang *et al.* showed that CBD and/or THC inhibited pancreatic cancer cell growth *in vitro* and *in vivo* through the Human p21-activated kinase (PAK1)-dependent pathway, by suppressing the Kirsten rat sarcoma virus (KRas)-activated pathway (20). An interesting study was reported by Emhemmed *et al.*, which demonstrated that extract from Cannabis Sativa induced the accumulation of intracellular superoxide ions, affected the mitochondrial membrane potential, induced G1 cell cycle arrest, and promoted apoptosis in Human Pancreatic 3D Cancer Models (21). Recently Zeppa *et al.*, investigated the effects of cannabigerol (CBG) on PANC1 and MIAPaCa-2 cells (22). They demonstrated that CBG inhibited the growth of PANC1 and MIAPaCa-2 cells. Similarly, CBG induced autophagy by inhibiting Akt/mTOR and EGFR pathways. Moreover, CBG interfered with the EGFR-RAS pathways. Finally, an *in vivo* study was conducted on a human pancreatic ductal adenocarcinoma (PDAC) xenograft nude mice model treated with a cannabinoid solution (THC: CBD at 1:6) at a dose of 1, 5, and 10 mg/kg body weight compared to the negative control (sesame oil) and positive control (5-fluorouracil). This study showed that cannabinoids (THC: CBD) (1:6) could inhibit the proliferation and induce apoptosis in human PDAC xenograft nude mice models probably by interfering with the intrinsic apoptosis pathway (23). In 2022 research focused on the potential mechanisms through which cannabinoids may inhibit cancer cell growth and promote apoptosis (programmed cell death) in these cancer types (24). Their findings indicated that selective activation of cannabinoid receptors resulted in reduced proliferation and increased apoptosis in both pancreatic and breast cancer cells, suggesting that certain cannabinoid agonists could be promising agents in cancer therapy.

Taken together, these studies suggest that cannabinoids play anticancer roles in pancreatic cancer, and should be further studied for use as therapeutic agents in the treatment of pancreatic cancer

Cannabinoids in patients with pancreatic cancer: an overview of clinical studies. Only two studies have published results on

Table I. *Antitumor effect of cannabinoids in pancreatic cancer: an update from in vitro and in vivo preclinical studies.*

Model	Substance	Effects	Mechanism	Reference
MIA PaCa-2 cells	WIN-55,212-2, CB_1/CB_2 receptor agonist; ACEA, CB1 receptor-set; JWH-015; AM251 and SR141716A, AM630	Cell growth inhibition; induction of apoptosis and cytotoxicity network	CB1-R independent mechanism; JAK/STAT and MAPK signaling	12
MIA PaCa-2 cells; Panc1 cells Orthotropic model generated from MiaPaCa-2 cells in immunodeficient mice	THC THC (15 mg/kg/day/ in mice)	Induction of apoptosis, increased ceramide levels, up-regulation of the stress protein p8 mRNA levels.	CB2-R dependent mechanism and *de novo* synthesized ceramide-dependent up-regulation of p8 and ATF-4 and TRB3 genes	13
PaCa44, PaCa3, Panc1, CFPAC1, T3M4, and MiaPaCa2 Cells,	GW, ACPA, and SR1 in combination with GEM	Inhibition of cell growth and proliferation; inhibition of apoptosis provoked by GEM	Gemcitabine stimulated the mRNAs of both CB1 and CB2 *via* an NF-κB-mediated mechanism. Increase of ROS levels	14
Panc1 cells	ACPA, GW	Inhibition of metabolism, induction of autophagy; inhibition of cell proliferation	Increase of AMPK phosphorylation; Increase of ROS.	15
Panc-02 cells heterotopic model generated from Panc-02 cells in immunodeficient mice	CBD with RT or smart biomaterials	Increased tumor cell death, inhibition of tumor growth; and DNA damage induced by radiation. Prolonged survival rate in mice	Increase of ROS	16
PDAC cells	CBD and GEM	Inhibition of cell proliferation and growth	Activation of MAPK	17
Panc1, MIA PaCa-2 cells	CBD and O2/O3	Inhibition of cell viability and migration; induction of cytotoxicity	Inhibition of Ras pathways and MAPK signaling; Reduction of the expression of different genes of the PI3K pathway; reduced expression of NF-kB-related genes	18
Panc1 cells and AsPC-1 cells		Inhibition of tumor growth; induction of cytotoxicity	Unknown	19
PANC1, CFPAC1, Capan2, SW1990, HPAF11, and MiaPaCa2 Cells Murine PC cells TB33117 were subcutaneously injected into flanks of 6-week old, male C57BL6 of PAK1 wild type (WT) and knockout (KO) mice.	CBD, THC CBD, THC (250 µl, CBD to THC at 1:1)	Inhibition of cell proliferation	Inhibition of PAK1-pathway, and suppression of the *Kras* activated pathway.	9

Table I. *Continued*

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Model	Substance	Effects	Mechanism	Reference
AsPC-1, ATCC® CRL-1682 Cells	CBD, CBDA, Δ^9-THC, Δ^9-THCA, Δ^8-THC, CBL, CBN, CBC, CBCA, CBDV, CBDVA, CBG, CBGA and THCV	Induction of apoptosis, accumulation of intracellular superoxide ions, changing in mitochondrial membrane potential	Cycle arrest in pancreatic cancer cells in the G0/G1 phase	20
MIA PaCa-2 Cells; Panc1 Cells	CBG	Cell growth inhibition	*Via* CB2-R	21
Heterotopic model generated from Capan–2, HBT–80 cells in immuno-deficient mice				22
PANC-1	Different concentrations (1-20 μM, at 37˚C) of pure cannabidiol	Induction of cytotoxicity	CIK cells	23
PANC-1	L-759633 (a selective CB2 receptor agonist), ACPA (a selective CB1 receptor agonist) and ACEA (a selective CB1 receptor agonist)	Cell proliferation, clonogenicity, and apoptosis	Annexin V, Bcl-2-associated X protein (Bax) and Bcl-2	24

CB1-R: Cannabinoid receptor 1; CB2-R: cannabinoid receptor 2: CBD: cannabidiol; THC: delta-9-tetrahydrocannabinol; JAK: Janus kinase; STAT: signal transducer and activator of transcription 3; MAPK: mitogen-activated protein kinase; ATF-4: activating transcription factor 4; TRB3: tribbles homolog 3: ROS: reactive oxygen species; GEM: gemcitabine; AMPK: AMP-activated protein kinase; RT: radiotherapy; PAK1: human p21-activated kinase: KRas: Kirsten rat sarcoma virus; CBN: cannabinol; CBG: cannabigerol; CBC: cannabichromene; TRPV1: vanilloid transient receptor potential vanilloid type-1; ROS: reactive oxygen species; AKT: protein kinase B; mTOR: mechanistic target of rapamycin; ER: endoplasmic reticulum; PPARγ: peroxisome proliferator-activated receptor gamma; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; NF-□B: nuclear factor.

the use of cannabis as an anti-tumor agent, both focusing on glioblastoma rather than pancreatic cancer. Currently, there are no published studies investigating the anti-tumor effects of cannabis specifically in pancreatic cancer. Instead, the available literature primarily centers on the use of cannabis for managing symptoms associated with pancreatic cancer therapy and progression, such as anorexia, pain, and nausea.

In contrast to the preclinical studies mentioned above, few clinical studies on the antitumor effects of CBs have been conducted in patients with pancreatic cancer, probably due to scarce knowledge about the mechanism of action of cannabinoid receptors.

A notable exception in the literature is the case series by Nahler and Likar, which presents the only published data suggesting a potential survival benefit associated with cannabis use in patients with pancreatic cancer. In this series, the authors observed an improvement in survival outcomes, possibly linked to the use of CBD alongside conventional treatments (24). Although the study is limited by its small sample size and lacks a control group, it provides a preliminary indication that CBD might influence survival in pancreatic cancer patients. To date, an update on clinical trials on the effects of cannabinoids on the treatment of cancer pain is available at https://clinicaltrials.gov/ and is

Table II. *Cannabinoids in pancreatic cancer management: an update from clinical trials.*

ClinicalTrials.gov ID	Phase	Status	Conditions	Intervention/Treatment	Primary endpoint
NCT03245658	Phase 2	Withdrawn	Neoplasms Pancreatic; Cachexia; Cancer; Cannabis Appetite Loss; Palliative Medicine; Morbidity; Mortality	THC and CBD Mixture	Energy and protein intake [Time frame: The outcome measure will be assessed at day 0 and at week 4] Dietary history (% of estimated needs - NRS 2002)
NCT02423239	Phase1	Unknown status	Hepatocellular carcinoma; Pancreatic cancer	Dexanabinol; Sorafenib; Nabpaclitaxel Gemcitabine	MTD of dexanabinol given in combination with standard chemotherapies; Number of AEs in patients receiving dexanabinol monotherapy; Number of AEs in patients receiving dexanabinol in combination with standard chemotherapies
NCT03984214	Phase 2	Recruiting	Pancreatic cancer non-resectable; Chemotherapy-induced Nausea and vomiting; Pancreatic cancer metastatic	Dronabinol in oral dosage form; Placebo in oral dosage form	Standardized area under the curve of the European Organisation for Research and Treatment of EORTC QLQ-C30 symptom summary score over the on-treatment period.
NCT04155008	Phase 4	Not yet recruiting	Oncologic complications Quality of life nutrition poor	Dexamethasone; Dronabinol; Mirtazapine; Nutrition Intervention.	To assess the impact on quality of life for the oncology patients by using an algorithm for nutrition intervention and appetite stimulants through utilizing Functional Assessment of Cancer Therapy-General Population (FACT-GP).
Nahler G, Likar R: Clinical Oncology and Research, pp. 1-4, 2020	Case series (9 cases)	Published	Overall survival	CBD capsules or liquids (20% CBD) (from 100 mg to 400 mg daily)	Survival rate 11.8 months

THC: Tetrahydrocannabinol; CBD: cannabidiol; MTD: maximum tolerated dose; AEs: adverse events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ: quality of life questionnaire; FACT-GP: Functional Assessment of Cancer Therapy-General Population.

summarized in Table II. Altogether these few pieces of clinical evidence, highlight the potential role of cannabinoids in cancer pain management, although more high-quality clinical studies are necessary.

Conclusion

The exploration of cannabinoids as potential therapeutic agents in pancreatic cancer has yielded compelling preclinical evidence, though clinical data remain sparse. Cannabinoids, including THC and CBD, have shown potential as anticancer agents through their interaction with various cellular and molecular pathways. Preclinical studies highlight several mechanisms by which cannabinoids may exert anti-tumor effects, such as promoting apoptosis, inducing cell cycle arrest, inhibiting angiogenesis, modulating the immune environment, and reducing oxidative stress. These effects are primarily

mediated by CB-R1 and CB-R2, which are expressed in pancreatic cancer cells, as well as by non-cannabinoid receptors and signaling pathways like MAPK, NF-κB, and JAK/STAT.

Despite this promising preclinical data, there is a distinct lack of clinical studies focusing on the anti-tumor properties of cannabinoids in pancreatic cancer. For pancreatic cancer patients, existing literature on cannabinoids focuses mainly on symptom management – addressing issues such as pain, nausea, and anorexia associated with cancer therapy and disease progression – rather than on direct anti-cancer effects. This limited clinical focus underscores both the challenges in translating preclinical findings to patient settings and the urgent need for human studies specifically addressing cannabinoids' therapeutic potential in pancreatic cancer treatment.

The translation of cannabinoid research from preclinical to clinical settings faces several obstacles, including the need to standardize cannabinoid formulations, doses, and delivery methods. Furthermore, the complex interaction between cannabinoids and the tumor microenvironment requires a deeper understanding of how these compounds interact within the unique landscape of pancreatic cancer, which is often marked by a dense and immunosuppressive stroma. As the therapeutic landscape of pancreatic cancer evolves, cannabinoids could serve as valuable adjunct therapies, potentially improving patient responses to traditional treatments or helping to overcome drug resistance.

In conclusion, while the preclinical findings on cannabinoids' anti-cancer effects in pancreatic cancer are promising, the evidence from clinical studies remains limited and inconclusive. To advance cannabinoids from experimental to practical use in pancreatic cancer treatment, there is an urgent need for well-designed clinical trials that rigorously assess their efficacy, safety, and potential to enhance patient outcomes. Future research should prioritize exploring cannabinoids' direct anti-tumor effects in human subjects, including trials that assess combinations with existing chemotherapeutic agents or radiotherapy. Such studies are essential to determine whether cannabinoids can effectively and safely serve as a complementary therapeutic strategy, offering new hope in the treatment of one of the most challenging cancers.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Conceptualization: S. Bimonte, D. Nocerino, M. Crisci, A. Cuomo. Writing – original draft preparation: S. Bimonte. Writing – review and editing: S. Bimonte. All Authors have read and agreed to the published version of the manuscript.

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