

TRANSLATIONAL APPROACH OF CANNABINOIDS IN ONCOLOGY: IN VITRO, IN VIVO, AND CLINICAL APPLICABILITY

Ph.D. Thesis

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“The harder you work, the more luck you seem to have.”

-Thomas Jefferson

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1 LIST OF ABBREVIATIONS

2AG	2-Arachidonoylglycerol
5-HT	5-Hydroxytryptamine
AEA	Anandamide
AIDS	Acquired immunodeficiency syndrome
Akt	Protein kinase B (Akt)
ATF4	Activating Transcription Factor 4
A δ fibers	A-delta nerve fibers
BPI	Brief Pain Inventory
CACS	Cancer-associated anorexia-cachexia syndrome
cAMP	Cyclic adenosine monophosphate
CB1R	Cannabinoid Receptor 1
CB2R	Cannabinoid Receptor 2
CBC	Cannabichromene
CBD	Cannabidiol
CBG	Cannabigerol
CBR	Cannabinoid receptor
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CINV	Chemotherapy-induced Nausea and Vomiting
CIPN	Chemotherapy-induced Peripheral Neuropathy
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
DAGL	Diacylglycerol lipase
DASS-21	Depression, Anxiety and Stress Scale
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethylsulfoxide
DNAse	Deoxyribonuclease
DRG	Dorsal root ganglion
ECS	Endocannabinoid system
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EMT	Epithelial-mesenchymal transition
EO	Eosinophils
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Core Quality of Life Questionnaire
EQ-5D	EuroQol-5 Dimension
ERK	Extracellular signal-regulated kinase
ESAS	Edmonton Symptom Assessment Scale
FAAH	Fatty acid amide hydrolase
FACT	Functional Assessment of Cancer Therapy
FBS	Fetal bovine serum
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
G-CSF	Granulocyte Colony-stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-stimulating Factor

GMP	Good Manufacturing Practice
GPCR	G protein-coupled receptor
GPR55	G protein-coupled receptor 55
GR	Red blood cells
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
H&E	Hematoxylin-Eosin
HB	Hemoglobin
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
i.p.	Intraperitoneal
IC50	50% inhibitory concentration
ICAM-1	Intercellular adhesion molecule 1
ID1	Inhibitor of DNA binding 1
IFN- γ	Interferon-gamma
IL-10	Interleukin-10
IL-1 β	Interleukin-1 beta
IL-2	Interleukin-2
IL-6	Interleukin-6
LY	Lymphocytes
MAGL	Monoacylglycerol lipase
MAPK	Mitogen-activated protein kinase
MASCC	Multinational Association of Supportive Care in Cancer
MBASE	Excerpta Medica Database
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MD	Mean difference
MDSC	Myeloid-derived suppressor cells
MEDLINE	Medical Literature Analysis and Retrieval System Online
MMP-2	Matrix metalloproteinase-2
MONO	Monocytes
MRAW	Raw mean
MRI	Magnetic Resonance Imaging
mTOR	Mechanistic target of rapamycin
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NAPE-PLD	N-acyl-phosphatidylethanolamine phospholipase D
NaV1.7/8	Voltage-gated sodium channel subunits 1.7/1.8
NC1	Cannabixir® Medium Flowers extract ($\approx$ 15.6% Δ^9 -THC, <1% CBD)
NC2	Cannabixir® High THCA extract ($\approx$ 20% Δ^9 -tetrahydrocannabinolic acid)
NEU	Neutrophils
NF- κ B	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer cells
NK ₁	Neurokinin-1 receptor
NOS	Nitric oxide synthase

NRS	Numerical Rating Scale
ns	Non-significant
OD	Optical density
OR	Odds ratio
OS	Overall survival
OSI	Organosomatic index
p.o.	Per os (by mouth)
PAG	Periaqueductal gray
PBS	Phosphate-buffered saline
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PLGF	Placental growth factor
PPAR _s	Peroxisome proliferator-activated receptors
PPAR- γ	Peroxisome proliferator-activated receptor gamma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PSQI	Pittsburgh Sleep Quality Index
PTX	Paclitaxel
RCT	Randomised controlled trial
ROB2	Risk of Bias 2 tool
ROBINS-I	Risk of Bias in Non-randomized Interventional Studies
ROI	Regions of interest
ROS	Reactive oxygen species
RPMI 1640	Roswell Park Memorial Institute Medium
RTC	Reticulocytes
RVM	Rostral ventromedial medulla
SD	Standard deviation
SGR	Specific tumor growth rate
SMD	Standardised mean difference
SR141716A	Rimonabant
STAT3	Signal Transducer and Activator of Transcription 3
Th1	T helper 1
THC	Delta-9-tetrahydrocannabinol
THCV	Tetrahydrocannabivarin
TNF- α	Tumor necrosis factor- α
TR	Platelets (Thrombocytes)
TRB3	Tribbles Homolog 3
TRP	Transient receptor potential (ion) channels
TRPV1	Transient receptor potential vanilloid type 1
UN	United Nations
US	Ultrasound
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEM	Mean corpuscular volume
WBC	Leukocytes

2 STUDENT PROFILE

2.1 Vision and mission statement, specific goals

Vision: Enhancing the quality of life of individuals with cancer by promoting the safe, evidence-driven incorporation of cannabinoids into oncologic care. **Mission:** To connect preclinical and clinical research by exploring the therapeutic potential of cannabinoids and developing adjuvant strategies that enhance treatment tolerability and patient well-being. **Specific Goals:** To identify cannabinoids with optimal efficacy and safety, elucidate their mechanisms of action, and establish standardized, GMP-certified frameworks for their clinical use in symptom relief, toxicity reduction, and quality-of-life improvement in cancer care.



2.2 Scientometrics

Number of all publications:	17
Cumulative IF:	71.7
Av IF/publication:	4.2
Ranking (SCImago):	Q1:14, Q2:3
Number of publications related to the subject of the thesis:	6
Cumulative IF:	28.1
Av IF/publication:	4.68
Ranking (Sci Mago):	Q1:6
Number of citations on Google Scholar:	182
Number of citations on MTMT (independent):	25
H-index:	8

The detailed bibliography of the student can be found on pages 94-97.

2.3 Future plans

In the future, I aim to integrate my clinical work in medical oncology with academic teaching and translational research. As a clinician, I aspire to provide patient-centered cancer care while educating medical students and young professionals in evidence-based oncology. In parallel, I plan to continue exploring the mechanistic pathways underlying cannabinoid action and to validate my preclinical findings through well-designed clinical studies, bridging laboratory discoveries to real-world therapeutic applications.

3 SUMMARY OF THE THESIS

This thesis offers an integrated preclinical and translational assessment of several previously unexamined cannabinoids, including the synthetic compounds JWH-182, JWH-007, MAB-CHMINACA, and AM-694, as well as the natural extracts Cannabixir® Medium Flowers and Cannabixir® High THCA. The evaluation is situated within an oncologic framework, emphasizing their neuroprotective, analgesic, antitumor, and safety profiles.

The *in vitro* studies addressed two main objectives. The first investigated neuroprotection in primary dorsal root ganglion neurons exposed to paclitaxel, showing that cannabinoids significantly delayed axonal degeneration in a dose-dependent manner. The second evaluated cytotoxicity across breast (4T1), cervical (HeLa), and gastric (AGS) cancer cell lines, alongside fibroblasts (V79), revealing that some cannabinoids exerted selective tumor toxicity while others displayed mild protumoral effects, overall suggesting the presence of a potential therapeutic window.

The *in vivo* study conducted in a breast cancer model treated with paclitaxel, showed that cannabinoids alleviated neuropathic pain, improved hematologic and immune parameters, and modestly reduced metastases, while maintaining acceptable tolerability. Although not superior to paclitaxel's direct antitumor effect, their modulatory actions on pain, inflammation, and tumor microenvironment highlight adjuvant potential.

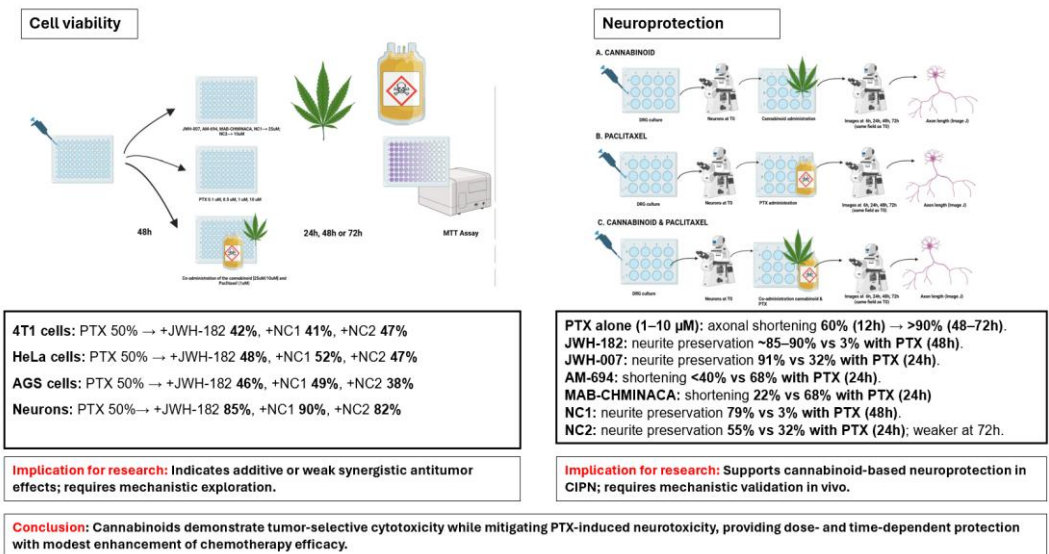
Complementary meta-analyses provided translational context. The first confirmed clinical benefits of cannabinoids for pain, nausea, and anxiety in cancer patients but emphasized variability by active molecule ratio and safety concerns, mainly with tetrahydrocannabinol-dominant formulations. The second component synthesized preclinical evidence of antitumor activity, revealing consistent efficacy, either alone or in with chemotherapy, in glioblastoma and breast cancer models, while demonstrating mixed or even protumoral effects in gastrointestinal cancers.

Overall, the findings support cannabinoids as multifunctional agents in oncology, capable of improving symptom control, enhancing chemotherapy tolerability, and possibly influencing tumor progression. Standardized, Good Manufacture Practice certified formulations and mechanistic clinical studies are essential to confirm these benefits and ensure safe, evidence-based integration into cancer care.

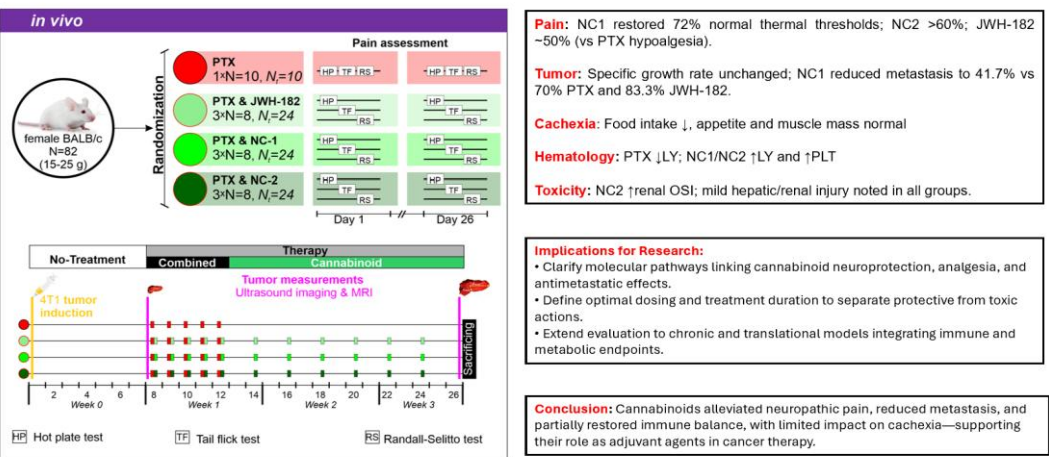
4 GRAPHICAL ABSTRACT

Study I – Evaluation of the neuroprotective effects for paclitaxel-induced neurotoxicity in primary dorsal root ganglion neuronal cultures

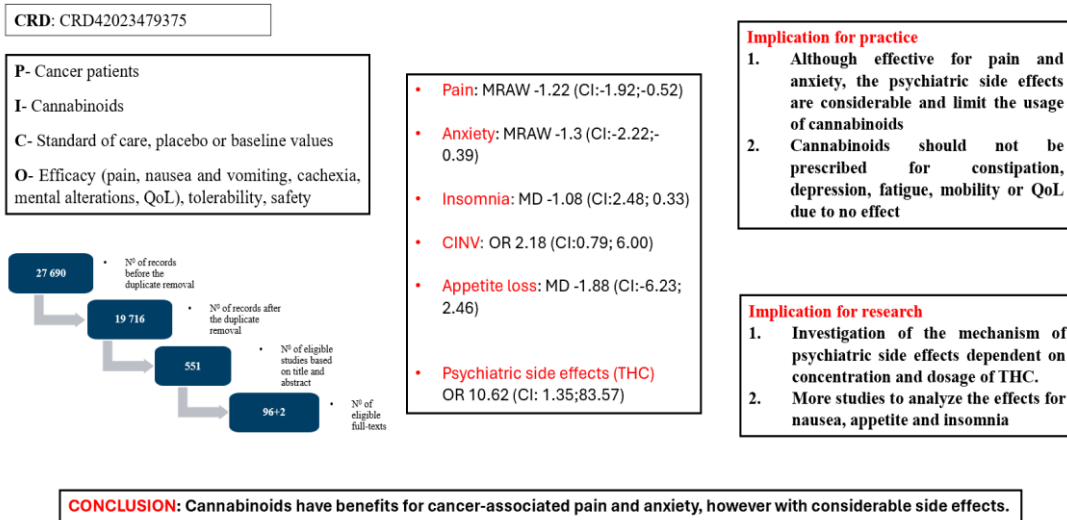
Study II – Evaluation of the cytotoxic profile of cannabinoids in malignant and non-malignant cell models



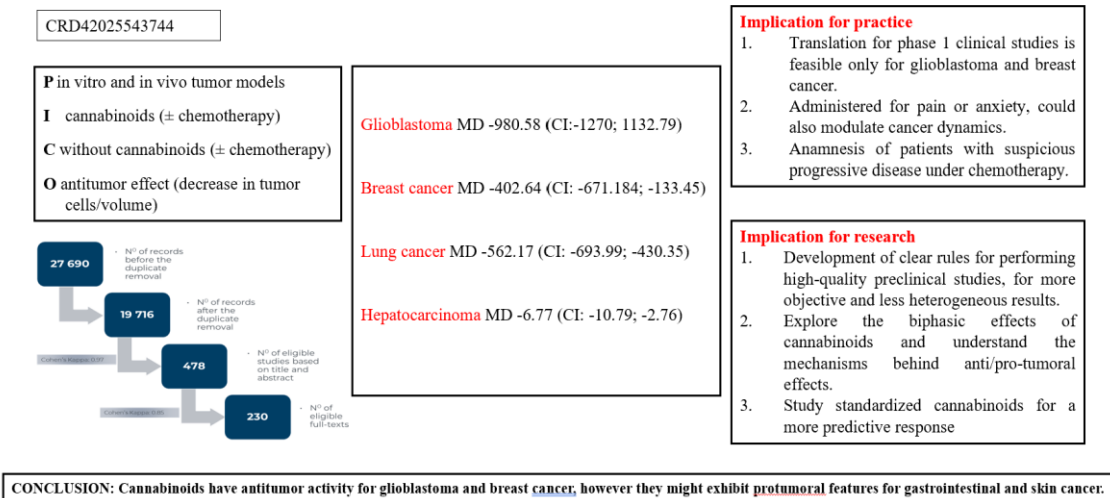
Study III – Evaluation of the efficacy, antitumor potential, and safety of cannabinoids in a murine model of breast cancer with CIPN



Study IV – Efficacy and safety of cannabinoids for cancer-related symptom management: a systematic review and meta-analysis of clinical studies



Study V: Evaluation of the efficacy, antitumor potential, and safety of cannabinoids in a murine model of breast cancer with CIPN



5 INTRODUCTION

5.1 Overview of the topic

Cannabinoids, are being reconsidered for medical use, particularly in oncology. There are more than 500 active molecules in the cannabinoid family, however the main are CBD and THC. Different parts of the Cannabis sativa plant served diverse therapeutic purposes: roots for inflammation, infections, and tumors, and leaves or inflorescences for epilepsy, glaucoma, insomnia, and chronic pain (1). Cannabinoids were widely used until their prohibition in 1937, which stopped medical research (2). Renewed scientific interest in the 21st century has been accompanied by challenges of terminology, poor standardization, and variable product composition, all of which hinder reproducibility (3). Recent evidence supports the use of cannabinoids in oncology for symptoms and adjuvant antitumor therapy. Clinically, they may alleviate pain, CINV, anorexia-cachexia, anxiety, and sleep, improving both quality of life and treatment adherence (4). Mechanistically, these effects involve modulation of the ECS, with CB1R and CB2R distributed across the central, peripheral, and immune system (5). Beyond symptom control, preclinical research highlights their antitumor properties, including inhibition of proliferation, modulation of invasion and metastasis, programmed cell death, or angiogenesis (6). Some cannabinoids also act as chemosensitizers. However, effects are highly dose- and context-dependent, with biphasic patterns, antiproliferative at higher concentrations, but sometimes neutral or protumoral at lower doses (6).

5.2 What is the topic

Despite expanding scientific interest and cancer patient's preference, progress with cannabinoid research and translation in clinical trials remains constrained by strict regulation, product heterogeneity, and limited high-quality evidence. Cannabis remains under Schedule I of the UN 1961 Convention, despite recognition of its medical potential in 2020 (7). Cannabinoids have emerged as multimodal agents, combining analgesic effects, with potential to improve appetite, sleep, and anxiety, thereby enhancing quality of life and treatment tolerance. Moreover, experimental data suggests they modulate tumor biology, positioning them as potential multi-purpose compounds. However, despite widespread off-label, regulatory agencies such as the FDA and EMA have not approved cannabis itself for oncologic indications, citing insufficient evidence and lack of

standardized formulations (8). This underscores the need for rigorous translational research to delineate efficacy, safety, and mechanisms of action.

5.3 What is the problem to solve?

Cancer incidence and treatment costs continue to rise globally, while symptom burden remains substantial (9). Despite therapeutic advances, pain, neuropathy, nausea, and cachexia remain inadequately managed, impairing both quality of life and treatment continuity (10). Traditional analgesics and antiemetics are often limited by tolerance or side effects, frequently necessitating dose reduction or discontinuation. Cannabinoids offer a multi-target strategy, addressing pain modulation, inflammation, appetite regulation, and sleep restoration through overlapping molecular pathways. Their dual potential, to alleviate symptoms and influence tumor biology, makes them a uniquely versatile class within supportive oncology. They require standardized, evidence-based approaches to dosing, receptor targeting, and patient selection, ensuring efficacy without compromising safety.

5.4 What would be the impact of our research results?

A standardized translational research framework is essential to clarify when and how cannabinoids can be used safely and effectively to manage cancer-associated symptoms, while also evaluating their interactions with conventional oncologic treatments. Evaluating GMP-certified formulations will ensure reproducible, clinically relevant outcomes, allowing accurate definition of dose-response relationships and therapeutic windows for symptom relief or adjuvant use. Because current evidence is heterogeneous and context-dependent, systematic integration of preclinical and clinical data is needed to identify consistent efficacy and safety patterns, optimize formulations, and establish evidence-based clinical guidelines. While preclinical studies reveal antitumor actions, responses vary, making it yet not suitable for human studies. This research utilizes immune-competent models, standardized dosing, and receptor-selective compounds to distinguish when cannabinoids act as therapeutic allies for symptom palliation or anticancer agents, versus when they pose potential risks. By exploring existing evidence through comparative and meta-analysis approaches, this work can define reliable benefit-risk patterns, supporting the safe and rational integration of cannabinoids into oncology for symptom management as well as tumor modulation.

6 OBJECTIVES

Study I. Evaluation of the neuroprotective effects for paclitaxel-induced neurotoxicity in primary dorsal root ganglion neuronal cultures. The objective was to investigate the neuroprotective potential of selected cannabinoids in an in vitro model of chemotherapy-induced neuronal injury. Specifically, the study evaluated the effects of several synthetic cannabinoids (JWH-182, JWH-007, MAB-CHMINACA, and AM-694) as well as phytocannabinoid-based formulations (Cannabixir® Medium dried flowers, NC1, and Cannabixir®THC Full Extract, NC2) in primary dorsal root ganglion (DRG) primary neuronal cultures exposed to PTX. The purpose of this work was to assess whether these compounds could prevent, attenuate, or delay axonal degeneration, a central pathological mechanism underlying CIPN. By examining changes in neuronal morphology and axonal integrity following PTX exposure, the study aimed to determine the extent to which cannabinoid treatment may protect sensory neurons from chemotherapy-induced damage and thereby contribute to the development of potential neuroprotective strategies for CIPN management.

Study II. Evaluation of the cytotoxic profile of cannabinoids in malignant and non-malignant cell models. The objective of Study II was to evaluate the antitumor activity and overall cytotoxic profile of selected cannabinoids across several malignant and non-malignant cell models. Specifically, the study investigated the effects of these compounds in three different cancer cell lines, representing distinct tumor types, breast cancer (4T1), cervical cancer (HeLa), and gastric cancer (AGS). In parallel, experiments were performed on non-malignant fibroblast cells (V79) to assess potential toxic effects on normal cellular populations. The purpose of this investigation was to determine whether the tested cannabinoids exert selective cytotoxic effects against tumor cells while sparing non-malignant cells, thereby helping to define a potential therapeutic selectivity window. By comparing cellular responses across malignant and non-malignant models, the study aimed to distinguish tumor-specific antiproliferative activity from nonspecific cytotoxicity, providing important insights into the safety profile, biological selectivity, and translational potential of cannabinoid-based compounds as anticancer agents.

Study III. Evaluation of the antalgic, antitumor activity, and safety of cannabinoids in a breast cancer with CIPN murine model. The primary objective of Study III was to evaluate the therapeutic efficacy and safety of selected cannabinoids in a PTX-treated

murine breast cancer model presenting CIPN. The study focused on the potential of cannabinoids to improve symptoms, particularly neuropathic pain, appetite loss, and cachexia, conditions that frequently affect patients undergoing chemotherapy. In addition, systemic safety and tolerability were assessed through hematological analyses and histopathological evaluation of major organs. The aim was to determine whether cannabinoids could improve chemotherapy tolerability and supportive care outcomes without interfering with the antitumor efficacy of PTX.

Study IV. Therapeutic impact of cannabinoids on cancer-related symptom burden: quantitative synthesis of clinical evidence. The objective of Study IV was to conduct a systematic review and meta-analysis of clinical studies evaluating the role of cannabinoids in the management of cancer-related symptoms. This analysis aimed to integrate available clinical evidence regarding the effects of cannabinoid-based therapies on commonly reported symptoms in oncology patients, including pain, nausea and vomiting from chemotherapy, appetite loss, insomnia, anxiety, and overall quality of life. In addition to symptomatic outcomes, the study also sought to quantitatively evaluate the balance between therapeutic benefits and potential adverse effects associated with cannabinoid use. A further objective was to explore patterns related to cannabinoid formulation, THC/CBD composition, and dosing, in order to identify factors that may influence treatment efficacy and safety.

Study V. Anticancer activity of cannabinoids across tumor models: quantitative synthesis of preclinical evidence. The objective was to perform a comprehensive synthesis of preclinical evidence regarding the antitumor effects of different cannabinoids across a broad range of *in vitro* and *in vivo* cancer models. This systematic review and meta-analysis aimed to integrate experimental findings from multiple tumor types in order to better understand the extent and consistency of cannabinoid-mediated anticancer activity. The analysis focused on identifying tumor-specific responses to cannabinoid exposure, as well as evaluating variability in underlying biological mechanisms, including pathways related to apoptosis, proliferation, angiogenesis, and metastasis. In addition, the study examined the interaction between cannabinoids and conventional anticancer therapies, particularly chemotherapy, to determine whether cannabinoids may enhance treatment efficacy through chemosensitizing effects or influence therapeutic outcomes through pharmacological interactions.

7 METHODS

7.1 Study I and II

7.1.1 Drugs and animals

Synthetic cannabinoids (JWH-007, JWH-182, MAB-CHMINACA, AM-694) were obtained from Cayman Chemical (Ann Arbor, MI, USA). The THC-rich extract Cannabixir® (NC2) was purchased from FYTA Company B.V. (Netherlands), and Cannabixir® Medium dried flowers (NC1) from Cansativa GmbH (Germany). All cannabinoids were prepared in 0.1% DMSO. PTX was sourced from Sigma-Aldrich (Saint Louis, USA). **Study I:** The source of the reagents was Sigma-Aldrich and ThermoFisher Scientific (Waltham, MA, USA). We used cell media RPMI 1640, penicillin based antibiotic solution, collagenase, Glutamax*, B27*, Neurobasal A*, Percoll, poly-D-lysine, laminin, trypsin inhibitor, DNase and trypsin-EDTA 0.25%. **Study II:** We chose the V79 (fibroblast), 4T1 (triple negative breast cancer), HeLa (cervical cancer), and AGS (gastric adenocarcinoma) cell lines (ATCC, Virginia, USA). The cells were grown in DMEM 5% medium, supplemented with FBS and antibiotic. Trypsin-EDTA (Sigma-Aldrich) was used for cell detachment. For the viability assays, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide was utilized, and resulting crystals were dissolved with DMSO, both sourced from Sigma-Aldrich.

Study I: Female Swiss Albino mice were housed individually in individually ventilated cages (IVCs) and maintained under controlled environmental conditions, including an ambient temperature of 20 ± 4 °C, relative humidity of $50 \pm 5\%$, and a 12-hour light-dark cycle (07:00-19:00). Animals had free access to standard food and water throughout the experiment. All experimental procedures were performed at the Grigore T. Popa University of Medicine and Pharmacy, Iași, Romania, within the Advanced Center for Research and Development in Experimental Medicine “Prof. Ostin C. Mungiu” (CEMEX). Anesthesia was induced using 2% isoflurane (ISOFLUTEK, KARIZOO, Spain) in accordance with previously described protocols (17). All experimental procedures complied with Directive 2010/63/EU on the protection of animals used for scientific purposes and were conducted only after obtaining approval from the University Ethics Committee (No. 342/7.09.2023) as well as authorization from the Veterinary and Food Safety Authority (DSVSA) (No. 70/26.01.2024).

7.1.2 Experimental assays

Study I. Primary DRG- derived neurons were used as a standard model to assess neurotoxicity, method adapted from Öztürk et al. (11). Mice were deeply anesthetized, euthanized, and the spinal column was exposed under sterile conditions. Dorsal root ganglia were identified under a stereomicroscope, detached, and kept in cold RPMI with antibiotics. Ganglia were enzymatically digested first with collagenase, then with trypsin-EDTA, followed by DNase and gentle triturated to obtain a single-cell suspension. Neurons were separated and isolated using a Percoll gradient, washed, and resuspended in prewarmed growth medium (Neurobasal A, supplemented with B27 and GlutaMax). In order to support neural adhesion, culture plates were treated for 24h with first poly-D-lysine, then with laminin. Neurons were seeded in the center of the wells and incubated at 37°C, 5% CO₂. Cell growth and neurite morphology were monitored at 24 and 48h using a microscope. Almost 900-1000 DRG-derived neurons were cultured in 96-well plates as described and further treated either with PTX (dosage range: 0.1-10 µM) or with cannabinoids 25 µM for synthetics and NC1 or 10 µM for NC2, administered either alone or mixed. For combination experiments, 1 µM PTX was used. MTT assay was performed to check cell viability, where absorbance was read at 570nm, using the EZ Read 400 plate reader (Tecan, Männedorf, Switzerland). Cell viability (calculated as percent relative to control) was calculated as (optical density of treated / untreated) × 100. The same experiment was repeated three times for accuracy, final results are expressed as mean ± SD. Neuroprotective efficacy was analyzed in three steps: determining the PTX dose that induces neurite shortening, evaluating each cannabinoid in monotherapy, and testing cannabinoid-PTX combinations on neuronal morphology. After neuronal adhesion and neurite extension, the same microscopic fields were photographed at baseline (T0) and at 6, 24, 48, and 72h using a CMOS camera. Neurons were then exposed either to cannabinoids (25 µM for synthetics and NC1, or 10 µM for NC2) or to 1 µM PTX, depending on the experimental phase. For combination treatments, mature neurons were incubated simultaneously with cannabinoids and 1 µM PTX, a dose previously shown to induce maximal neurite shortening while maintaining viability (204-206). Two controls were used: a negative control, cell media supplemented with 0.1% DMSO and a positive control, neurons treated with 1 µM PTX. Data were obtained from two independent experiments, each with four replicates, analyzing 5-8 fields per slide. Neurite lengths were

measured in ImageJ following Pemberton et al., using images calibrated with standardized reference scales (207). Images were processed (background removal, 8-bit conversion), and neurites were traced with the Neurite Tracer plugin. Measurements were taken at the same fields and on the same neurons at all time points (6, 24, 48, 72h), ensuring accuracy and consistency. **Study II:** Toxicity tests were performed on cell cultures using the 4T1, HeLa, AGS and V79 cell lines. For this analysis, 3000 cells were grown into plates and incubated for 24h at physiological environment. After incubation, cells were exposed to increasing concentrations of cannabinoids (5-25 μ M) or PTX (0.1-10 μ M). In the next phase, the cannabinoids with the strongest monotherapy antitumor effects were combined with PTX, using doses based on their IC₅₀ values, treatments lasting for 24h. Negative controls received culture medium with matching DMSO (0.1%), and positive controls received the PTX IC₅₀ dose for each cell line. Cell viability was measured with the MTT assay, where color intensity reflects metabolic activity. PBS-washed cells were incubated for 2h with 0.5% MTT, with absorbance read at 570 nm. Results were calculated and expressed as for study I.

7.1.3 Statistical analysis

Studies I and II. Cell viability was expressed as the percentage of viable cells relative to the untreated control group and reported as mean $\pm$ SD from three independent experiments performed under identical conditions. Statistical comparisons with the control group were conducted using one-way analysis of variance (ANOVA), with $p < 0.05$ considered statistically significant. **Study II.** Neuroprotective effects were evaluated by measuring neurite length at 6, 24, 48, and 72 hours and normalizing each value to the corresponding baseline measurement (T₀), yielding the percentage of axonal retraction. Normality of the data was evaluated with the Shapiro-Wilk test, while the homogeneity of variances was appreciated with Levene's test. Group-level differences were examined with two-way ANOVA, then pairwise t-tests adjusted using the Bonferroni method. When variance equality was not met, Welch (Satterthwaite) corrections were applied. Statistical significance was set as for study I.

7.2 Study III.

7.2.1 Drugs and animals

The compounds JWH-182, NC1, NC2, and PTX were included in this study, obtained as noted earlier. JWH-182 was dissolved in a vehicle composed of 0.9% saline

and Polysorbate 80 and administered intraperitoneally at 0.20 mL per 10 g body weight. NC1 plant material was milled, passed through a 125- μ m sieve, and suspended in a sodium carboxymethylcellulose-distilled water mixture for similar oral dosing. NC2 was prepared in a distilled water-Polysorbate 80 solution and delivered orally at the same volume. PTX was reconstituted in 0.9% serum solution, Cremophor, and ethanol and administered intraperitoneally at 0.10 mL per 10 g.

For this experiment, female BALB/c mice aged 8-12 weeks and weighing between 20 and 40 g were utilized. The animals were maintained under standardized housing conditions at the CEMEX facility, including controlled temperature and humidity, a 12-hour light-dark cycle, and ad libitum access to food and water, as previously described. All experimental procedures complied with European Union regulations governing the care and use of laboratory animals, and the study was conducted following prior ethical approval, as indicated previously for Study I.

7.2.2 Experimental assays

Healthy animals were randomized into four experimental groups. Baseline nociception was assessed prior to any intervention, after which tumors were induced orthotopically (day 1). After seven days, tumor establishment was confirmed, and baseline imaging was performed using ultrasonography (US) or magnetic resonance imaging (MRI) to document initial tumor size and anatomical characteristics. An induction dose of cannabinoids was administered on day 8, followed by combined cannabinoid and PTX treatment from days 9 to 12, corresponding to the chemotherapy phase of the protocol. From days 13 to 26, cannabinoids were administered every other day as maintenance treatment without PTX, allowing evaluation of their sustained effects. On the final experimental day (day 26), nociceptive assessments and imaging investigations were repeated to evaluate treatment-related changes in pain behavior and tumor progression. Animals were then euthanized according to ethical protocols, and blood samples and key organs were collected for hematological, biochemical, and histopathological analyses. Experimental animals were allocated into four different groups: JWH-182 (n=24), NC1 (n=24), NC2 (n=24), and a positive control group receiving PTX + saline (n=10). For analgesic evaluation, each cannabinoid group was further subdivided into three subgroups (n=8, each), corresponding to the three pain tests. Positive control animals underwent all pain tests on separate days. Tumor induction was

performed using 4T1 murine breast cancer cells, which were cultured in complete DMEM supplemented with 10% serum at 37°C in a humidified atmosphere containing 5% CO₂. Once cultures reached 80-90% confluence, cells were passaged at a 1:10 ratio using 1% trypsin. For inoculation, 4T1 cells were washed, trypsinized, centrifuged, and resuspended in fresh medium, then counted by Trypan Blue exclusion to assess viability and adjusted to a final concentration of 1×10^5 cells in 50 μ L DMEM. Mice were anesthetized with 2% isoflurane, and the cell suspension was injected orthotopically into the left sixth mammary fat pad under aseptic conditions. Tumor development was monitored clinically, and after seven days a firm, adherent tumor mass (~ 0.2 cm) was detectable by palpation and subsequently confirmed by ultrasonographic (US) examination. *Figure 1* highlights macroscopic aspects, while *figure 2* shows US features of the tumors.

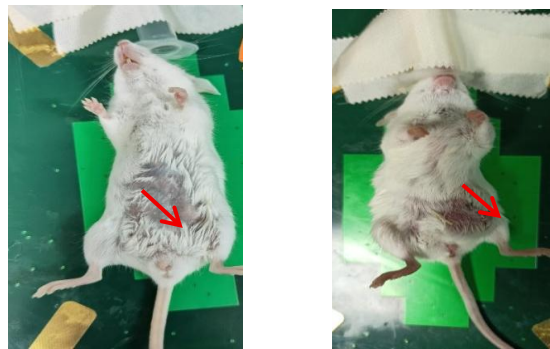


Figure 1. Tumor development at the 4T1 inoculation site (left-baseline, right-end of experiment). Tumors showed slow progressive growth, becoming ulcerated about three weeks after nodule appearance.

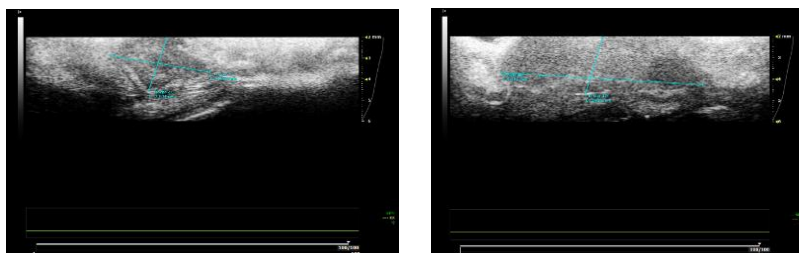


Figure 2. Ultrasound assessment of the 4T1 tumor: at detection (left), the lesion appears hypoechoic with internal heterogeneity and measures 4.5×2.6 mm. By the end of the experiment (right), the tumor shows marked enlargement 2.8×9.6 mm, while maintaining the same heterogeneous, hypoechoic pattern.

Cannabinoids were dosed according to their established effective doses. For the synthetic cannabinoid, the effective dose (ED) was previously determined by our group

as 2.627 mg/kg intraperitoneal (208). For NC1 we chose 75 mg/kg gavage (209) and NC2 12.72 mg/kg gavage. All mice were administered PTX at 2 mg/kg intraperitoneal. to induce neuropathic pain while maintaining its antitumor activity, a dosing regimen commonly cited as producing consistent CIPN models (208,210). Positive controls received only PTX and saline. Dosing schedule was the following: one induction dose of each cannabinoid on day 8, followed by four days of combined cannabinoid + PTX (days 9-12). From days 13-26, cannabinoids were given every other day without PTX, while controls received saline.

Animals were evaluated using nociceptive assays, performed at baseline and at the end of experiment, in order to determine functional changes. HotPlate test was chosen to evaluate supraspinal thermal hyperalgesia. Briefly, mice were placed on a surface heated at 52.5 ± 0.1 °C, and the latency to a nociceptive reaction (paw withdrawal, licking, or jumping) was recorded, with a maximum exposure time of 30s, to prevent tissue damage. Outcomes were expressed as the % Maximum Possible Effect (%MPE), calculated as % Inhibition = $[(Tx - T0) / (Tm - T0)] \times 100$, where T0 represents baseline latency, Tx the post-treatment latency, and Tm the cut-off value. For the assessment of the thermal spinal reflex response, we used Tail Flick, which consisted of 52 ± 0.1 °C heat stimulus applied to the tail for maximum 15s. Results were converted to %MPE using the same formula. Mechanical nociception was evaluated with the Randall-Selitto assay, in which a progressively increasing force was applied to the hind paw until withdrawal or vocalization occurred. Data were expressed as % Inhibition = $[(gx - g0) / (gm - g0)] \times 100$, where g0 is the initial mechanical threshold, gx is the post-administration threshold, and gm is the cut-off force set to avoid injury. Animals were categorized based on the change in responsiveness: normal nociceptive function (-30% to +30%), allodynia (-100% to -30%), and hypoalgesia (+30% to +100%). These predefined ranges support standardized comparison between pre- and post-treatment measurements and are consistent with established methodologies in pain research (26,27).

Tumor growth dynamics were monitored by mammary US and MRI at two key time points: before treatment (day 8) and at the end (day 26). VisualSonics Vevo® 2100 (Fujifilm Visual Sonics, Toronto, Canada) was used for US, including a 30 MHz MS400 probe, with standard high-resolution settings. Mice were anesthetized with isoflurane, and each scan lasted 3-5 minutes, recording tumor morphology and three-plane dimensions.

NanoScan® PET/MRI (Mediso, Budapest, Hungary), 1T system with a 35 mm coil was used for the MRI scans. Two sequences were collected: T1 GRE and T2 FSE, with a total scan time of about 15 minutes per mouse. InterView Fusion v.20 (Mediso, Budapest, Hungary) was used for image processing and to obtain accurate three-dimensional tumor measurements. The difference between tumor volumes at the beginning vs the end of experiment was analysed using the tumor specific growth rate (SGR), which analysed the pattern of growth rather than dimensions. Assuming exponential growth, SGR was calculated according to Mehrara et al. (2007) (19), by the formula $SGR [\%/day] = \ln(V_2 / V_1) / (t_2 - t_1)$, V_1 and V_2 are tumor volumes at times t_1 and t_2 . For the pretreatment period (days 1-8), an initial arbitrary volume of 1 mm³ was assigned at tumor induction, and V_2 was measured by US/MRI on day 8. For the treatment period (days 8-26), V_1 was the day 8 volume and V_2 the day 26 volume. This approach allowed a more precise evaluation of tumor growth patterns and treatment impact (20,21).

Cancer cachexia was assessed through weekly body-weight monitoring, daily appetite evaluation, and MRI-based measurement of psoas and paraspinal muscle area. Body weight was recorded weekly, while food intake was measured every two days by weighing premeasured pellets (20 g) and calculating consumption from the remaining amount. Muscle mass was quantified from MRI scans acquired as described previously (22). The key region of interest was arbitrarily set at the level of L4-L5 vertebrae, using a single axial slice, quantifying the cross-sectional area of the bilateral psoas and paraspinal muscles. Regions of interest (ROIs) were manually delineated using the same anatomical reference points between study animals.

On day 26, animals were sacrificed after anesthesia, and blood was for hematology evaluation. Full necropsies were performed, examining the general aspect, and all internal cavities. Key organs (tumor, brain, lungs, liver, kidneys, spleen) were measured and weighed, and organo-somatic indices (OSI) were calculated as organ weight relative to body weight. Blood was analyzed within 30 minutes using a HEMAVET 950 analyzer, quantifying: WBC, NEU, EO, BAZ, MONO, LY, RBC, HB, HT, MCV, MCH, MCHC, RTC, and PLT. For histopathology, liver and kidneys were fixed in 10% formalin and sectioned according to standard rodent tissue-processing guidelines (23). Organ section processing was performed with the Excelsior AS system, included in paraffin, cut at 4 µm with a CUT 5062 microtome, mounted and stained with H&E.

Scanning of the slides was done using an Aperio AT2 DX at 400×, and evaluated against controls for signs of toxicity. Metastasis was assessed by identifying tumor foci in organ parenchyma; presence of at least one lesion classified an organ as metastatic. Metastasis rate was calculated as the proportion of study animals per group showing at least one metastatic lesion.

7.2.3 Statistical analysis

Data distribution was examined with the Shapiro-Wilk test, and homogeneity of variances was verified prior to performing group comparisons. When assumptions for parametric testing were satisfied, analyses were carried out using ANOVA; if not, non-parametric alternatives such as the Kruskal-Wallis or Wilcoxon rank-sum tests were used. Post-hoc pairwise comparisons (paired t-tests or Wilcoxon tests) were adjusted using the Bonferroni method. Categorical variables were evaluated using Chi-square tests or Z-tests for proportion differences.

7.3 Study IV and Study V.

7.3.1 Protocol and registration

The meta-analysis was conducted following internationally recognized standards for systematic review methodology, strictly aligning with the PRISMA 2020 reporting framework (24) and the guidance provided in the Cochrane guidelines (25). The study's protocols were prospectively registered in the PROSPERO database (CRD42023479375 and CRD42025543744).

7.3.2 Literature search and eligibility

a) Literature search. Systematic searches were performed across three electronic databases, PubMed, Embase and Central Cochrane. The precise search dates and detailed search strategies are documented in the original publications (26).

b) Eligibility criteria. *Study IV:* This meta-analysis examined whether cannabinoids offer a safe and more effective option than standard care or placebo for alleviating cancer-related symptoms. Both interventional and observational studies were eligible, without restrictions on publication date or language. Studies were included if they enrolled (P) patients with cancer-of any age, sex, tumor type, or disease stage-who received (I) cannabinoid-based therapies in any formulation, dose, or route of administration for symptom management. Comparators (C) included standard care,

placebo, non-cannabinoid control groups, or pre-treatment baseline values. The (O) outcomes of interest were symptom relief (analgesia, CINV, sleep disturbances, anxiety, depression, appetite suppression, mobility, and quality of life) and safety profiles. Eligible (S) study designs comprised randomized controlled trials and observational studies. Grey literature (conference abstracts), case reports and series or review articles were excluded. **Study V:** We investigated whether cannabinoids have antitumor activity compared to controls in preclinical tumor models. This review included (P) in vitro tumor cell lines of human or animal origin and in vivo tumor-bearing animals, the (I) intervention comprised any natural or synthetic exogenous cannabinoid, regardless of formulation, dose, schedule, or administration route, while the (C) comparators were vehicle-treated or untreated controls and conventional chemotherapeutics. The (O) outcomes were in vitro cell viability following cannabinoid exposure and in vivo tumor volume quantified by calipers or imaging. We excluded human and non-cancer models, studies on endogenous cannabinoids, and those lacking proper controls or outcomes, as well as reviews, abstracts or protocols.

7.3.3 Selection and data extraction

a) Article collection

The article selection process was carried out using EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). Duplicate articles were excluded automatically or manually. Two independent reviewers checked the studies, first based on the content of the title and abstract, then by reading the full text. The interrater agreement was evaluated by calculating the Cohen's kappa index, whenever disagreements appeared, they were adjudicated by an extra reviewer.

b) Data extraction

Two different reviewers independently extracted data using a predefined Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet, resolving discrepancies by consensus. Corresponding authors were contacted when information was incomplete, and WebPlotDigitizer was used for extracting graphical data. **Study IV:** We collected general study characteristics (authors, year, country, design, duration, number of centers), patient information (eligibility criteria, demographics, cancer type and stage, prior treatments), and all cannabinoid-related details (type, concentration, administration route, daily dose, treatment duration). **Study V:** Extracted variables included bibliographic details, model

characteristics (species, strain, sex, tumor type/site, model type, sample size), and intervention/comparator data (cannabinoid type, receptor affinity, dose, schedule, route, formulation, co-treatments).

7.3.4 Quality assessment

Study IV: RCTs were assessed blindly by two reviewers using the ROB2 tool, and observational studies using ROBINS-I (27). GRADEpro platform was used to assess the overall certainty of the evidence (28). **Study V:** Two reviewers independently evaluated the animal studies using SYRCLE's risk-of-bias tool (29). For the *in vitro* experiments, risk of bias was assessed using an adapted method inspired by the one proposed by Vidhi et al., with studies categorized as low risk, some concerns, or high risk according to methodological quality and reporting standards (30).

7.3.5 Data synthesis

Study IV: Because substantial heterogeneity was anticipated, we used a random-effects model. Binary outcomes were analyzed using OR, and continuous outcomes using MDs or SMDs when scales differed. Estimates were based on sample sizes, means, and SD, with indirect calculations when necessary. Results were statistically significant when the 95% CI excluded the null and were displayed in forest plots. **Study V:** Continuous outcomes (cell viability, tumor volume, tumor weight) were summarized as MDs or SMDs with 95% CIs. Due to expected biological and methodological variability, all pooled analyses used random-effects models, and proportions were synthesized using random-intercept logistic regression. For both studies, heterogeneity was quantified using τ^2 and I^2 , and prediction intervals were reported only when at least five studies were available (31). Funnel plots evaluated the publication bias and appropriate tests (Egger, Pustejovsky, Harbord) were performed, while recognizing their limitations with fewer than ten studies (32). Outliers were evaluated using graphical and influence diagnostics, and subgroup analyses were performed by THC:CBD ratio. All statistical analysis were conducted in R programme, specifically using the meta and dmetar packages.

8 RESULTS

8.1 Study I

To ensure consistency, the same microscopic field was examined at each time point. At baseline (T0), neurons showed normal, healthy morphology, with round, bright cell bodies, clear nuclei and long, thin, well-extended neurites forming interconnected networks. After exposure to the tested compounds, time-dependent changes appeared, with progressive neurite shortening, or even cell death as shown in *Figure 3*.

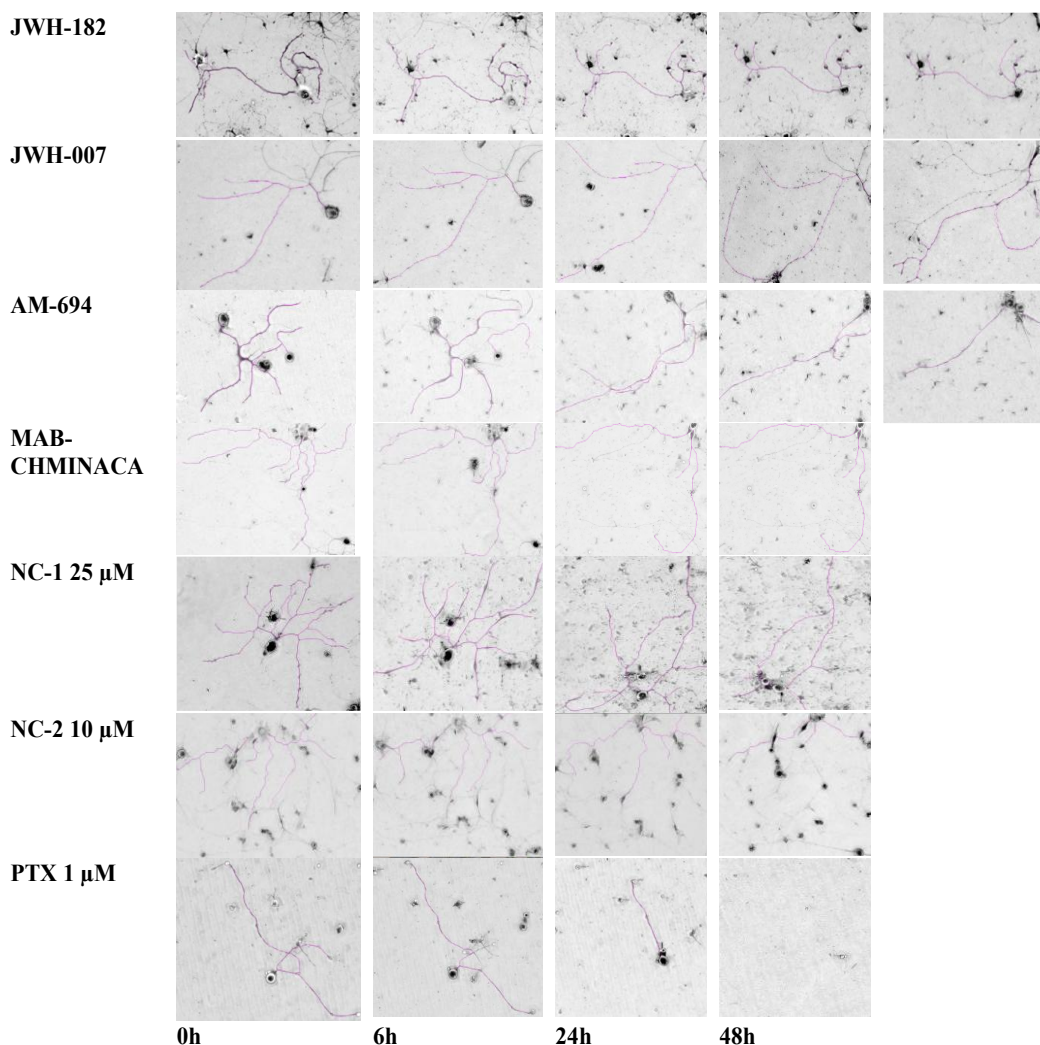


Figure 3. Microscopic changes showing time-dependent axonal shortening (at different time points after treatment administration), according to treatment type. PTX induced axon shortening as soon as 6h after treatment, with complete cellular death at 48h; in contrast, cannabinoid-treated neurons preserved long, elongated axons, preventing cell death, with neurons alive at 72h after combination treatment, especially after JWH-182, JWH-007 and AM-694.

Six hours after treatment was administered, axons presented with longer lengths compared to baseline values. Soon after, the axons shortened, however they were still visible 72 hours after treatment administration. Neurons treated with JWH-007 presented with a neurotrophic phase in the first 24h, when axons enlarged, however shortening occurred soon after. At 72 hours, neurons and their axons were still viable. AM-694 made similar effects on neurons, with axons slightly shortening 24h after administration, with lowest dimensions after 72h, however with viability still preserved. MAB-CHMINACA was a cannabinoid that conducted to axonal shortening as soon as 6h after administration. Also, neurons lost their viability after 48h, cellular death occurring. NC1 produced time-dependent axonal shortening, with minimal lengths observed at 48h. Soon after, neuronal viability was lost, cellular death occurring. The same trend was observed also for NC2 treated neurons, with maximal axonal shortening at 48h after treatment. PTX exerted its toxic effects soon after administration, neurons presented with an increased degree of axonal shortening, with maximum at 24h after administration. Interestingly, neuronal death occurred as early as 48h after treatment exposure.

Regarding toxicity to PTX, at 24h, only doses $\geq 0.5 \mu\text{M}$ caused significant reductions ($p < 0.05$), while $0.1 \mu\text{M}$ showed no significant change. At 48h, all doses decreased viability, with strongest effects at 1 and $10 \mu\text{M}$ ($p < 0.01$). At 72h, every PTX dose caused marked cytotoxicity ($p < 0.05$), and $10 \mu\text{M}$ reduced viability below 30%. The 0.5, 1, and $10 \mu\text{M}$ groups no longer differed significantly, indicating a plateau of toxicity over time (figure presented in the original article (33)). Cannabinoid toxicity on neurons is shown in *Figure 4*. For JWH-182, at 24h and 48h, cell viability was similar to control ($p < 0.0001$). The combination also preserved viability (85%, $p < 0.001$). At 72h, while PTX caused a drop in viability of 40%, JWH-182 maintained $> 80\%$ ($p < 0.0001$). Co-treatment kept 65-70% ($p < 0.0001$) from initial values. For JWH-007, all neurons were viable at 24h and 48h post administration ($p < 0.01$). Co-treatment showed viability drop to 85% at 48h ($p < 0.001$). At 72h, PTX treated neurons had a viability of 35%, while co-treatment reached 75% ($p < 0.001$) and monotherapy 90% ($p < 0.0001$). AM-694 monotherapy kept viability high (100% at 24h; 85% at 48-72h), significantly above PTX ($p < 0.01-0.0001$). AM-694 combined with PTX also reduced toxicity, keeping viability 90% at 24h and $> 70-75\%$ at later times ($p < 0.001-0.0001$), showing strong, consistent protection. For MAB-CHMINACA, monotherapy kept near-control levels ($p < 0.001$) only for 24h. At

48h, viability dropped for both monotherapy and co-treatment to almost 70-75% ($p < 0.001$). At 72h, while PTX remained highly toxic (35-40%), MAB-CHMINACA preserved 65-70% of cellular viability ($p < 0.001$), showing moderate but steady protection. NC1 alone preserved survival and differed strongly from PTX ($p < 0.0001$) at all time points. At 72h, NC1 maintained 90% viability alone and 75% when co-administered with PTX ($p < 0.0001$). NC2 maintained high viability in the first 24h ($p < 0.001$), with a tendency towards decrease to 80-82% at 48h and 72h. While PTX reduced viability to 40%, combination of NC2 and PTX kept at 48h 75% ($p < 0.001$) and at 72h, 70% ($p < 0.001$), indicating sustained but moderate protection.

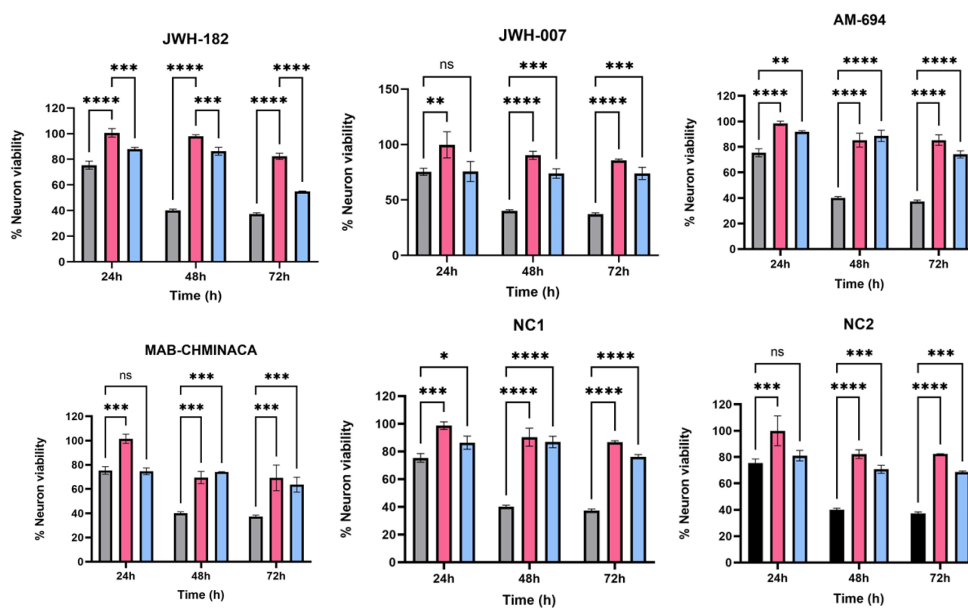


*Figure 4. Neuronal viability following treatment with JWH-182, JWH-006, AM-694, MAB-CHMINACA, NC1, NC2 administered alone or in combination with PTX (1 μ M). Viability is presented as the percentage of surviving cells and was assessed at 24, 48, and 72h after treatment administration.. Results represent the mean $\pm$ SD from three different experiments. Statistical significance is marked as * $p < 0.05$, ** $p < 0.01$; “ns” indicates non-significant differences.*

Axonal-shortening analysis demonstrated a rapid and dose- as well as time-dependent neurotoxic effect of PTX on primary neuronal cultures. Within the first 24 hours of exposure, all PTX-treated groups showed substantial neurite loss, indicating early structural neuronal damage. At 12 hours, exposure to 10 μ M PTX resulted in approximately 60% axonal shortening, while lower concentrations (0.1-1 μ M) produced

moderate but clearly detectable reductions in neurite length, ranging between 20% and 40%. By 24 hours, axonal shortening exceeded 60% across all PTX concentrations, with the highest dose producing the most pronounced neurotoxic effect. At later time points (48-72 hours), neurite loss progressed further and surpassed 90% in all treated groups, reflecting advanced axonal degeneration and suggesting limited regenerative capacity under sustained PTX exposure. These findings confirm the strong and progressive neurotoxic potential of PTX in vitro and are consistent with the axonopathy observed in CIPN. Among the tested concentrations, the 1 μ M PTX dose produced a stable and reproducible intermediate phenotype, characterized by substantial but not complete neurite loss. This concentration therefore represents a reliable and biologically relevant in vitro model for PTX-induced neurotoxicity and was considered appropriate for subsequent neuroprotection experiments. *Figure 5* present the time dependent effect on neurite lengths after treatment administration. Outcomes are presented as the percentage of axonal length decrease relative to each neuron's initial measurement. Controls included neurons maintained in standard growth medium and those exposed to PTX (1 μ M) alone. Analyses were based on two different experiments with four repetitions per experiment, examining 8-5 randomly selected fields per slide, with each containing one to five neurons. Data are reported as mean $\pm$ SD. Statistical significance is shown as * p <0.05, p <0.01, while “ns” indicates non-significant differences. JWH-182 showed strong neuroprotection; at 6h, neurites even increased slightly in length, and axonal shortening stayed far lower than with PTX alone, with viability preserved up to 72h (p <0.0001). Combination with PTX was protective at all time points (p <0.0001), but real effects appeared after 24h, where reduced axonal loss was noted. Notably, at later points, combination with PTX preserved neurites better than JWH-182 alone. JWH-007 produced early neuroprotection increasing neurite length at 6h. At 24h, neurons retained 91% of baseline length versus 32% with PTX (p <0.0001). Protection persisted at 48h and 72h. Co-administration reduced axonal loss compared with PTX alone (p <0.001), although protection was weaker than monotherapy. AM-694 increased neurite length at 6h but later induced moderate shortening. Axonal loss remained far lower than with PTX at all time points (p <0.001-0.0001). Adding PTX accelerated degeneration compared with AM-694, but the combination still protected better than PTX (p <0.01-0.001). MAB-CHMINACA caused progressive axonal shortening, but less than PTX. At 24h,

shortening was 22% vs 68% with PTX ($p<0.01$). Protection persisted at 48h, though by 72h neuronal loss increased, suggesting limited long-term benefit. Combined treatment preserved neurites better than PTX alone ($p<0.01$), but protection was moderate.

NC1 produced short-term neurotrophic effects (neurite length +7% at 6-24h; $p<0.01$). Over time, neurites shortened but remained markedly longer than with PTX. At 48h, NC1 preserved 79% of baseline length vs 3% with PTX. Combined treatment substantially reduced axonal degeneration at 24-48h ($p<0.001$). NC2 caused progressive neurite shortening, but less severe than PTX at 24 and 48h ($p<0.01$). At 72h, neuronal loss became similar to PTX, indicating limited long-term protection. Combined NC2 and PTX decreased axonal damage at 24-48h (neurite preservation 55% and 32% vs 32% and 3% with PTX), yet overall protection remained modest. Cannabinoid efficacy on neuroprotection is presented in *Figure 5*.

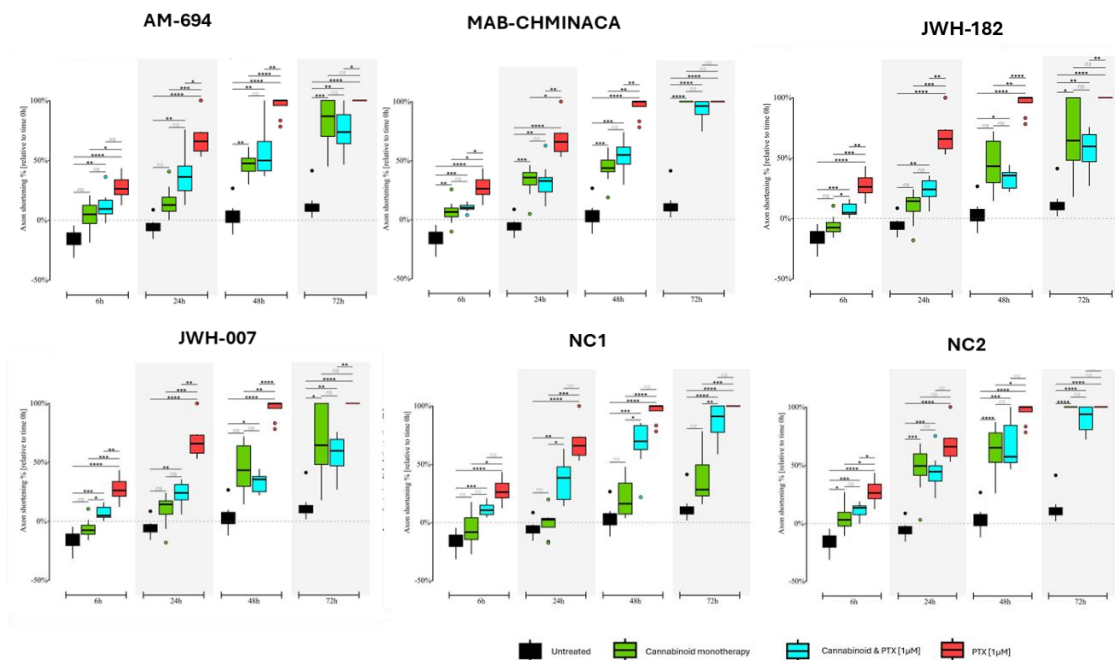


Figure 5. Axonal length responses to JWH-182, JWH-006, AM-694, MAB-CHMINACA, NC1, NC2 in DRG neurons were assessed at 6, 24, 48, and 72 hours, both as single agents and in combination with PTX (1 μ M). Outcomes are presented as the percentage of axonal length decrease relative to each neuron's initial measurement. Control conditions included neurons maintained in standard medium and those exposed to PTX (1 μ M) alone. Analyses were based on two different experiments with four repetitions per experiment, examining 8-5 randomly selected fields per slide, with each containing one

to five neurons. Data are reported as mean $\pm$ SD. Statistical significance is shown as $*p < 0.05$, $p < 0.01$, while “ns” indicates non-significant differences.

8.2 Study II

Figure 6 show the cell viability of different cell lines treated with cannabinoids. Data are presented as mean $\pm$ SD, resulted from three independent experiments. Results are not statistically significant. General toxicity was assessed in the V79 fibroblast line. Most cannabinoids did not alter viability, which remained close to control levels. NC2 was the exception, showing clear dose-dependent toxicity and reducing viability to about 35% at 25 μ M, indicating higher sensitivity for normal cells.

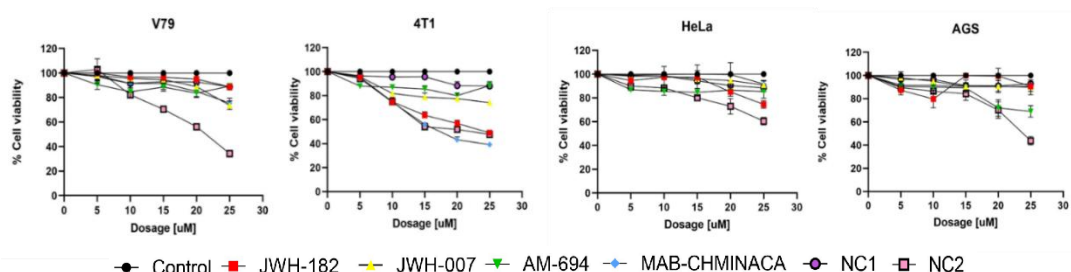


Figure 6. Cell viability (% , assessed with MTT) following exposure to increasing dosages of cannabinoids (5-25 μ M) in V79, 4T1, AGS, and HeLa cell lines, relative to untreated controls. NC2 showed consistent dose-dependent toxicity across all models, with the strongest effects in V79 and AGS cells. JWH-182 and NC2 were most active in 4T1 cells, while HeLa cells were largely resistant. Other cannabinoids induced only mild or negligible effects. Data are presented as mean $\pm$ SD, resulted from three independent experiments. Results are not statistically significant.

In 4T1 breast cancer cells, JWH-182 and NC2 showed notable cytotoxicity (55% and 57%), while NC1 had no effect. JWH-007 and AM-694 produced moderate decreases (78% and 85%). HeLa cells were less sensitive overall, maintaining viability near control even at the highest doses. NC2 was again the only compound causing a substantial reduction (60% at 25 μ M). JWH-182 and AM-694 caused mild decreases (77% and 82%), whereas JWH-007, MAB-CHMINACA, and NC1 showed minimal impact. In AGS gastric cancer cells, NC2 produced the strongest cytotoxic effect, reducing viability to 40% at 25 μ M. AM-694 also decreased viability, 70% at high doses. JWH-182 and NC1 showed limited effects, while JWH-007, MAB-CHMINACA, and NC1 did not significantly differ from control. Results are not statistically significant regardless of cell

line. PTX showed clear dose-dependent cytotoxicity across all tumor cell lines. At 0.1 μ M, AGS cells were highly sensitive (50%), while 4T1 showed a moderate response (75%) and HeLa remained the most resistant (85%). Increasing PTX to 1 μ M reduced AGS viability below 40%, 4T1 to 60%, and HeLa to 65%. At 10 μ M, all lines showed marked toxicity, with viabilities of 49% (4T1), 53% (HeLa), and 35% (AGS). Calculated IC₅₀ values were 5.6 μ M (4T1), 5.1 μ M (HeLa), and 1.5 μ M (AGS), confirming highest PTX sensitivity in AGS.

Results presenting the effects of various cell line of cannabinoids and PTX are presented in *Figure 7*. Data are presented using the same format and analytical approach as in the preceding figures. In 4T1 breast cancer cells, PTX administered at its IC₅₀ concentration reduced cell viability to approximately 50%. Co-treatment with cannabinoids produced modest and predominantly additive cytotoxic effects, with viability values of 42% for PTX+JWH-182, 41% for PTX+NC1, and 47% for PTX+NC2, without evidence of strong synergistic interactions. These results suggest that, in this model, cannabinoids provided only a limited enhancement of PTX-induced cytotoxicity. In HeLa cervical cancer cells, PTX at its IC₅₀ similarly resulted in approximately 50% cell viability, and the addition of cannabinoids produced only minor variations, with viability values of 48% for JWH-182, 52% for NC1, and 47% for NC2, indicating a limited or negligible enhancement of antitumor activity under these conditions. In AGS gastric cancer cells, PTX at its IC₅₀ also reduced viability to around 50%. Among the tested cannabinoids, only NC2 showed a measurable potentiation of PTX cytotoxicity, reducing viability to 38%, whereas JWH-182 and NC1 produced only modest reductions (46% and 49%, respectively), suggesting weak additive or slightly antagonistic interactions. Overall, these differences between treatment groups did not reach statistical significance.

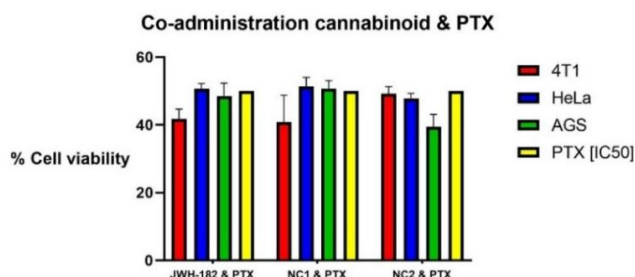
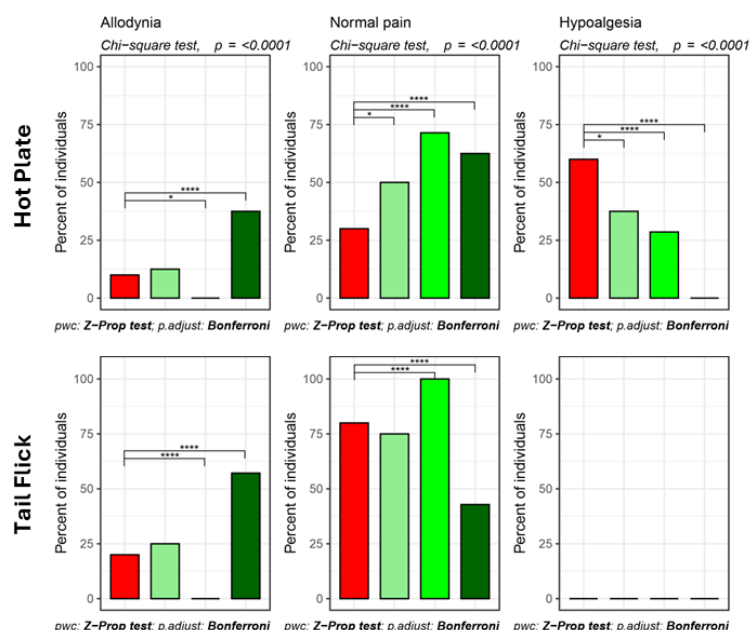


Figure 7. Cell viability after combination of Paclitaxel and JWH-182, NC1 or NC2 on the survival of 4T1, HeLa, and AGS cells. Cannabinoids produced mainly modest,

additive effects with PTX in 4T1 and HeLa cells, without clear synergism. In AGS cells, only NC2 enhanced PTX cytotoxicity, while JWH-182 and NC1 showed minimal interaction. Data are presented using the same format and analytical approach as in the preceding figures. Results are not statistically significant.

8.3 Study III

Individual responses in the nociceptive assays varied, yet clear treatment-related trends emerged, as illustrated in *Figure 8*. In the Hot Plate test, more than two-thirds of mice receiving PTX alone exhibited hypoalgesia, consistent with the development of PTX-induced neuropathy. In contrast, approximately 72% of animals treated with PTX + NC1 retained normal thermal sensitivity ($p < 0.0001$), demonstrating marked neuroprotective effects; only 28% displayed neuropathic alterations. NC2 offered similar benefit, with over 60% returning to baseline-like sensitivity ($p < 0.0001$). JWH-182 had moderate effects, normalizing thresholds in about half the animals. In the Tail Flick test, PTX caused allodynia in only 25% of animals, suggesting milder spinal involvement. NC1 and PTX fully preserved reflex thresholds ($p < 0.0001$). NC2 and JWH-182 also improved responses, though less consistently than NC1. Mechanical testing (Randal-Selitto test), showed nerve impairment in over half of PTX-treated animals. NC2 performed best, restoring normal mechanical thresholds in more than one-third of animals, suggesting stronger protection against mechanical hypersensitivity ($p < 0.0001$).



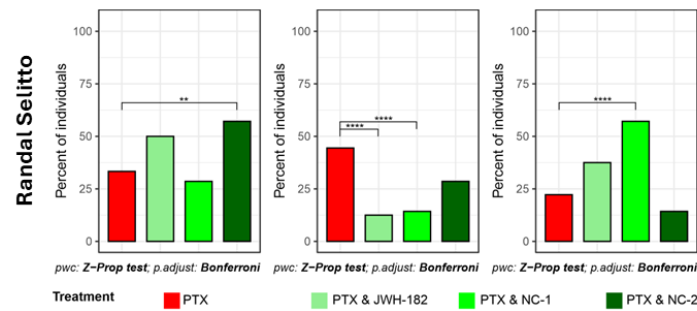


Figure 8. Pain perception assessed by pain inducing tests. Across the three modalities (central thermal, spinal thermal, and mechanical nociception), PTX alone shifted most animals into pathological pain categories (allodynia or hypoalgesia), confirming PTX-induced neuropathy and impaired nociceptive processing. In contrast, co-administration of cannabinoids consistently restored pain thresholds toward the normal physiological range, significantly reducing both allodynia and hypoalgesia ($p < 0.0001$).

To evaluate tumor growth dynamics, 3D ultrasonography and magnetic resonance imaging measurements were performed at two key time points: before treatment (day 8) and at the end of treatment administration (day 26). Tumor size was quantified in three planes, and the SGR was calculated as daily percent volume increase, following the exponential growth model of Mehrara et al. (211) and defined as the daily percentage increase in tumor volume under the assumption of exponential growth, calculated separately for the pre-treatment and post-treatment periods. Between inoculation and tumor appearance (days 1-8), SGR values were not different in a significant manner between groups ($p=0.13$), showing a rapid tumor growth in all groups. This pattern confirmed comparable baseline tumor volumes. During treatment administration period (days 8-26), all groups showed a uniform decrease in SGR, indicating an overall antitumor effect. Although slight variations were observed among treatment groups, the cannabinoid-treated groups did not differ significantly from the PTX-only group ($p=0.073$; $p=0.39$), with tumor volumes being comparable in volumes at all time points throughout the experiment. Graphs are presented in Figure 9 (first, ultrasound tumor assessment, then MRI tumor assessment).

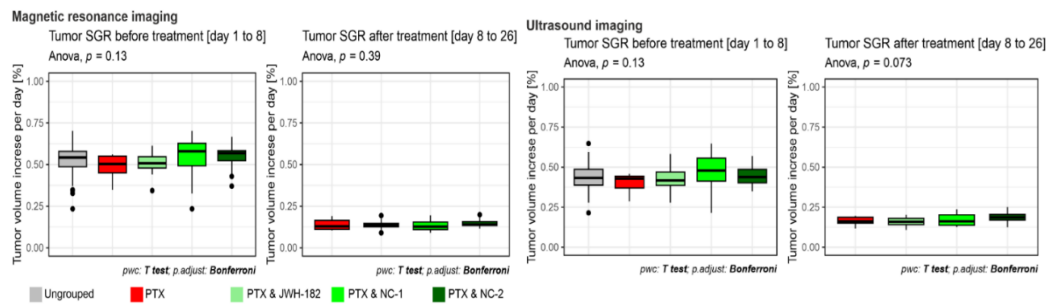


Figure 9. Tumor volumes evaluated by MRI before treatment administration (left, day 1-8), after treatment administration (right, day 8-26). Tumor volumes evaluated by ultrasonography before treatment administration (left, day 1-8), after treatment administration (right, day 8-26).

Cachexia was evaluated through food intake, body weight, and skeletal muscle size (psoas and paraspinal muscles on MRI) (Figure 10). PTX-only animals showed a marked, sustained drop in food intake, reflecting chemotherapy-induced metabolic and appetite suppression. PTX + JWH-182 partially improved appetite, with values trending back toward baseline by week 3 ($p < 0.001$). On contrary, NC1 and NC2 further decreased food intake compared with both baseline and PTX ($p < 0.001$). Despite appetite changes, body weight remained relatively similar across all groups during the 26-day study, with no significant differences between PTX and cannabinoid-treated animals, suggesting metabolic compensation. Muscle loss was assessed by MRI at baseline and day 26. A significant reduction was found in case of animals treated with NC2, where the left psoas muscles had smaller dimensions compared to controls ($p < 0.05$). On the other hand, the dimensions of the right psoas and the paraspinal muscle did not differ significantly between groups. Overall, cannabinoids exerted only minimal effects on sarcopenia, and muscle atrophy did not display a consistent pattern across treatment conditions (44).

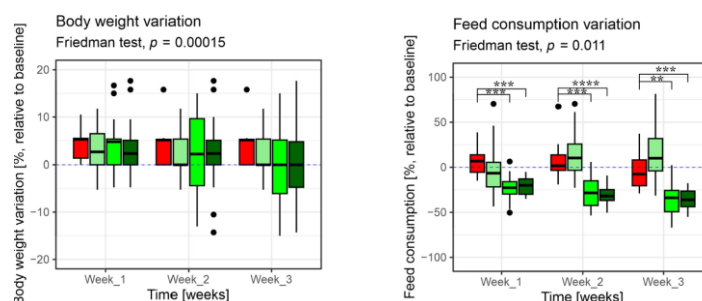


Figure 10. Variations body weight throughout the experiment period (left) and variations of food consumption throughout the experiment period (right).

All groups showed high WBC counts, consistent with the leukemoid reaction typical of the 4T1 model. LY levels differed ($p=0.0005$): PTX lowered LY, while PTX + NC1 or NC2 increased them, suggesting immune activation. MO and NE were also higher with cannabinoids ($p<0.0001$ and $p=0.017$). PLT counts were partly normalised, mainly with NC2 ($p=0.03$). RBC were numerically more in case of cannabinoid-treated animals, as for the PTX-only cohort ($p=0.027$), whereas hemoglobin and hematocrit values showed no meaningful differences, shown in *Figure 11*.

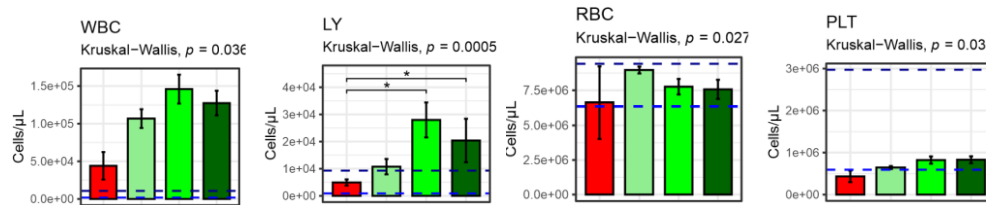


Figure 11. Main findings of blood analysis, graph showing white blood cells, lymphocytes, red blood cells and platelets values of tested animals.

At organosomatic index evaluation (OSI), NC2 increased kidney OSI ($p<0.0001$), indicating possible renal stress. Spleen OSI was elevated in all groups, consistent with leukemoid splenomegaly, but without significant differences ($p=0.26$). Tumor weights were comparable between groups ($p=0.09$), similar to imaging results. Graphs are presented in the original article (34). Histology showed treatment-dependent toxicity. In the liver, controls had mild leukemoid clusters; JWH-182 increased congestion; NC1 caused moderate granular degeneration; NC2 produced the most damage, with sinusoidal dilation, many pyknotic nuclei, and dense leukemoid infiltration. Renal injury followed the same trend: mild tubular changes in controls, moderate injury with JWH-182, marked brush-border loss and focal glomerular sclerosis with NC1, and severe tubular necrosis and glomerular atrophy with NC2. Cardiac tissue was normal in controls but showed mild to moderate vacuolization and focal degeneration with NC1. Tumors, lungs, and liver confirmed the aggressive 4T1 profile: poor differentiation, pleomorphism, high mitotic activity, and frequent necrosis. Lung metastases (perivascular and leukemoid) appeared in all groups; liver tissue showed one classic metastasis per group plus sinusoidal leukemoid clusters; renal lesions were rare; one NC1 mouse had a brain metastasis. Regarding the evaluation of metastatic burden, results varied by treatment. JWH-182 presented the highest rate (83.33%), PTX-only had 70%, NC2 showed an intermediate effect (58.33%), and NC1 reduced metastasis most strongly (41.67%, $p<0.001$). Lesions

were more prevalent in PTX and JWH-182 lots and fewer in NC1 and NC2, indicating treatment-dependent suppression of spread, as presented in *Figure 12*. The rest of the graphs and figures are presented in the original article (34).

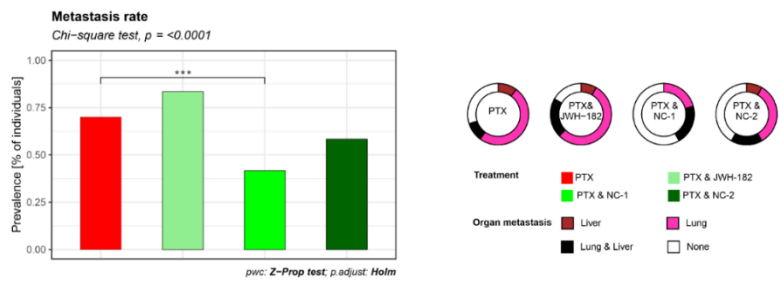


Figure 12. Quantification of lung and liver metastases, expressed as prevalence (% of animals with at least one metastasis) and mean number of metastases per animal. NC1 treatment significantly reduced metastasis rates ($p<0.001$) compared with all other groups. Lung metastasis were the most prevalent.

Daily monitoring showed clear tolerability differences (details presented in *Figure 13*). PTX-only animals displayed major adverse effects, with frequent sedation (41-60%) and poor general condition (61-80%). JWH-182 caused fewer issues, though mild sedation persisted in 11-20% of animals. PTX + NC1 reduced sedation but occasionally caused dyspnea (up to 10%) and visible physical decline. NC2 caused no sedation but led to marked deterioration in overall condition (80-100%), suggesting late systemic toxicity.

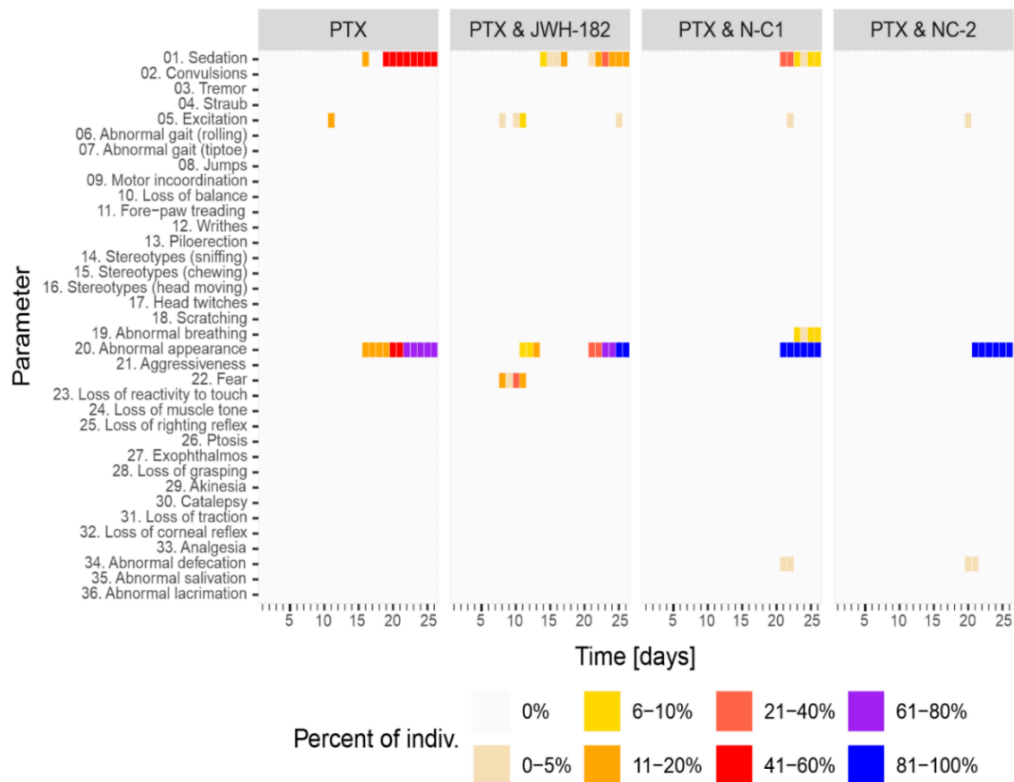


Figure 13. Heatmap of adverse events associated with cannabinoid treatment. Color gradients represent the normalized intensity of each adverse event, allowing visual comparison of tolerability profiles between groups.

8.4 Study IV

The systematic search identified 27,690 records, but only 98 were included, based on the eligibility criteria, along with two additional studies found via citation chaser. The full selection process is summarized in *Figure 14*.

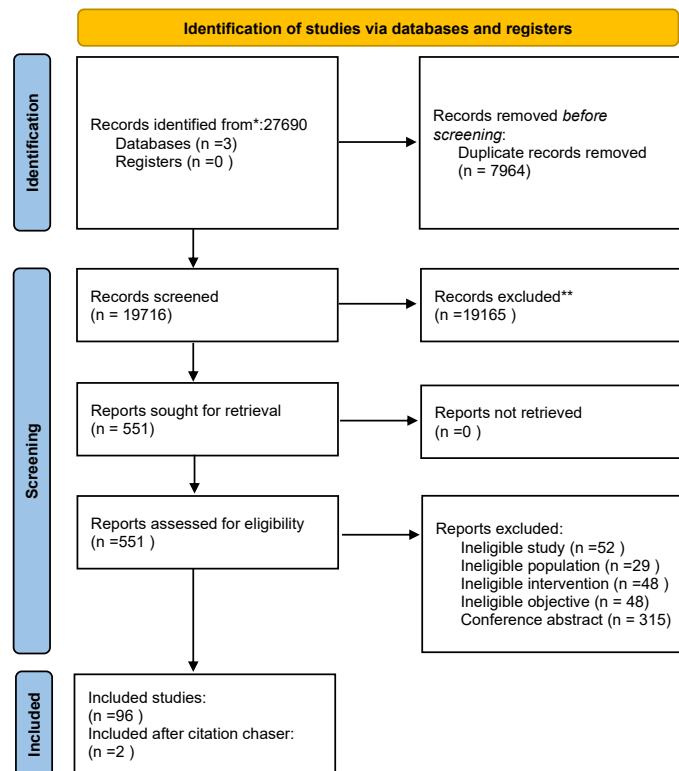


Figure 14. PRISMA diagram of eligible articles for study IV (26).

The analysis included 56 RCT (35–88), 13 non-randomised trials (89–101) and 29 observational studies (79,102–126), with a total of 21,397 patients. Patients were undergoing either curative cancer therapy or palliative care and received different cannabinoid-based treatments. Regimens included THC-dominant, CBD-dominant, or balanced THC:CBD drugs, given as fixed or patient-adjusted doses. Administration routes included inhaled, oral, intramuscular, and topical options. More details are found in the original article (26). Twelve studies (65,79,80,84,88,90,102–105,111,118),

evaluated a total of 2,591 cancer patients to assess the analgesic effects of cannabinoids (Figure 15). The interventions varied widely, including THC-dominant, CBD-dominant, and balanced THC:CBD formulations, so subgroup analyses were performed based on cannabinoid composition. In single-arm studies, pain intensity was compared from baseline to post-treatment using the NRS, with 0=no pain; 10=worst pain. Cannabinoid therapy resulted in a significant decrease in pain perception, independent of the administered THC:CBD ratio (MRAW-1.22;CI:-1.92;-0.52). Patients receiving THC-dominant preparations appeared to experience stronger analgesic effects (MRAW-2.50; CI:-19.2;14.22), suggesting a potential central role of THC in modulating nociception.

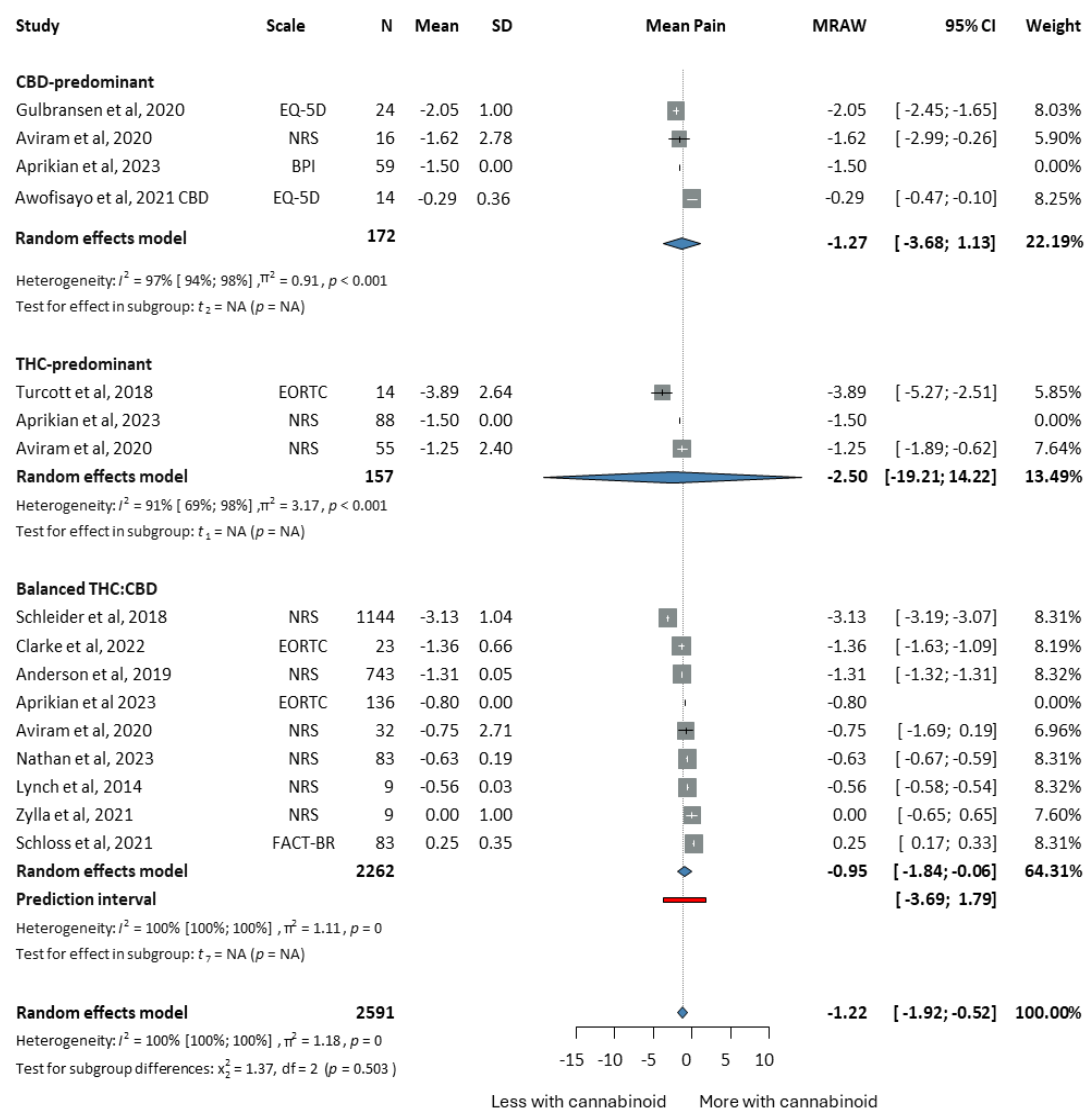


Figure 15. Forest plots illustrating pain outcomes in cancer patients treated with cannabinoids. Results come from the analysis of 2591 patients enrolled, where baseline

pain values were compared to after cannabinoid treatment values and expressed as MRAW with 95%CI. Subgroups were performed based on the THC and CBD content of drugs. Overall, pain decreased with MRAW -1.22 (CI:-1.92;-0.52), with better results for THC-predominant drugs.

In total, 1,039 patients enrolled in single-arm studies were included in the anxiety analysis (80,90,95,102,104,105,111,118). Anxiety scores were compared from baseline to post-treatment to assess the direct effect of cannabinoids. Overall, cannabinoids significantly reduced anxiety (MRAW-1.30; CI:-2.22;-0.39) (Figure 16). The greatest reduction was seen in patients using high-CBD products (MRAW-2.35; CI: -5.79;1.10), supporting the hypothesis that CBD exerts independent anxiolytic effects.

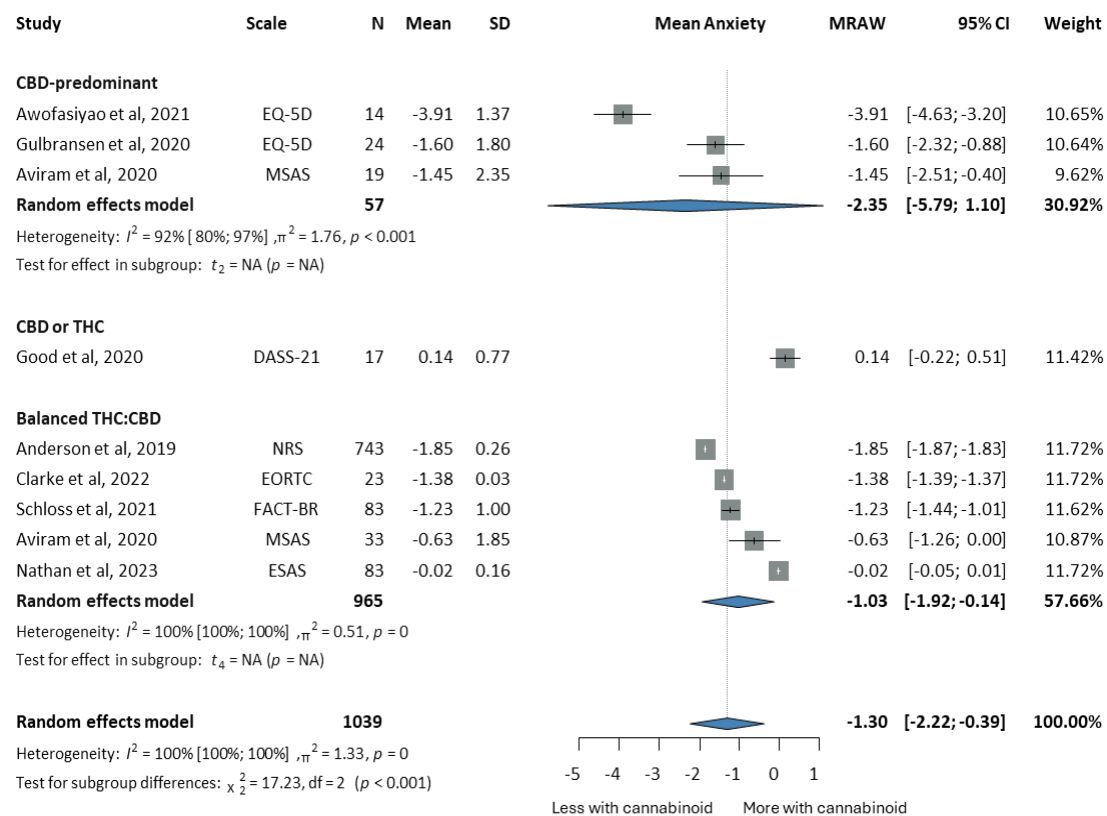


Figure 16. Forest plots depicting anxiety levels in cancer patients receiving cannabinoid therapy. Results come from the analysis of 1039 patients enrolled, where baseline pain values were compared to after cannabinoid treatment values and expressed as MRAW with 95%CI. Subgroups were performed based on THC and CBD content of the drugs. Overall, anxiety decreased with MRAW -1.30 (CI:-2.22;-0.39), with better results for CBD-predominant drugs.

Appetite improved in patients receiving cannabinoids than at baseline; however, the effect did not reach statistical significance, with MRAW -1.88 (CI: -6.23; 2.46) in single-arm studies and MD 0.57 (CI: -0.33; 1.48) in placebo-controlled analyses. Regarding CINV, cannabinoids produced a decrease in symptom intensity compared with baseline, but again without statistical significance (MRAW-0.75;CI:-1.80;0.30). Studies comparing cannabinoids to prochlorperazine similarly showed no clear benefit, with OR 1.22 (CI: 0.45; 3.28) for vomiting and OR 1.13 (CI: 0.49; 2.62) for nausea. Findings for insomnia followed the same pattern: although single-arm studies indicated a non-significant trend toward improvement (MRAW 1.08; CI: -2.48; 0.33), this effect disappeared in placebo-controlled comparisons (MD -0.27; CI:-0.47; 0.28). Forest plots are presented in the original article (26). In placebo-controlled comparisons, cannabinoids did not provide clinically meaningful improvements for several frequent cancer-related symptoms. No significant effects were observed for asthenia (MD 0.30; CI: -1.24; 1.83), constipation (MD -0.19; CI: -0.68; 0.30), mobility (MD -0.05; CI: -0.42; 0.32), or QoL (MD 0.16; CI: -0.02; 0.35). The corresponding forest plots are presented in the original article (26). Analysis of adverse events (Table I) indicated that cannabinoid use was linked to nearly a twofold increase in gastrointestinal events (OR 1.88; CI:1.14;3.11). The most commonly reported symptoms included stool modifications, abdominal discomfort, nausea, vomiting, xerostomia, and stomatitis. Neurological adverse effects, such as confusion, impaired concentration, coordination difficulties, and dizziness, were also observed. These reactions occurred at roughly twice the frequency in patients treated with cannabinoids compared with those in the control groups (OR 2.06; CI:1.15;3.68), regardless of the THC/CBD ratio of the products. A distinct category consists of psychiatric effects, which are of particular clinical relevance. These ranged from hallucinations, delusional ideas, and paranoid episodes to psychosis, nightmares, severe anxiety, and abrupt mood changes. The data indicate that such reactions were about three times more frequent in cannabinoid-treated groups (OR 3.24; CI:1.48;7.1), and up to ten times more likely when THC-dominant products were used (OR 10.62; CI:1.35;83.57). Overall, the treatment discontinuation rate due to adverse effects was estimated at OR 1.53 (CI:0.99;2.35), indicating a tendency toward increased therapy withdrawal. This likelihood was even higher with THC-rich products, where the risk of discontinuation was approximately three times greater (OR 3.01; CI:0.32;27.89). The majority of the

evaluated RCTs were categorised as having high or some concerns regarding the risk of bias. The most frequent shortcomings involved unclear or insufficiently described randomization procedures, some did not respect the proposed intervention, others missed outcome data, or had limitations in outcomes measurement details, and selective reporting. A similar pattern was observed in the observational studies, although the underlying sources of bias differed. Key issues included uncontrolled confounding, participant selection methods that could introduce baseline imbalances, incomplete or missing data, and selective reporting of outcomes (36).

Table I. All adverse effects of cannabinoids, grouped according to the THC/CBD content of the administered drug (26). Abbreviations: THC= tetrahydrocannabinol, CBD=Cannabidiol, CI=confidence interval, OR=Odds Ratio.

Adverse events	INTERVENTION	OR (95%CI)
Neurological	All	2.26 (1.33; 3.84)
	THC	2.24 (1.15; 4.35)
	THC:CBD	2.12 (1.06; 4.24)
Psychiatric	All	4.32 (1.37; 13.66)
	THC	10.62 (1.35; 83.57)
	THC:CBD	2.58 (0.20; 33.12)
Pain	All	0.89 (0.45; 1.62)
Hematological	All	1.07 (0.78; 1.46)
Asthenia	All	1.47 (0.81; 2.67)
	THC	1.84 (1.56; 2.18)
	THC:CBD	1.63 (0.20; 12.95)
Anorexia	All	0.51 (0.08; 3.32)
Dyspnea	All	1.76 (0.81; 3.79)
Cardiovascular	All	1.03 (0.51; 2.09)
	THC	1.40 (0.34; 5.80)
	THC:CBD	0.95 (0.31; 2.90)
Somnolence	All	1.51 (0.95; 2.40)
	THC	0.73 (0.35; 1.54)
	THC:CBD	2.63 (1.77; 3.89)
Gastrointestinal	All	1.88 (1.14; 3.11)
	THC	2.69 (0.73; 9.90)
	THC:CBD	1.79 (0.92; 3.49)
Tumor progression	THC:CBD	1.16 (0.70; 1.92)
Stopped due to toxicity	All	1.61 (0.89; 2.90)
	THC	2.68 (0.37; 19.56)
	THC:CBD	1.32 (1.04; 1.67)

Most outcomes showed moderate to high heterogeneity ($I^2=48\%-100\%$), except insomnia and quality of life in two-arm studies, which were homogeneous ($I^2=0$). Publication bias was evident for several key symptoms, including anxiety, appetite, insomnia, nausea, pain, and quality of life, indicating that reported benefits may be overestimated. GRADE assessments evaluated the certainty of evidence as low to very low due to heterogeneous populations and wide variation in cannabinoid types, doses, and administration methods. Overall, these limitations require cautious interpretation and highlight the need for more standardized, well-designed clinical trials (26).

8.5 Study V

Of the 27,690 records screened, 189 studies were eligible according to predefined criteria, and 52 were eligible for meta-analysis (*Figure 17*). Eight studies reported only *in vitro* data (172-179), 33 used animal models (180-212), and 11 included both (213-222). Breast cancer was the most frequently studied tumor type, followed by glioblastoma and gastrointestinal cancers. Lung, prostate, and skin cancers were less represented. Most investigations evaluated phytocannabinoids, while synthetic cannabinoids appeared in fewer studies as well. Only 16 studies examined cannabinoid-chemotherapy combinations.

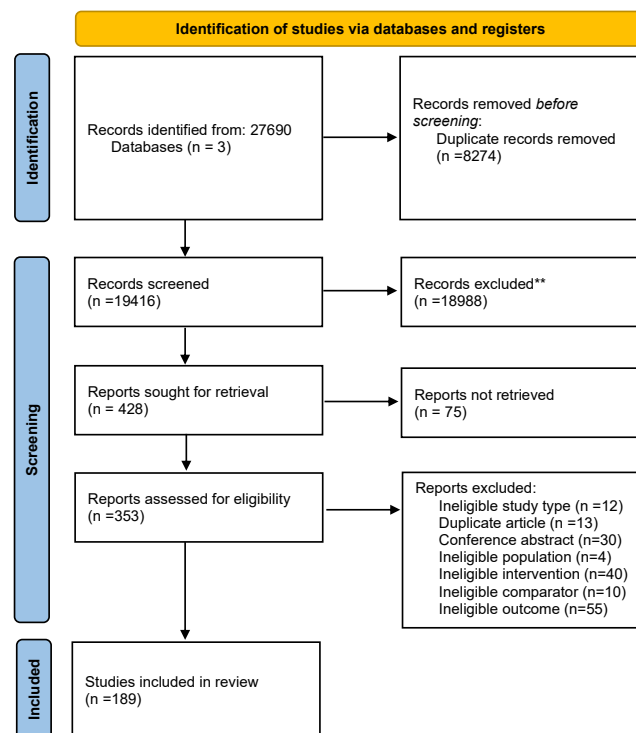


Figure 17. PRISMA flowchart of article selection for study V.

In breast cancer xenograft models, cannabinoid treatment was associated with a statistically significant reduction in tumor volume compared with vehicle-treated control groups, with a pooled mean difference of -402.64 mm³ (95% CI: -671.84; -133.45). The detailed quantitative results of this analysis are presented in *Figure 18*. Synthetic cannabinoids showed the strongest effect, followed by CBD and THC:CBD products, while THC-rich formulations showed a slight protumoral trend. Combination with chemotherapy enhanced outcomes: CBD plus doxorubicin markedly reduced tumor size and adding THC to chemotherapy improved its effect. *In vitro* data showed a small, nonsignificant reduction in cell viability.

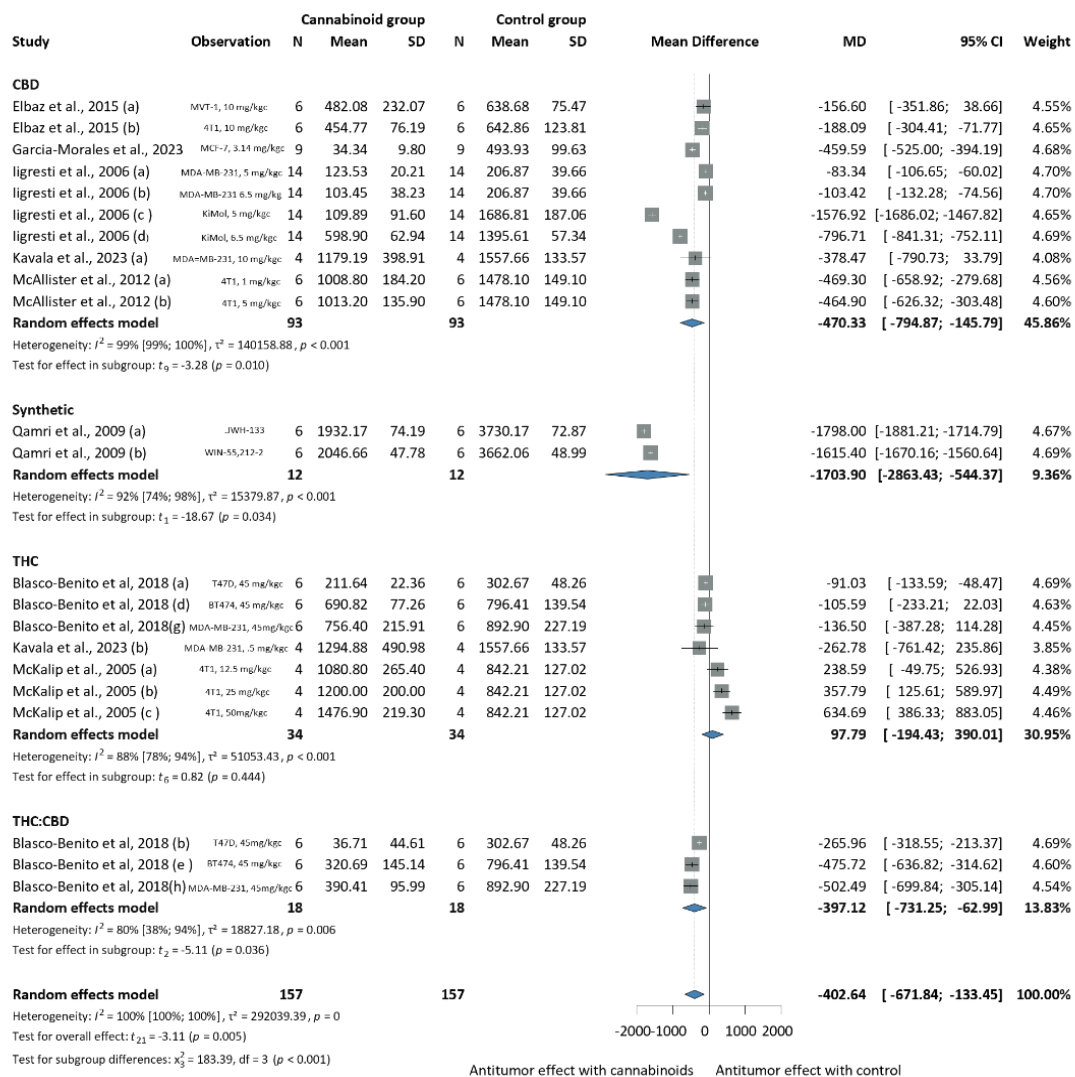


Figure 18. Effects of cannabinoids on breast cancer xenograft tumor volume (mm³) analysed in 157 animals. Forest plot illustrating the mean difference (MD) in tumor volume (mm³) between cannabinoid-treated and vehicle-treated animals, with a

statistically significant reduction in tumor volume MD -402 (CI: -671.84;-133.45). Subgroup analyses are stratified by THC/CBD/synthetic content of the drugs.

Glioblastoma xenograft models demonstrated the most consistent and pronounced antitumor responses among all tumor types (Figure 19). Across all evaluated cannabinoids, treatment was associated with a substantial reduction in tumor volume, with an overall pooled mean difference of -980.58 mm³ (95% CI: -1270.28; -690.88). The narrow confidence interval and the large magnitude of the effect indicate a robust and statistically significant inhibition of tumor growth in glioblastoma models. THC-rich, CBD-rich, and THC:CBD formulations all demonstrated strong antitumor activity; synthetic cannabinoids produced variable but generally favorable effects. Limited combination therapy data showed nonsignificant benefit. In vitro analyses indicated moderate reductions in cell viability, with CBD showing the most pronounced effect despite high heterogeneity.

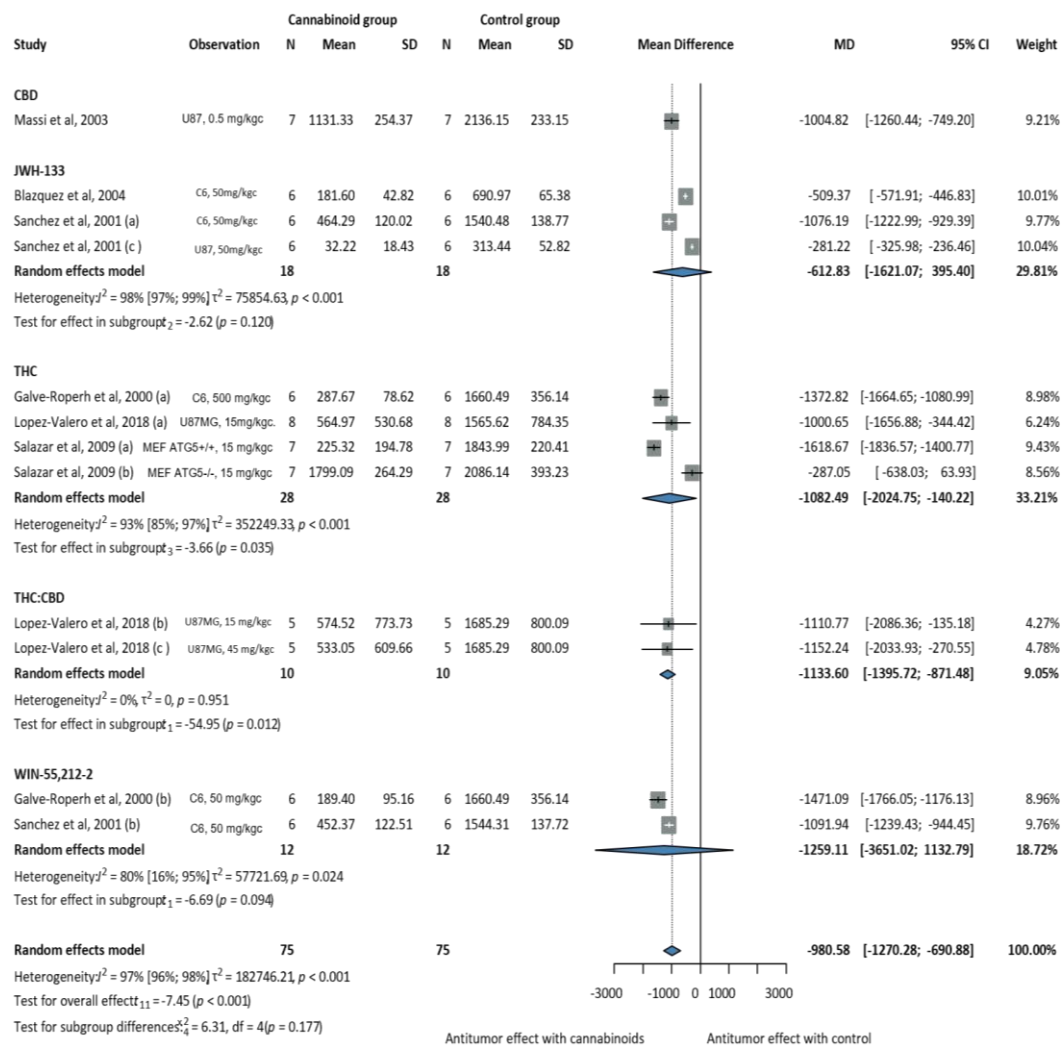


Figure 19. Effects of cannabinoids on glioblastoma xenograft tumor volume (mm³) analysed in 75 animals. Forest plot illustrating the mean difference (MD) in tumor volume (mm³) between cannabinoid-treated and vehicle-treated animals, with a statistically significant reduction in tumor volume MD -980.58 (CI: -1270.28;-690.88). Subgroup analyses are stratified by THC/CBD/synthetic content of the drugs.

In lung cancer xenograft models, treatment with cannabinoids resulted in a significant reduction in tumor volume compared with vehicle-treated controls, with a pooled mean difference of -562.17 mm³ (95% CI: -693.99; -430.35). Subgroup analyses indicated that CBD produced the largest antitumor effect among the evaluated cannabinoids. However, the magnitude of CBD-mediated tumor reduction showed considerable variability between studies. The detailed results of this analysis are presented in Figure 20.

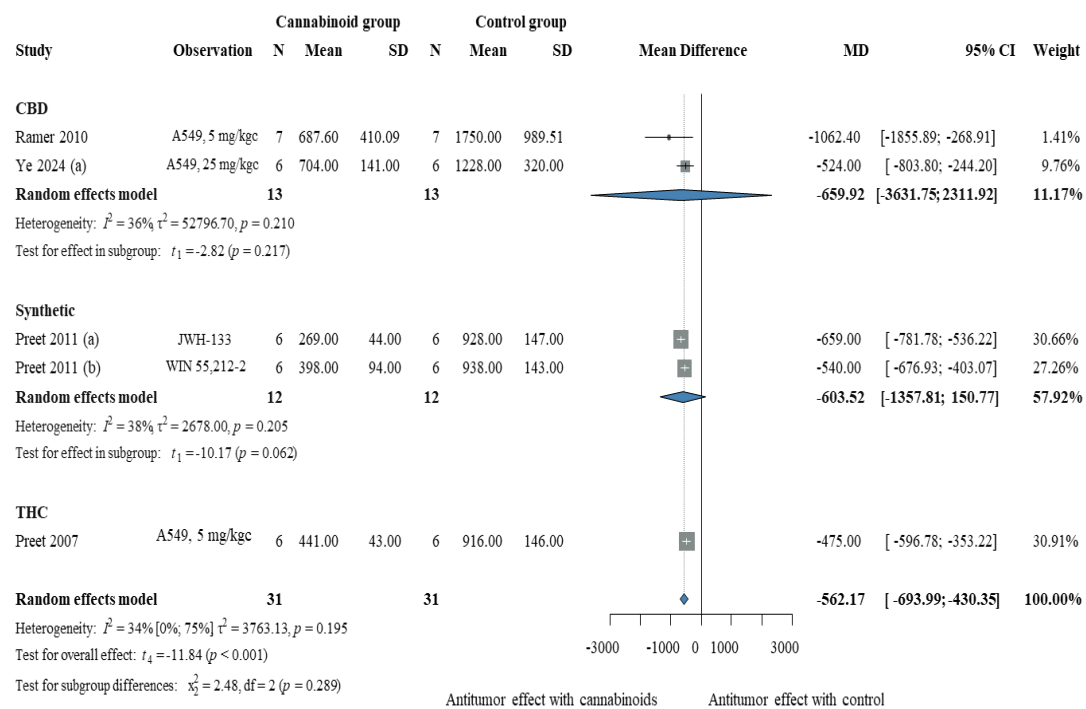


Figure 20. Effects of cannabinoids on lung cancer xenograft tumor volume (mm³). Forest plot illustrating the mean difference (MD) in tumor volume (mm³) between cannabinoid-treated and vehicle-treated animals, with a statistically significant reduction in tumor volume MD -562.17 (CI: -693.99; -430.35). Subgroup analyses are stratified by THC/CBD/synthetic content of the drugs.

In prostate cancer models, cannabinoid treatment was associated with a pooled reduction in tumor volume of -394.32 mm³ (95% CI: -793.91; 5.26). Although this

estimate suggests a trend toward tumor growth inhibition, the confidence interval crossed zero, indicating that the overall effect did not reach clear statistical significance across studies. Subgroup analyses revealed that formulations combining THC and CBD demonstrated the most pronounced antitumor activity, producing a statistically significant reduction in tumor volume compared with control conditions. Detailed results of these analyses are presented in *Figure 21*.

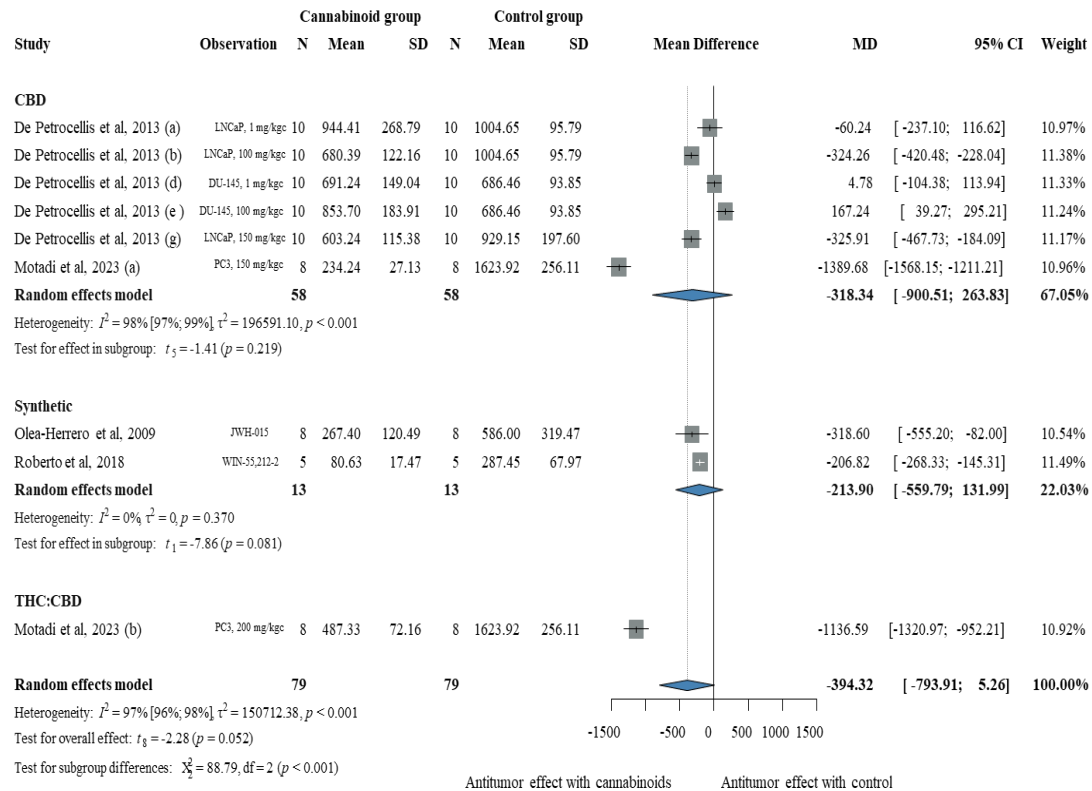


Figure 21. Effects of cannabinoids on prostate cancer xenograft tumor volume (mm³). Forest plot illustrating the mean difference (MD) in tumor volume (mm³) between cannabinoid-treated and vehicle-treated animals, with a statistically significant reduction in tumor volume MD -394.32 (CI: -793.91;-5.26). Subgroup analyses are stratified by THC/CBD/synthetic content of the drugs.

In colon cancer xenografts, cannabinoid monotherapy showed a nonsignificant pooled reduction (MD-123.74 mm³, CI:-760.83;513.34), with CBD trending toward benefit, and THC trending toward harm. Against chemotherapy, cannabinoids performed worse. In hepatocellular carcinoma, monotherapy showed minimal effect (MD-2.01 mm³, CI:-4.55;0.53), while pancreatic cancer models showed modest, nonsignificant reductions (MD-50.42 mm³, CI:-124.15;23.32) and a nonsignificant shift toward tumor growth when

combined with chemotherapy. In skin cancer, cannabinoids had a near-neutral effect (MD-2.02 mm³, CI:-5.47;1.43), with combination therapy showing a nonsignificant trend toward increased tumor volume. Corresponding Forest plots are seen in the original article. In colon cancer xenografts, cannabinoid monotherapy showed a nonsignificant pooled reduction (MD-123.74 mm³, CI:-760.83;513.34), with CBD trending toward benefit, and THC trending toward harm. Against chemotherapy, cannabinoids performed worse.

Most studies presented a high risk of bias. *In vivo* experiments often lacked details on randomization, blinding, housing conditions, and outcome selection. Baseline tumor comparability was rarely reported and missing data and selective reporting were generally low risk. *In vitro* studies showed similar problems, with no sample size calculations, randomization, or blinding, though outcome measurements and statistical methods were usually well described. Results are presented in the original article.

9 DISCUSSION

9.1 Summary of findings, international comparisons

9.1.1 Study I: Our study shows that cannabinoids provide clear neuroprotective benefits against PTX-induced neuronal damage, although these effects were dependent on both the timing of administration and the specific cannabinoid used, findings that are consistent with previous reports (127,128). All tested compounds reduced axonal loss compared with PTX treatment alone, indicating a general protective effect against chemotherapy-induced neuronal injury. However, the magnitude of neuroprotection varied between cannabinoids, suggesting differences in their pharmacological properties and mechanisms of action. All tested compounds reduced axonal loss compared with PTX alone, though the strength and duration varied between cannabinoids. Cannabinoids have been widely investigated for their neuroprotective actions in experimental models of neurological disorders as well as in CIPN (129,130). Their therapeutic rationale is primarily based on the ability to prevent or limit axonal degeneration, which represents a central pathological mechanism underlying neuropathic pain and sensory dysfunction. By preserving neuronal structure and function, cannabinoids may reduce the severity of chemotherapy-induced neuronal injury and improve neurological outcomes. This concept is supported by several experimental studies demonstrating direct neuroprotective and anti-inflammatory effects of cannabinoid compounds. For example, the synthetic CB1R/CB2R agonist WIN-55,212-2 has been shown to suppress TNF- α -induced nitric oxide synthase activity in DRG neurons and to attenuate neuropathic pain (131). In addition, WIN-55,212-2 has demonstrated neuroprotective properties in models of neonatal hypoxic-ischemic encephalopathy (132) and has been shown to protect hippocampal neurons against excitotoxic injury (133), further supporting the role of cannabinoid receptor activation in neuronal preservation across different models of neural damage. DRG neurons express a wide range of ion channels and receptors that play essential roles in nociceptive signaling and sensory transmission (134). PTX disrupts this finely regulated molecular machinery by inducing alterations in transient receptor potential channels, voltage-gated sodium and calcium channels, glutamatergic receptors, and purinergic receptors, changes that contribute to neuronal hyperexcitability and ionic imbalance, key mechanisms underlying CIPN (135). These molecular disturbances lead to abnormal sensory processing and increased susceptibility to neuropathic pain.

Cannabinoid-mediated neuroprotection involves activation of classical cannabinoid receptors, but also engagement of additional signaling pathways, including peroxisome proliferator-activated receptors (PPARs), transcriptional regulators, and 5-HT_{1A} receptor signaling (136). Through these mechanisms, cannabinoids may modulate many of the same molecular targets affected by PTX, contributing to the stabilization of neuronal excitability and the preservation of axonal integrity. This overlap in molecular pathways provides a mechanistic basis for the observed protective effects of cannabinoids against PTX-induced neurotoxicity. This study's results show that all tested cannabinoids delayed or reduced PTX-induced axonal shortening, indicating a consistent and meaningful neuroprotective effect. In the combined treatment groups, neurite length was consistently better preserved compared with PTX alone, suggesting that cannabinoids were able to attenuate the structural neuronal damage induced by chemotherapy. These findings support the potential role of cannabinoids in limiting axonal degeneration. However, when administered as monotherapy, several cannabinoids induced a degree of axonal shortening after 24 hours of exposure, suggesting a mild intrinsic neurotoxicity at the tested concentrations. Only JWH-182, JWH-007, and NC1 produced a transient neurotrophic-like response, with neurite lengths comparable to untreated controls during the early observation period. Although all compounds eventually induced some degree of axonal shortening over time, the extent of neuronal damage remained substantially lower than that observed with PTX alone. This pattern indicates that, despite limited toxicity in isolated exposure, cannabinoids exhibit a more favorable and tolerable neurotoxicity compared with PTX while maintaining overall neuroprotective activity in the combined treatment setting. This dual “yin-yang” behavior, in which cannabinoids exert both protective and potentially deleterious effects on neurons, is consistent with previous observations and likely reflects the influence of experimental conditions and pharmacological variables. Cannabinoid actions are highly dependent on dose and exposure duration: higher concentrations administered over shorter periods often produce classical neuroprotective effects, whereas lower concentrations or prolonged exposure may induce cellular stress and subtle neurotoxic changes (137). In addition, *in vitro* experimental systems lack several key components of the neural microenvironment, including glial support cells and vascular elements, which play important roles in neuronal survival and repair. The absence of these regulatory mechanisms may limit the

full expression of cannabinoid-mediated neuroprotection and may partly explain why stronger and more consistent protective effects are often observed in *in vivo* models (138). Together, these considerations suggest that the balance between neuroprotection and toxicity depends not only on the intrinsic properties of cannabinoids but also on the biological context in which they are studied. An interesting observation is that, after 48 hours, cannabinoid monotherapy caused greater axonal shortening than the combination with PTX, which may reflect overlapping mechanisms. While PTX disrupts mitochondrial membrane potential and calcium-dependent transport, causing neuronal hyperexcitability (139), cannabinoids modulate G-protein-coupled receptor pathways that reduce cAMP and alter calcium and potassium channel activity, tempering glutamate release (140). These intersecting mechanisms may produce partial antagonism, where cannabinoids mitigate PTX neurotoxicity while displaying mild intrinsic toxicity. When comparing the effects of natural versus synthetic cannabinoids, we observed that JWH-182 and JWH-007, both synthetic cannabinoids, and NC1, produced the most favorable results in terms of axonal protection and preservation of neurite length, particularly when administered as monotherapy. It is well established that different species and strains of *Cannabis sativa* may vary substantially in their chemical composition, containing more than 500 bioactive compounds, capable of modulating cannabinoid activity through a synergistic mechanism known as the “entourage effect” (141). These complex interactions among plant-derived compounds may not only enhance cannabinoid activity but may also independently modulate specific pharmacological effects, including neuroprotective and analgesic actions. Synthetic cannabinoids, although generally more selective and potentially more potent, do not benefit from this entourage effect because they lack the secondary bioactive molecules present in whole-plant cannabis extracts. The absence of such complementary compounds may explain why the simplified chemical structure of JWH-007 resulted in more pronounced neuroprotective effects when administered in combination with PTX, compared with NC1, which showed more modest results, possibly due to unknown interactions between plant-derived metabolites and the chemotherapeutic agent. Structurally, JWH-182 and JWH-007 (naphthoylindoles) are high-affinity agonists of CB1R and CB2R ($K_i=9.5$ nM and 2.94 nM). AM-694 and MAB-CHMINACA are also CB1R agonists, although their receptor affinities differ significantly. AM-694 exhibits a K_i value of 0.08 nM for CB1R and an 18-fold selectivity

for CB2R ($K_i=1.44$ nM), suggesting predominantly central activity (142). MAB-CHMINACA, on the other hand, is a potent CB1R agonist ($K_i=0.289$ nM), although its clinical efficacy remains unconfirmed (143). The JWH family includes more than 100 substances with high affinity for CR and has been widely used in preclinical studies to evaluate analgesic and neuroprotective effects. For example, JWH-133 and JWH-015, reduce mechanical allodynia in nerve-ligature models (142), supporting CB-mediated analgesia. Regarding the phytocannabinoids tested, Cannabixir® Medium dried flowers (NC1) contain 15.6% THC and <1% CBD and represent a whole-plant extract of *Cannabis sativa* L., while Cannabixir® THC full extract (NC2) is a THCA-enriched extract containing approximately 20% THC. Although THC acts as a mixed CB1R/CB2R agonist, preclinical studies have demonstrated that it may exert analgesic and neuroprotective effects in the context of peripheral neuropathy (144).

9.1.2 Study II: The investigated cannabinoids exhibited dose-dependent antitumor effects, with variable efficacy depending on the cell line used. Although extensive evidence regarding the antitumor activity of cannabinoids is available in the literature (29, 30, 31), our study is the first to evaluate the effects of JWH-182, JWH-007, AM-694, and MAB-CHMINACA, NC1 and NC2. We observed that the antitumor potency of cannabinoids varied according to tumor type and cellular model, indicating a certain degree of selectivity. For example, in the 4T1 breast cancer cell line, the strongest antitumoral effects were observed with NC2 and MAB-CHMINACA, whereas in the HeLa cervical cancer cell line, the most pronounced effects were obtained with JWH-182 and NC2. In the gastric cancer cell line, AM-694 and NC2 demonstrated the highest cytotoxic activity. Notably, among the phytocannabinoids tested, NC2 showed consistent antitumor activity across all cell lines, whereas NC1 produced cell viability values comparable to the control, suggesting limited cytotoxic activity. Studies with similar findings as the presented results have been reported in the literature. For example, CBD administration produced comparable IC₅₀ values in two ovarian cancer cell lines (OVCAR-3 and SK-OV-3), indicating similar efficacy, whereas in triple-negative breast cancer, considerable variability in response has been observed (145). Likewise, a THC-rich cannabinoid extract did not enhance PTX cytotoxicity in MDA-MB-231 cells, suggesting no additive or synergistic benefit (146). Conversely, the same extract boosted Cisplatin antiproliferative effects in the same line, highlighting cancer- and drug-specific

variability, similar to the results presented in our study. The differential sensitivity observed across tumor cell lines may partly reflect variations in cannabinoid receptor expression and intracellular signaling pathways. Previous studies have shown that the expression levels of CB1R and CB2R, as well as non-cannabinoid targets such as TRPV1 channels and PPAR receptors, differ substantially between tumor types and may influence responsiveness to cannabinoid treatment (147). Activation of these pathways has been associated with apoptosis induction, inhibition of proliferation, and modulation of mitochondrial function, mechanisms that are known to contribute to cannabinoid-mediated tumor growth inhibition (148). The heterogeneous responses observed in our study are therefore consistent with the concept that cannabinoid efficacy depends not only on the pharmacological properties of the compounds but also on the molecular characteristics of the tumor cells. Regarding the interaction between cannabinoids and PTX, it appears that the two drugs have overlapping mechanisms, which appear to be complex, explaining why preclinical studies report both synergistic and non-interactive (or antagonistic) effects depending on the experimental context. In some tumor cell lines, cannabinoids may enhance the cytotoxic activity of PTX, which may result from complementary mechanisms of action, including the promotion of apoptosis, modulation of cell-cycle progression, and increased susceptibility of tumor cells to chemotherapy-induced stress (149). For example, in 4T1 breast cancer cells, the combination of CBD and PTX produced an additive effect, whereas in MDA-MB-231 cells, the same combination resulted in clear synergism (121), while our tested cannabinoids, either synthetic or natural presented clear antitumor activity. On the other hand, similarly to some of our findings, other studies have shown that the simultaneous administration of cannabinoids and chemotherapeutic agents may lead to antagonism or to the absence of a clear antitumor benefit, suggesting possible competition between mechanisms or even partial protection of tumor cells against chemotherapy (122). From a translational perspective, these findings suggest that cannabinoid-based therapies may require a tumor-specific approach, rather than a uniform treatment strategy. The variability in cytotoxic responses observed across cell lines indicates that cannabinoids may be more effective in selected tumor types or molecular subgroups. In addition, the consistent activity observed with certain compounds, particularly NC2 and selected synthetic cannabinoids, supports the rationale for further investigation in *in vivo* tumor models and combination regimens

with standard chemotherapy. Another essential aspect in the evaluation of antitumor agents is selectivity and the absence of harmful effects on normal cells, which in our study was assessed through experiments performed on the fibroblast cell line V79. Evaluating cytotoxicity in non-malignant cells provides important information regarding the therapeutic window and safety profile of candidate compounds, helping to distinguish true antitumor activity from nonspecific cellular toxicity. In our experiments, the tested cannabinoids generally showed a more favorable effect on normal fibroblasts compared with tumor cell lines, suggesting a degree of tumor selectivity. The dose-dependent cytotoxic effects observed in our experiments further support the pharmacological activity of cannabinoids in tumor cells and are consistent with previously reported concentration-dependent responses. Cannabinoids typically exhibit biphasic effects, with lower concentrations sometimes producing limited or neutral activity, while higher concentrations induce more pronounced antiproliferative and proapoptotic effects (137). This behavior may reflect differences in receptor activation thresholds, intracellular signaling cascades, and metabolic adaptation of tumor cells. The clear dose-response relationships observed in several of the tested compounds strengthen the interpretation that the antitumor effects identified in this study represent true pharmacological activity rather than nonspecific toxicity, particularly in the context of the preserved viability observed in normal fibroblast cells.

9.1.3 Study III: Despite advances in oncology, many disease and treatment-related symptoms, such as chronic pain, nausea, anorexia, cachexia, remain under-controlled. In this context, cannabinoids have attracted increasing interest from both patients and researchers, being frequently considered as complementary or alternative therapeutic options with potential symptomatic benefits (150). In this context, the present study comparatively evaluated the benefits and potential risks of a synthetic cannabinoid, JWH-182, and two phytocannabinoid preparations, Cannabixir® dried flowers (NC1) and Cannabixir® THC extract (NC2). These compounds have not previously been tested in an experimental tumor model, and their effects on cancer-related symptoms, tumor progression, and immune responses remain largely unknown. Using an orthotopic murine model of triple-negative 4T1 breast cancer with CIPN, we investigated the analgesic, antitumor, metabolic, and immunomodulatory effects of these cannabinoids. Unlike classical neurotransmitter systems, the ECS operates predominantly as a retrograde

signaling system, allowing postsynaptic cells to regulate presynaptic stimuli in response to changes in cellular needs. Pain modulation by cannabinoids includes effects generated through the modulation of endocannabinoid system. This includes CB1R/CB2R, enzymes implicated in synthesis (NAPE-PLD, DAGL) or for degradation (FAAH, MAGL), and ligands AEA and 2-AG (151). CB1R is abundant in CNS pain circuits, and reduces excitatory transmitter release and enhances descending inhibition (152), while CB2R is found on immune cells and dampens pro-inflammatory cytokines, relevant to neuropathic pain and tumor microenvironment (153). The Hot Plate test, considered the gold standard for evaluating supraspinal nociception (154), measures centrally mediated behavioral responses to thermal stimuli, such as paw licking or jumping. These responses involve C and A δ fibers and are integrated in higher brain regions including the thalamus, somatosensory cortex, and descending pain-control pathways (155). In our experiment, PTX-treated animals showed a significantly reduced response threshold, suggesting impairment of descending inhibitory pathways, likely related to neuroinflammation, glial activation, and oxidative stress. Activation of spinal microglia promotes the release of proinflammatory cytokines such as IL-1 β and TNF- α , amplifying nociceptive signaling (156). Treatment with NC1 and NC2 restored near-normal response thresholds, suggesting reduced neuroinflammation and neuroprotective effects. These findings are consistent with our *in vitro* experiments, where co-administration of cannabinoids with PTX prevented neurite shortening in DRG neuronal cultures, an early marker of neuronal injury. THC-mediated effects may be explained by CB1R activation, leading to reduced glutamate and substance P release and decreased central sensitization (157), as well as modulation of glial activation and inflammatory mediators (158). The Tail Flick test, used to assess spinal reflex responses to thermal pain (159), showed moderate hypersensitivity in PTX-treated animals, consistent with spinal hyperexcitability typical of CIPN (128). NC1 and NC2 restored nociceptive thresholds toward normal values, suggesting inhibition of dorsal horn neuronal hyperexcitability. This effect may involve CB1R activation on inhibitory interneurons, enhancing GABAergic transmission and reducing spontaneous neuronal firing (160), as well as modulation of nociceptive ion channels such as NaV1.7 and NaV1.8 (161). The Randall-Selitto test, which evaluates mechanical nociception (162), provided information on peripheral sensitization. PTX-treated animals showed significantly reduced mechanical pain thresholds, reflecting

peripheral nociceptor injury through axonal degeneration, mitochondrial dysfunction, and neurogenic inflammation (163). NC2 showed the strongest protective effect, possibly through modulation of CB1R at peripheral nerve endings and CB2R on immune cells, resulting in reduced inflammatory mediator release, including IL-6 and TNF- α (164). The differences observed among the three tests highlight the hierarchical complexity of pain processing and the distinct roles of supraspinal, spinal, and peripheral mechanisms in CIPN pathogenesis. The analgesic effects of cannabinoids across these levels support a dual, central and peripheral, role in pain modulation. From a translational standpoint, NC1, with its predominantly central action, appears suitable for diffuse pain, central sensitization, and psycho-emotional symptoms such as anxiety or insomnia. NC2, showing broader pharmacological activity and stronger peripheral effects, may be beneficial for localized pain with mechanical allodynia, hypersensitivity, and peripheral inflammation, as seen in chemotherapy-induced axonal neuropathies. Conversely, JWH-182 produced moderate antinociceptive effects, acting mainly at the central level without significantly affecting peripheral sensitization, suggesting utility in neuropathic pain with predominant spinal or central mechanisms but limited peripheral involvement. The orthotopic model induced using the 4T1 tumor cell line mimics triple-negative breast cancer, closely resembling the clinical setting and being characterized by a highly aggressive, invasive, and metastatic behavior (165). In this model, cannabinoid treatment did not significantly reduce primary tumor growth (Specific Growth Rate, SGR) but produced notable and compound-dependent effects on metastatic spread. *In vitro* experiments showed a clear synergistic interaction between PTX and cannabinoids, reducing tumor cell viability below 50%, as presented in study II. This effect is supported by previous studies indicating that cannabinoids may enhance chemotherapy through mechanisms such as apoptosis induction and inhibition of drug-efflux pumps (166,167). However, this antitumor feature did not translate into a significant reduction in tumor growth *in vivo*. Imaging assessments showed no major differences in tumor progression between PTX- and cannabinoid-treated groups. In contrast, metastatic rates differed substantially between groups, suggesting that cannabinoids may influence tumor dissemination through mechanisms independent of primary tumor proliferation. Among the tested compounds, NC1 showed the strongest antimetastatic effect, significantly reducing both the incidence and volume of lung and liver metastases. It produced the

lowest number of metastases per animal and the highest proportion of metastasis-free animals. This effect may be related to its moderate THC content and terpene-rich composition, which may support immune regulation within the tumor microenvironment (168). In contrast, JWH-182 was associated with the highest metastatic rates, even exceeding those observed with PTX alone, suggesting a possible protumoral effect related to CB1R activation (169). NC2 showed intermediate activity, reducing metastases compared with PTX but less effectively than NC1. Histological analysis of primary tumors revealed extensive central necrosis in treated groups, suggesting indirect cytotoxic effects, possibly through hypoxia, vascular alterations, or apoptosis. This indicates a potential adjuvant role of cannabinoids in tumor remodeling despite the absence of clear antiproliferative effects. Metastasis involves multiple processes, including invasion, circulation, and colonization, regulated by inflammation, angiogenesis, and extracellular matrix remodeling (170). Cannabinoids may influence these steps by inhibiting MMP-2 and MMP-9 (171), suppressing NF- κ B signaling (172), and modulating angiogenesis (173). The discrepancy between unchanged primary tumor growth and reduced metastasis suggests that cannabinoids mainly act through tumor microenvironment modulation rather than direct antiproliferative effects, consistent with the known importance of immune interactions and matrix remodeling in advanced cancer (174). Differences between *in vitro* and *in vivo* findings may also reflect pharmacokinetic factors and the dose-dependent biphasic effects of cannabinoids, which may produce either antitumor or protumor responses depending on context (175). An additional mechanism that may explain the tumor-related effects observed in our study is the immunomodulatory activity of cannabinoids. Hematological analyses revealed significant changes in leukocyte subpopulations, reflecting the interaction between PTX-induced immunosuppression and the immunomodulatory effects of cannabinoids. The immune system plays a dual role in cancer progression, either suppressing or promoting tumor growth depending on the nature of the response. All animals presented with leukemoid reaction: increased leukocytes, monocytes, and neutrophils, consistent with tumor-driven myelopoiesis and systemic inflammation (176), a known feature of this aggressive 4T1-induced tumor model. Histological findings, including megakaryocytes in spleen and liver and inflammatory tumor infiltrates, confirmed systemic inflammatory activation, which appeared less pronounced in the NC1 group, possibly contributing to its antimetastatic

effect. Total leukocyte counts were elevated in all groups, consistent with aggressive tumor behavior (177). PTX-treated animals showed reduced lymphocytes, reflecting chemotherapy-induced immunosuppression, whereas NC1 and NC2 increased lymphocyte and platelet counts, suggesting immune restoration. CB2R activation on lymphocytes may promote survival and adaptive immune responses (178). Increased monocytes in cannabinoid-treated groups may support differentiation into tumor-associated macrophages, potentially favoring an antitumor M1 phenotype (179). Platelet counts, markedly reduced by PTX, were partially restored by cannabinoids, especially NC2, indicating improved hematopoietic function without increased metastasis (180). Red blood cell parameters were also better preserved in cannabinoid-treated groups, particularly NC2, possibly reflecting reduced inflammation and improved erythropoiesis (181). Differences in immunomodulatory effects may be explained by receptor specificity: THC-rich preparations (NC1 and NC2), which activate both CB1R and CB2R, showed stronger hematological recovery than JWH-182, a selective CB1R agonist with mainly central effects. Cancer cachexia is a major complication of advanced cancer, characterized by weight loss, anorexia, systemic inflammation, and muscle wasting (182). In this model, PTX-treated animals showed reduced food intake, consistent with chemotherapy-related appetite suppression mediated by hypothalamic dysfunction and inflammatory cytokines (183). The effects on appetite varied by compound administration. While JWH-182 produced a modest increase in food intake during the early phase, likely through central CB1R-mediated orexigenic effects (184), NC1 and NC2 induced a paradoxical anorexigenic effect despite their high THC content, possibly related to peripheral CB2R activation and the presence of terpenes with sedative or aversive properties (185). Despite differences in food intake, body weight remained relatively stable across groups, suggesting compensatory mechanisms such as metabolic adaptation or fat mobilization. This dissociation between appetite and body weight highlights that short-term appetite changes do not necessarily reflect cachexia severity. Moreover, MRI assessment of muscle mass showed no consistent evidence of muscle atrophy in treated groups, except for a localized reduction in left psoas area in the NC2 group, possibly related to the proximity of the tumor. Regarding histopathological analysis, there were modifications revealed when analysing the hepatic and renal preparations. In case of liver modifications, control and JWH-182 showed severe

sinusoidal congestion, hepatocellular ballooning, and inflammation, while NC1 and NC2 presented milder inflammation but diffuse vacuolar degeneration, indicating impaired cellular homeostasis. In case of kidney modifications, all groups showed glomerular injury. Control and JWH-182 presented mild ischemic and tubular changes, whereas NC1 and NC2 caused extensive glomerular atrophy, tubular degeneration, and acute necrosis, suggesting greater ischemic susceptibility with PTX plus phytocannabinoids.

9.1.4 Study IV: By conducting a comprehensive meta-analysis, Study IV makes an important contribution by providing, for the first time, robust and clinically relevant evidence supporting the benefits of cannabinoids in reducing cancer-related pain and anxiety. Our analysis also suggests potential improvements in appetite, sleep disturbances, and CINV. However, these benefits must be considered alongside the safety profile, which indicates increased risks of neurological, psychiatric, and gastrointestinal adverse effects. Pain has shown inconsistent responses to cannabinoid treatment. Previous RCT-based meta-analyses focused mainly on Nabiximols, an oromucosal spray with 1:1 ratio of THC and CBD, failed to demonstrate clear clinical benefit (186–188). In contrast to these studies, our meta-analysis integrates data from both randomized and observational studies, encompassing a broader range of cannabinoid-based therapies, with results supporting the hypothesis that cannabinoids may provide a real benefit in the management of cancer-related pain. Interpretation is complicated by the heterogeneous etiologies of cancer pain (nociceptive, neuropathic, bone, and visceral), which could not be analyzed separately in our study. In addition, patients were included at different stages of disease (from curative to metastatic settings), resulting in substantial variability in reported symptom severity. Another limitation is the lack of uniform product standardization, as only five studies reported the use of GMP-certified preparations, potentially affecting the consistency and reproducibility of the findings (65,80,84,90,104,111). Anxiety was generally evaluated in trials as a secondary outcome, and previous meta-analysis assessments, including the Multinational Association of Supportive Care in Cancer (MASCC) evaluation, were unable to recommend cannabinoids for anxiety, depression, or insomnia due to data heterogeneity (189). Nevertheless, our analysis shows that oncology patients using cannabinoids experienced a clinically significant reduction in anxiety levels, particularly those receiving CBD-based products. Although these findings are promising and represent one of the first clear

reports of benefits for both pain and anxiety, the certainty of evidence remains low according to GRADE, mainly due to the variability of study populations and interventions. Only four of the eight studies evaluating anxiety used standardized cannabinoid formulations (80,90,95,102,104,111). Balanced THC:CBD formulations showed a tendency to improve appetite, contrasting with RCT-only meta-analyses that found no clear benefit and led to the absence of guideline recommendations (190). Cannabinoids such as dronabinol or nabilone, as well as balanced THC:CBD preparations, remain recognized adjuncts for refractory CINV, although evidence is moderate (191). Much of the available literature analysed originates from the 1980s, before the introduction of modern antiemetic strategies. Our analysis provides a more updated perspective, suggesting possible benefits of cannabinoids for nausea and insomnia, although without sufficient statistical strength for firm recommendations. The safety profile revealed important risks, emphasizing the need for careful and individualized dose titration, particularly in cannabinoid-naïve patients (191). Psychiatric adverse events were the most frequent, often leading to treatment discontinuation, especially with THC-dominant products, consistent with the known psychiatric effects of recreational THC use (192). In contrast, CBD appears to mitigate THC-induced psychotropic effects, and its co-administration significantly reduced psychiatric adverse events (193). Common neurological symptoms included confusion, dizziness, impaired concentration, coordination difficulties, and somnolence, likely related to the high density of cannabinoid receptors in the central nervous system (5). One issue is the lack of dosing standardization across trials, as many patients self-adjusted doses, contributing to substantial variability. Interpretation is further complicated by the biphasic effects of cannabinoids, whereby low THC doses may reduce pain while higher doses may worsen pain and anxiety (76,194). Differences in administration routes and THC/CBD composition also contributed to heterogeneity. Subgroup analyses suggested that balanced THC:CBD products may be most effective for sleep and appetite, CBD-dominant products for anxiety, and THC-dominant products for pain and nausea. Moreover, the chemical complexity of cannabis, which contains more than 500 bioactive compounds contributing to the entourage effect, likely represents an additional source of variability in clinical outcomes (141).

9.1.5 Study V: This study provides the most comprehensive systematic synthesis to date of preclinical evidence regarding the antitumor effects of cannabinoids across a wide spectrum of cancer models. A major strength of this work is the explicit distinction between monotherapy and combination strategies, which revealed distinct and clinically relevant activity patterns. Overall, cannabinoids produced consistent and statistically significant antitumor effects in glioblastoma and breast cancer models, with additional supportive evidence in lung and prostate cancer. In contrast, findings were more variable in digestive tract tumors, largely neutral in hepatocellular carcinoma, and occasionally protumoral in colon, pancreatic, and selected prostate models, particularly when THC was administered as monotherapy. The chemosensitizing potential of cannabinoids emerged most clearly in breast cancer models, where both CBD and THC enhanced the efficacy of cytotoxic agents. These observations are consistent with mechanistic studies showing that cannabinoids may sensitize tumor cells through autophagy induction, ceramide accumulation, and endoplasmic reticulum stress pathways (195). Such findings suggest that cannabinoids may function primarily as potentiators rather than replacements of conventional chemotherapy, an approach that is particularly attractive given the dose-limiting toxicities associated with standard cytotoxic treatments. However, antagonistic interactions observed in prostate cancer models indicate that not all cannabinoid-chemotherapy combinations are beneficial, emphasizing the need for careful preclinical evaluation prior to clinical translation. Among all tumor types, glioblastoma showed the most consistent and reproducible evidence base, with robust monotherapy activity and a coherent mechanistic rationale across experimental models. These findings are supported by clinical data: a phase Ib randomized trial demonstrated that nabiximols combined with temozolomide improved survival in patients with recurrent glioblastoma making glioblastoma the most compelling candidate for cannabinoid-based therapeutic strategies (196). Breast cancer also appears promising, although heterogeneity in outcomes suggests that factors such as cannabinoid type, tumor subtype, and receptor expression patterns may influence therapeutic response (197). By contrast, gastrointestinal cancers, particularly colorectal and pancreatic tumors, have shown inconsistent or unfavorable responses, possibly reflecting differences in receptor distribution, tumor microenvironment, or oncogenic signaling pathways (148). The divergent activity patterns observed across tumor types also highlight the importance of compound

selection. CBD demonstrated the broadest and most favorable antitumor profile, with consistent inhibitory activity across multiple tumor models and the advantage of an established clinical safety record (198). Synthetic CB2R agonists also showed promising activity, although their limited clinical data require further evaluation in early-phase trials. In contrast, THC produced highly variable outcomes, ranging from strong tumor inhibition in glioblastoma to neutral or even protumoral effects in breast and colon cancer. These findings are consistent with reports suggesting that CB1-mediated immunosuppressive signaling may counterbalance direct cytotoxic effects (199). Formulations combining THC and CBD, may mitigate some of these limitations by balancing receptor-mediated effects and reducing the risk of protumoral activity (200). Nevertheless, therapeutic responses remained strongly tumor-type dependent, highlighting the need for individualized approaches in future cannabinoid-based research.

9.2 Strengths (including all studies)

Study I: This study successfully established and optimized primary DRG neuron cultures, a technically demanding model that offers high physiological relevance for studying CIPN. The use of these primary neurons allowed precise, time-resolved tracking of axonal degeneration from 6h to 72 hours. Another strength is the comparative evaluation of multiple synthetic and plant-derived cannabinoids, tested both alone and in combination with PTX, which provides a broad and nuanced view of their neuroprotective potential.

Study II: This study evaluated cannabinoids across multiple cancer cell lines, allowing clear comparison of tumor-specific sensitivity. It is the first to report antitumor effects of JWH-182, JWH-007, AM-694, MAB-CHMINACA, NC1 and NC2. The dose-response design enabled consistent assessment of cytotoxic potency. Including non-tumoral fibroblasts strengthened conclusions on selectivity and safety.

Study III: This study offers an integrated in vivo evaluation of synthetic and phytocannabinoids in a 4T1 breast cancer model combining pain, tumor progression, and cachexia. It employed multimodal methods, imaging, hematology, and histopathology, under rigorous ethical and methodological standards. Comparing JWH-182, NC1, and NC2 enabled insight into receptor-specific and multi-target cannabinoid effects with translational relevance for oncology.

Study IV: This review's strengths comes from the fact that it is the most comprehensive and up-to-date synthesis of cannabinoid use in oncology, combining RCTs and real-world studies, evaluating multiple cannabinoid types and formulations, and

covering a broad range of efficacy and safety outcomes. Its large sample allowed meaningful subgroup analyses, and the methodology followed guidelines with transparent reporting. **Study V:** The strengths of our review include its comprehensive integration of preclinical evidence, prospective protocol registration, rigorous methodology, and clear separation of monotherapy versus combination strategies. This design allowed us to identify cancer-specific response patterns and pinpoint settings where cannabinoids may have the greatest translational potential.

9.3 Limitations (including all studies)

Study I: As an in vitro system, the model lacks glial, immune, and vascular interactions that contribute to CIPN in vivo. Axonal length served as the main readout, but additional cellular markers (mitochondrial function, oxidative stress, apoptosis) would have strengthened mechanistic insight. The study also used fixed doses for each cannabinoid, so full dose-response profiles and optimal therapeutic windows remain to be defined.

Study II: Being an in vitro study, the findings may not fully reflect in vivo tumor complexity. Mechanistic pathways were not explored beyond viability assays. Long-term effects and resistance development were not assessed. **Study III:** The short study duration and single-dose design limit conclusions on long-term safety and dose-response relationships. Moreover, the aggressive 4T1 model may mask subtle effects. Lack of molecular analyses (e.g., receptor or cytokine profiling) restricts mechanistic interpretation. **Study IV:** The majority of the evidence comes from observational trials with high risk of bias, raising concerns about placebo effects and the reliability of quality-of-life outcomes. Significant heterogeneity across populations, interventions, and study designs further weakens certainty. Many included studies were older trials from the 1980s with high methodological risk, yet they still influence current clinical guidelines. **Study V:** The evidence base is limited by substantial variability in tumor models, cannabinoid formulations, and dosing regimens, which hinders direct comparison across studies. Most experiments used xenografts, restricting insight into immune-mediated effects and tumor-microenvironment interactions. Methodological quality was generally low, with frequent issues in randomization, blinding, and allocation concealment. Small sample sizes, heterogeneous protocols, and probable publication bias further complicate interpretation. These limitations reflect common challenges in preclinical oncology research and highlight the need for greater methodological standardization and transparency.

10 CONCLUSIONS

JWH-182, JWH-007, AM-694, and NC1 demonstrated sustained neuroprotective effects, preserving neuronal viability and markedly attenuating PTX-induced axonal degeneration in a clear, concentration-dependent manner. These effects were accompanied by improved neurite integrity and reduced markers of cytoskeletal disruption, supporting a direct protective action on neurons exposed to chemotherapeutic stress. In vitro antitumor activity was highly tumor-dependent: NC2 exhibited the most robust and consistent cytotoxicity across all tested cancer cell lines, whereas MAB-CHMINACA, JWH-182, and AM-694 showed moderate antiproliferative effects. In contrast, NC1 remained largely non-cytotoxic toward non-malignant cells, suggesting a favorable therapeutic index and supporting its use primarily as a symptom-modulating rather than antitumoral agent. In the murine breast cancer model, cannabinoid treatment significantly reduced neuropathic pain behaviors, partially restored immune and hematologic homeostasis, and limited metastatic dissemination, with overall favorable short-term tolerability. Notably, NC1 produced the most consistent central analgesic effects and the strongest suppression of lung and liver metastases, indicating a potential role in modulating both nociceptive processing and metastatic spread. NC2 was superior in alleviating mechanical hypersensitivity and promoting lymphocyte and platelet recovery, suggesting enhanced peripheral analgesic and immuno-supportive properties. JWH-182 provided moderate analgesia while improving appetite and preserving body weight, aligning with its mixed neuromodulatory and metabolic effects. Although none of the cannabinoids surpassed PTX in direct tumor growth inhibition, their combined modulation of pain pathways, systemic inflammation, immune balance, and the tumor microenvironment underscores their potential value as adjuvant agents rather than primary anticancer therapies. Systematic review and meta-analysis revealed clinically meaningful palliative benefits of cannabinoids on pain, anxiety, appetite loss, insomnia, and CINV. Analgesic efficacy was predominantly associated with THC-dominant formulations, whereas anxiolytic effects were more consistently observed with CBD-dominant products. However, clinical implementation remains constrained by psychiatric adverse effects, particularly with THC-rich regimens and higher doses. Data from the second meta-analysis confirmed clear antitumor benefits in several cancer murine models. Results were clearly tumor and cannabinoid specific, with CBD having greater

effects in breast cancer and THC showing more pronounced effects in glioblastoma, while showing additional chemosensitizing activity. However, cannabinoids conducted to protumoral activity in pancreatic cancer, warranting for caution with administration. Collectively, these data support a translational framework in which cannabinoids are positioned as multifunctional adjuvant agents in oncology, contributing to improved chemotherapy tolerability, symptom burden reduction, and selective modulation of tumor biology. At the same time, they highlight the critical need for standardized formulations, optimized dosing strategies, and rigorous long-term safety evaluation to enable rational and evidence-based clinical integration.

11 IMPLICATIONS FOR PRACTICE

Evidence from both experimental and clinical data supports the benefits of cannabinoids as adjuvant agents in oncology, primarily for symptom control. Cannabinoids may relieve pain, anxiety, and appetite loss while potentially improving sleep and reducing nausea and vomiting. Their ability to preserve neuronal integrity, normalize nociceptive thresholds, and stabilize hematologic parameters aligns with the need for opioid-sparing, multimodal pain strategies. However, careful dosing and patient selection are critical, given the psychiatric and neurological adverse effects. Regarding antitumor potential, cannabinoids should not be viewed as standalone cytotoxic but rather as supportive agents capable of enhancing chemotherapy tolerability and modulating tumor microenvironmental dynamics. Clinical translation should emphasize standardized THC:CBD formulations, controlled administration protocols, and robust safety monitoring. Multicenter trials integrating imaging, biomarkers, and pharmacovigilance endpoints are warranted to define optimal indications, dosage, and risk-benefit balance in cancer patients.

12 IMPLICATIONS FOR RESEARCH

Across both in vitro and in vivo investigations, as well as systematic review and meta-analyses, cannabinoids demonstrated multidimensional potential, ranging from neuroprotection and analgesia to modulation of tumor biology. Further research should explore the mechanistic underpinnings of these effects, focusing on molecular targets beyond CB1R/CB2R, such as TRP channels, PPARs, serotonergic pathways, and immune-related signaling cascades. Advanced in vitro co-culture systems (neurons, glia, endothelium) and chronic animal models are needed to better mimic CIPN and cachexia. For anticancer activity, future work must clarify the context-specific, sometimes biphasic actions of cannabinoids, defining when they act synergistically, additively, or antagonistically with chemotherapy. Mechanistic studies should assess angiogenesis, immune infiltration, and stromal remodeling to understand how cannabinoids influence the tumor microenvironment. Meta-analytical evidence confirms that while cannabinoids show preclinical antitumor efficacy, especially in glioblastoma and breast cancer, results remain inconsistent in gastrointestinal models. Standardized cannabinoid formulations, transparent reporting, and pharmacokinetic-pharmacodynamic profiling are essential to ensure reproducibility and guide translation toward early-phase clinical trials.

13 IMPLICATIONS FOR POLICYMAKERS

The combined findings from preclinical and meta-analysis research call for policy frameworks that enable the responsible integration of cannabinoids into oncology. Policymakers should recognize cannabinoids as legitimate therapeutic candidates for managing cancer-related symptoms and as potential adjuncts in cancer therapy. Regulatory pathways must ensure controlled access to standardized, GMP-certified formulations and facilitate the conduct of high-quality clinical trials focused on pain, cachexia, and adjunctive antitumor therapy. At a broader level, national research agendas should prioritize funding for translational studies that bridge laboratory and clinical evidence while promoting data transparency and safety monitoring. Establishing harmonized standards for cannabinoid research, covering formulation, dosing, and reporting, will foster international collaboration and accelerate the evidence base. Educational initiatives for healthcare professionals are equally vital to support informed prescribing, minimize misuse, and enhance patient safety. By promoting coherent regulation and sustained research investment, policymakers can transform cannabinoids from experimental tools into validated, evidence-based components of cancer care.

14 FUTURE PERSPECTIVES

Future research should seek to elucidate the molecular and cellular pathways underlying the dual neuroprotective and cytotoxic effects of cannabinoids, with particular attention to receptor specificity, dose-response dynamics, and their interactions with chemotherapeutic agents. Expanding research toward chronic and immunocompetent *in vivo* models will help capture long-term safety, immune modulation, and tumor-microenvironment dynamics. Standardization of cannabinoid formulations, pharmacokinetic profiling, and biomarker-based patient stratification are essential steps toward clinical translation. Large, well-designed clinical trials should evaluate cannabinoids as adjuvants for neuropathic pain, cachexia, and chemotherapy tolerance, while exploring their role as modulators of tumor progression. Ultimately, integrating cannabinoid-based strategies into oncology requires a multidisciplinary approach, linking basic science, clinical research, and regulatory policy, to develop safe, evidence-driven therapies that improve both quality of life and treatment outcomes for cancer patients.

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a. Publications related to the thesis

1. Should oncologists trust cannabinoids?

Authors: *Creanga-Murariu I*, Filipiuc LE, Cuciureanu M, Tamba BI, Alexa-Stratulat T.

Journal: Frontiers in Pharmacology

doi: 10.3389/fphar.2023.1211506.

IF, quartile: 4.8, Q1

2. JWH-182: a safe and effective synthetic cannabinoid for chemotherapy-induced neuropathic pain in preclinical models.

Authors: Filipiuc LE, *Creangă-Murariu I*, Tamba BI, Ababei DC, Rusu RN, Stanciu GD, Ștefanescu R, Ciorpac M, Szilagyi A, Gogu R, Filipiuc SI, Tudorancea IM, Solcan C, Alexa-Stratulat T, Cumpăt MC, Cojocaru DC, Bild V.

Journal: Scientific Reports

Doi: 10.1038/s41598-024-67154-y.

IF, quartile: 3.9, Q1

3. The potential neuroprotective effects of cannabinoids against paclitaxel-induced peripheral neuropathy: *in vitro* study on neurite outgrowth.

Authors: *Creanga-Murariu I*, Filipiuc LE, Gogu MR, Ciorpac M, Cumpat CM, Tamba BI, Alexa-Stratulat T. The potential neuroprotective effects of cannabinoids against paclitaxel-induced peripheral neuropathy: *in vitro* study on neurite outgrowth.

Journal: Frontiers in Pharmacology

doi: 10.3389/fphar.2024.1395951.

IF, quartile: 4.8, Q1

4. Indications of Cannabinoids for the Palliation of Cancer-Associated Symptoms: A Systematic Review and Meta-Analysis

Authors: *Creangă-Murariu I*, Rezuș II, Karami R, Rancz A, Zolcsák Á, Engh MA, Obeidat M, Tamba BI, Hegyi P, Bunduc S.

Journal: Current Oncology Reports

doi: 10.1007/s11912-025-01695-x.

IF, quartile: 5, Q1

5. Multifaced roles of cannabinoid therapy in cancer: balancing analgesia, antitumor potential, and systemic toxicity

Authors: *Creanga-Murariu Ioana* , Ciorpac Mitica , Gogu Raluca-Maria , Pricope Cosmin-Vasilica , Bild Veronica , Ababei Daniela-Carmen , Filipiuc Leontina-Elena , Szilagyi Andrei , Josan Claudiu-Laurentiu , Caruntu Irina-Draga , Lozneau Ludmila , Timofte Andrei , Solcan Carmen , Scripcariu Dragos-Viorel , Hegyi Peter , Alexa-Stratulat Teodora , Tamba Bogdan-Ionel.

Journal: Frontiers in Pharmacology

doi: 10.3389/fphar.2025.1691893

IF, quartile: 4.8, Q1

6. Antitumor Activity of Cannabinoids and Their Interaction with Chemotherapy: A Systematic Review and Meta-Analysis of Preclinical Evidence

Authors: Creangă-Murariu, I., Rezuș, I.-I., Karami, R., Makolli, A., Chifu, C., Rancz, A., Sipos, Z., Ferdinandy, P., Papp, R., Teutsch, B., Tamba, B.-I., Hegyi, P., & Bunduc, S

Journal: Pharmaceuticals

Doi: <https://doi.org/10.3390/ph19050768>

IF, quartile: 4.8, Q1

b. Publications not related to the thesis

1. Schreiner TG, **Creangă-Murariu I**, Tamba BI, Lucanu N, Popescu BO. In Vitro Modeling of the Blood-Brain Barrier for the Study of Physiological Conditions and Alzheimer's Disease. *Biomolecules*. 2022 Aug 18;12(8):1136. doi: 10.3390/biom12081136. PMID: 36009030; PMCID: PMC9405874. **IF 4.8, Q1**
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4. Filipiuc LE, Ștefănescu R, Solcan C, Ciorpac M, Szilagyi A, Cojocaru D, Stanciu GD, **Creangă I**, Caratașu CC, Ababei DC, Gavrilă RE, Timofte AD, Filipiuc SI, Bild V. Acute Toxicity and Pharmacokinetic Profile of an EU-GMP-Certified *Cannabis sativa* L. in Rodents. *Pharmaceuticals (Basel)*. 2023 May 3;16(5):694. doi: 10.3390/ph16050694. PMID: 37242477; PMCID: PMC10223347. **IF 4.8, Q1**
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