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REVIEW

Cannabidiol-Induced Tumor Cell Death: Molecular Mechanisms and Translational Perspectives in Cancer Therapy

Chi-Yang Wang[1,*], Jia-Xin Tan[1,*], Lu-Lin Chen[1], Qing-Zhong Li[2], Jie Liu[1], Xuan He[1], Quan-Zhi Qin[3], Teng Deng[2], Guo-Tian Ruan[4], Yi-Zhen Gong[1,5,6]

[1]Department of Clinical Research, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China; [2]Department of Neurosurgery, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China; [3]Department of Pharmacy, Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi, People's Republic of China; [4]Department of General Surgery, Beijing Friendship Hospital, Capital MedicalUniversity, Beijing, People's Republic of China; [5]University Engineering Research Center of Oncolytic & Nanosystem Development,Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China; [6]Guangxi Key Laboratory of Extremely Weak Magnetic Field in Cancer Medicine, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yi-Zhen Gong, Department of Clinical Research, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China, Tel +86-13607887067, Fax +86-771-5312000, Email gongyizhen@gxmu.edu.cn; Guo-Tian Ruan, Department of General Surgery, Beijing Friendship Hospital, Capital MedicalUniversity, Beijing, 100050, People's Republic of China, Email gxmuruanguotian@163.com

Background: Cannabidiol (CBD), a major non-psychoactive phytocannabinoid derived from Cannabis sativa, has attracted increasing attention as a potential anticancer agent because of its pleiotropic biological activities and favorable safety profile. However, the mechanisms by which CBD regulates tumor cell death and their therapeutic relevance remain incompletely understood.

Methods and Results: This review summarizes current evidence on the molecular mechanisms by which CBD regulates tumor cell death across different cancer models. Available studies indicate that CBD exerts antitumor effects through multi-target and multi-pathway mechanisms involving oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, calcium homeostasis imbalance, and modulation of signaling networks such as PI3K/Akt/mTOR, MAPK, NF-κB, and PPARγ. Through these interconnected processes, CBD can induce apoptosis, autophagy, ferroptosis, pyroptosis, and cell cycle arrest in a context-dependent manner. Notably, CBD may activate multiple regulated cell death pathways simultaneously or sequentially within the same tumor model, reflecting a broader stress-response network rather than a single cytotoxic mechanism.

Therapeutic Implications: By coordinately engaging multiple cell death pathways and modulating the tumor microenvironment, CBD provides mechanistic insights and potential opportunities for the development of novel anticancer strategies. However, current evidence remains predominantly preclinical, while challenges related to oral bioavailability, pharmacokinetic variability, dose optimization, and potential drug interactions continue to limit translational progress.

Conclusion: Collectively, available evidence suggests that CBD functions as a pleiotropic modulator of tumor cell fate rather than a classical single-target cytotoxic agent. Further mechanistic, pharmacological, and clinical studies are required to support the rational development of CBD-based anticancer therapies.

Keywords: cannabidiol, tumor cell death, signaling pathways, antitumor therapy

Research Background

Cancer remains one of the leading causes of morbidity and mortality worldwide, driven by complex dysregulation of genetic programs, metabolic networks, and intracellular signaling pathways.[1] Although surgical resection, radiotherapy, chemotherapy, and targeted therapies have improved clinical outcomes in certain malignancies, their long-term efficacy is frequently limited by systemic toxicity, drug resistance, and tumor heterogeneity.[2] Therefore, the identification of novel

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anticancer agents with favorable safety profiles and multifaceted mechanisms of action remains a critical priority in oncology and drug development.

Cannabidiol (CBD), a major non-psychoactive phytocannabinoid derived from Cannabis sativa, has attracted increasing attention as a potential anticancer agent due to its multimodal capacity to induce tumor cell death.[3–5] Accumulating evidence indicates that CBD influences tumor cell fate not only through the classical endocannabinoid system but also by engaging diverse cellular stress responses,[6] including oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction.[7–9] This multimodal regulation of cell death enables CBD to exert broad antitumor activity across multiple cancer models while exhibiting relatively low cytotoxicity toward normal cells, highlighting its potential therapeutic selectivity.

Research Significance

Nevertheless, a systematic understanding of how CBD selectively activates distinct cell death pathways across different tumor types—and how these mechanisms interact within an integrated regulatory network—remains limited.

This review aims to synthesize current knowledge regarding the molecular mechanisms by which CBD regulates tumor cell death and to evaluate their implications for anticancer drug development and therapeutic application. By integrating mechanistic insights with pharmacological and translational considerations, this review seeks to provide a conceptual framework to facilitate the progression of CBD-based anticancer strategies from preclinical investigation toward clinical translation.

Association Between the Biological Effects of Cannabidiol and the Regulation of Tumor Cell Death

CBD is a major non-psychoactive phytocannabinoid derived from Cannabis sativa, alongside Δ^9-tetrahydrocannabinol (Δ^9-THC) as a principal bioactive component. Although CBD and Δ9-THC share the same molecular formula (C21H30O2),[10,11] they differ in three-dimensional structure and conformational flexibility, which contributes to their distinct receptor pharmacology and to the lack of overt psychotomimetic effects of CBD.[12–16] Although CBD does not bind with high affinity to canonical endocannabinoid receptors,[17] emerging evidence indicates that it broadly modulates cellular functions through multi-target, multi-pathway interactions, thereby establishing a mechanistic basis for its role in regulating tumor cell death.[18] Beyond oncology, CBD has demonstrated therapeutic potential in neurological and inflammatory conditions, including Parkinson's disease,[19] Alzheimer's disease,[20] and refractory epilepsy.[21,22]

Although widely recognized for its anti-inflammatory and antioxidant properties, substantial preclinical evidence supports CBD's antitumor activity.[23] CBD exhibits high lipophilicity, facilitating widespread tissue distribution, blood-brain barrier penetration, and accumulation in adipose tissue—a pharmacokinetic profile that may contribute to its enrichment within tumor microenvironments. Extensive in vitro studies demonstrate that CBD inhibits the viability of diverse cancer cell types in a dose-dependent manner, including breast cancer,[24] glioma,[25] glioblastoma,[26] colorectal cancer,[27] gastric cancer,[28] and melanoma,[29] among others.

CBD undergoes extensive hepatic metabolism through both Phase I oxidation and Phase II conjugation. Current evidence suggests that UGT-mediated conjugation, particularly involving UGT2B7, may contribute substantially to overall CBD clearance, whereas CYP-dependent metabolism mainly participates in oxidative biotransformation, among the CYP enzymes, CYP2C19 and CYP2C9 appear to be major contributors to 7-hydroxylation, while CYP3A4 is thought to contribute predominantly to oxidation at sites other than the 7-position.[30,31] CBD itself can inhibit the activity of CYP2C19 and CYP3A4, raising the potential for drug-drug interactions when co-administered with agents such as clobazam, valproic acid, warfarin, certain calcium channel blockers, or immunosuppressants. These interactions may lead to elevated plasma concentrations of concomitant drugs and associated adverse effects, necessitating careful therapeutic monitoring of liver function and drug levels, as well as appropriate dose adjustments.[14,32] The capacity of CBD to modulate CYP450-mediated metabolism underscores the importance of vigilance in combination therapies and enhanced toxicity surveillance in clinical practice.

Mechanistically, the antitumor effects of CBD are not confined to a single receptor but involve the integrated modulation of diverse cellular processes—including redox balance, calcium signaling, energy metabolism, and stress responses—that collectively determine tumor cell fate. Overall, CBD exhibits a broad and complex pharmacological profile, extending beyond the endocannabinoid system to regulate cellular functions through multi-target, multi-pathway engagement. Its favorable safety record and pleiotropic biological activities[33] position CBD as a promising candidate for antitumor therapy.[34] Further elucidation of its receptor interaction landscape and downstream signaling networks will help clarify the molecular underpinnings of CBD-induced tumor cell death and provide a stronger rationale for its translational development in oncology.

Key Molecular Mechanisms of CBD in Regulating Tumor Cell Death

CBD has demonstrated substantial cytotoxicity across diverse tumor models.[26,28,29,35–37] Its antitumor mechanisms primarily involve the modulation of oxidative stress, mitochondrial function, endoplasmic reticulum stress, key signaling pathways, and the tumor microenvironment (Figure 1). These interconnected processes collectively drive metabolic dysregulation and promote programmed cell death in malignant cells.

Mechanisms Related to Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is a state in which the excessive accumulation of reactive oxygen species (ROS)—produced by mitochondrial respiration or exogenous stimuli—overwhelms the cellular antioxidant defense system.[38,39] This disruption of redox equilibrium leads to oxidative damage of macromolecules, including proteins, lipids, and DNA, subsequently perturbing signaling pathways, promoting inflammation, and inducing apoptosis or senescence.[38,39] Oxidative stress is intimately linked to the pathogenesis of numerous diseases.[40] A key mechanism through which CBD induces tumor cell death involves the dysregulation of oxidative homeostasis. CBD augments intracellular ROS generation while impairing antioxidant defenses—such as glutathione synthesis and superoxide dismutase activity—thereby disrupting redox balance and inflicting structural and functional damage on mitochondria.[41] Elevated oxidative stress can promote mitochondrial permeability transition, loss of $\Delta\Psi m$, and cytochrome c release, thereby facilitating caspase-dependent apoptosis.[42–44] Moreover, CBD interferes with mitochondrial metabolism by modulating the tricarboxylic acid cycle and oxidative phosphorylation, leading to reduced ATP synthesis and cellular energy depletion.[45] The convergence of persistent oxidative stress and bioenergetic crisis ultimately drives tumor cells into irreversible death programs.

Endoplasmic Reticulum Stress and Calcium Ion Homeostasis Imbalance

CBD can also modulate tumor cell fate by inducing endoplasmic reticulum (ER) stress. Under stress conditions, CBD can directly impair mitochondrial function and enhance ROS production, which secondarily disrupts intracellular Ca2+ handling and aggravates ER stress-associated apoptotic signaling.[9] Additionally, CBD may disrupt intracellular Ca2+ homeostasis and ER-associated Ca2+ handling, while impaired SERCA function may contribute to reduced Ca2+ reuptake and disturbed cellular Ca2+ balance.[46–48] This dysregulation potentiates CHOP- and caspase-12-mediated pro-apoptotic signaling pathways. In some resistant tumor models, CBD alone can induce ER stress and thereby promote cancer cell death or resensitization, highlighting ER stress as an important mechanistic node rather than presuming universal synergy with chemotherapy.[49]

Regulatory Mechanisms of Signaling Pathways

CBD exerts its biological effects not through a single molecular target but by modulating multiple receptors and signaling pathways. Although closely associated with the classical endocannabinoid system, CBD exhibits low direct affinity for cannabinoid receptors CB1 and CB2, and primarily functions as a negative allosteric modulator or an indirect antagonist.[50] This pharmacological profile allows CBD to influence downstream signaling cascades without eliciting pronounced psychoactive effects. Beyond the endocannabinoid system, CBD engages several atypical molecular targets. Among these, the transient receptor potential vanilloid 1 (TRPV1) channel serves as a key mediator. CBD activates TRPV1, leading to increased intracellular Ca^{2+} concentrations, which in turn trigger oxidative stress responses and initiate cell death signaling.[51] CBD also activates peroxisome proliferator-activated receptor γ (PPARγ), enhancing its transcriptional activity. This action

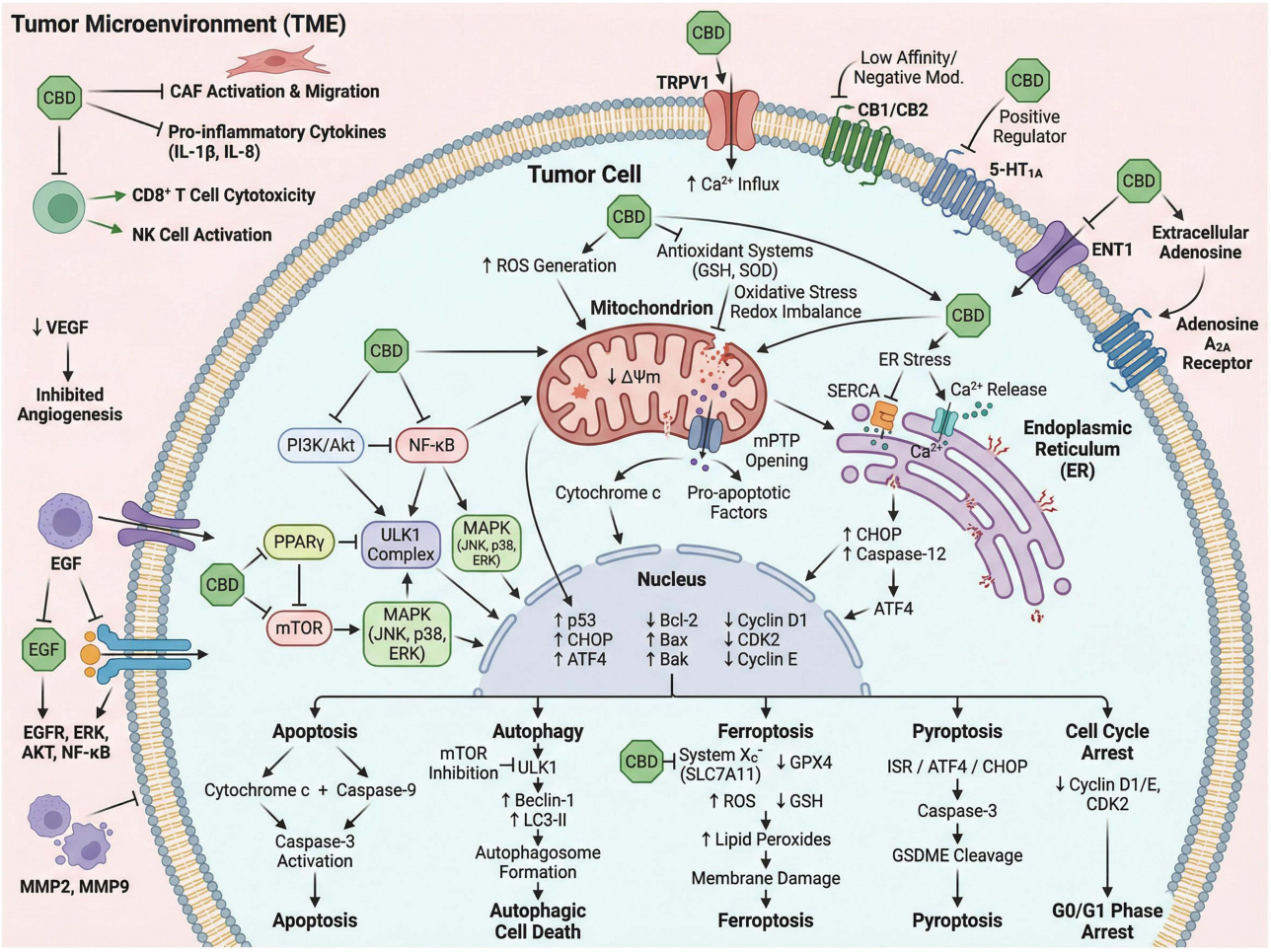

Figure 1 CBD coordinately regulates tumor cell death through multi-target and multi-pathway mechanisms, which mainly include: (1) Induction of apoptosis and programmed cell death. Activates the Transient Receptor Potential Vanilloid 1 (TRPV1) channel and inhibits Sarco/endoplasmic Reticulum Ca^2+ ATPase (SERCA), leading to mitochondrial dysfunction and oxidative stress, resulting in Reactive Oxygen Species (ROS) accumulation and Bcl-2/Bax ratio imbalance, thereby activating the caspase cascade. Meanwhile, CBD can induce autophagy by inhibiting the Mammalian Target of Rapamycin (mTOR) pathway and trigger Ferroptosis by suppressing Glutathione Peroxidase 4 (GPX4) and System Xc-. (2) Modulation of key signaling pathways and the cell cycle. Inhibits survival signals such as Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/Akt) and Nuclear Factor Kappa B (NF-κB), activates the Mitogen-Activated Protein Kinase (MAPK) pathway (eg JNK, p38, ERK), and downregulates cyclins Cyclin D1/E and Cyclin-Dependent Kinase 2 (CDK2), inducing G0/G1 phase arrest. (3) Remodeling of the Tumor Microenvironment (TME). Suppresses Cancer-Associated Fibroblast (CAF) activation and the secretion of proinflammatory cytokines Interleukin-1β/8 (IL-1β/8); downregulates Vascular Endothelial Growth Factor (VEGF) to inhibit angiogenesis; restrains invasion and metastasis by modulating Epidermal Growth Factor Receptor (EGFR)/Extracellular Signal-Regulated Kinase (ERK) signaling and Matrix Metalloproteinase 2/9 (MMP2/9) expression; and enhances the activity of CD8+ T cells and Natural Killer (NK) cells, coordinating anti-tumor immune responses. In summary, CBD exerts antitumor effects through multi-level and multi-mechanistic synergy, providing a theoretical basis for its application in precision oncology therapy.
Notes: ↑, increased/enhanced/promoted; ↓, decreased/reduced/inhibited.

suppresses the NF-κB signaling pathway, reduces pro-inflammatory cytokine production, and promotes tumor cell differentiation and apoptosis.[52] Additionally, CBD acts as a positive allosteric modulator of the serotonin receptor 5-HT1A, potentiating its signaling, which may contribute to apoptosis regulation by modulating the cellular stress response.[53] Furthermore, CBD inhibits the equilibrative nucleoside transporter 1 (ENT1), elevating extracellular adenosine levels and thereby enhancing adenosine A2A receptor activation—a mechanism that can modulate immune cell function and inflammatory processes within the tumor microenvironment.[54] In addition, CBD has been reported to modulate endocannabinoid metabolic enzymes such as FAAH, inhibit voltage-gated sodium channels, and interact with orphan or endocannabinoid-related GPCRs including GPR55.[51,55,56] Among these atypical targets, GPR55 appears particularly relevant to cancer-associated signaling, given the established involvement of the LPI/GPR55 axis in tumor proliferation, migration, and metastasis.[57–60]

Impact on the Tumor Microenvironment

The tumor microenvironment (TME) plays an important role in tumor progression and immune escape. Evidence from a small retrospective clinical series suggests that CBD may be associated with prolonged survival in patients with glioblastoma,[61] whereas mechanistic evidence for TME remodeling is still derived predominantly from preclinical models.[62] Mechanistically, CBD inhibits the activation and migration of cancer-associated fibroblasts (CAFs)[20] and reduces the secretion of pro-inflammatory cytokines such as IL-1β and IL-8, thereby attenuating pro-tumorigenic signaling within the TME. Additionally, CBD enhances the cytotoxic activity of $CD8^+$T cells and promotes natural killer (NK) cell activation, collectively reinforcing anti-tumor immunity.[63] Furthermore, CBD downregulates the expression of angiogenesis-related factors such as vascular endothelial growth factor (VEGF), thereby impairing tumor neovascularization and metastatic potential.[64] In breast cancer models, CBD suppresses EGF-induced activation of EGFR, ERK, AKT, and NF-κB pathways, as well as the secretion of matrix metalloproteinases MMP2 and MMP9.[37] Together, these findings suggest that CBD may modulate multiple components of the tumor niche, although these effects have been demonstrated predominantly in preclinical models and their generalizability across tumor types and dosing conditions remains uncertain.

Types of Tumor Cell Death Mediated by CBD

CBD activates multiple programmed cell death pathways in diverse tumors (Table 1). These pathways include apoptosis, autophagy, ferroptosis, and pyroptosis, they can function independently or interconnect.

Table 1 The Anti-Tumor Effects and Mechanisms of CBD Across Various Cancer Cell Lines

Cancer Type	Publication Year	Cell Lines	Main Mechanisms	Cell Death Mode	Reference
Colorectal Cancer	2025	RKO, HCT116, HT29, SW480, MC38	ROS↑; activation of TRPA1; phosphorylation of AMPK↑; LC3-II↑	Induction of apoptosis and autophagy	[35]
Colorectal Cancer	2024	HT-29, SW480, HCT-116, HCT-15	ROS↑; expression of ATF4 and CHOP↑; Endoplasmic Reticulum Stress↑; Atg7↑; phosphorylated Beclin-1 and LC3↑; activation of JNK, p38, ERK inhibited	Induction of apoptosis, proptosis, and autophagy	[27]
Melanoma	2024	B16F10, A375	ROS↑	Induction of apoptosis	[29]
Glioblastoma	2024	U87, U373	ROS↑; induced ERK activation; expression of autophagy-related proteins LC3-II, Atg7, Beclin-1↑; endoplasmic reticulum stress↑; GPX4 expression↓; TFRC↑, SLC7A11↓	Induction of autophagy and ferroptosis	[26]
Liver Cancer	2021	HepG2, HUH7, MHCC97H	Activation of the ISR-ATF4-CHOP pathway, promoting expression of pro-apoptotic proteins (Bax, Bak), thereby activating the caspase-3/GSDME axis	Induction of pyroptosis	[36]
Gastric Cancer	2019	SGC-7901	ROS↑; expression of ATM and p53↑; levels of CDK2 and Cyclin E↓; Bax↑, Bcl-2 expression and mitochondrial membrane potential↓; caspase-3/9 activity↑	Induction of apoptosis and cell cycle arrest	[28]
Breast Cancer	2018	T-47D, MDA-MB-231	PPARγ↑, mTOR, and Cyclin D1↓	Induction of apoptosis	[24]
Breast Cancer	2015	MDA-MB-231, SUM159, 4T1, MVT-1,	Epidermal Growth Factor (EGF) ↓; Phosphorylation of EGFR, AKT and ERK↓; MMP2, MMP9↓	Proliferation, clonogenicity, migration, and invasion	[37]
Glioma Cells	2006	U87	ROS↑; Cytochrome c release↑; Activation of caspase-3/8/9	Growth inhibition, induction of apoptosis	[25]

(*Continued*)

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Table 1 (Continued).

Cancer Type	Publication Year	Cell Lines	Main Mechanisms	Cell Death Mode	Reference
Osteosarcoma	2025	143B, U2OS	TNF-α/NF-κB/CCL5 pathway ↓	Inhibition of migration and invasion; induction of pyroptosis.	[65]
Prostate Cancer	2023	PC3	Oxidative stress ↑; Induction of caspase3/7 activation	Induction of apoptosis	[66]
Pancreatic Cancer	2024	Panc03.27, Panc1	Induction of endoplasmic reticulum stress via GRP78/ATF4/CHOP pathway	Induction of apoptosis, and chemosensitization	[67]
Endometrial Cancer	2020	Ishikawa, PCEM004a, PCEM004b, PCEM002, HEC-1A, MFE-280	LC3-II↑; Enhanced the efficacy of chemotherapy drugs targeting TRPV2	Inhibition of migration, cell cycle arrest, induction of autophagy, and chemosensitization.	[68]
Lung Cancer	2021	A549, H1299, H69	Activation caspase-3/7 ↑; Expressions of BAK1, BAX, BAD and TP53↑	Induction of apoptosis	[69]

Notes: ↑, increased/enhanced/promoted; ↓, decreased/reduced/inhibited.

Apoptosis

Apoptosis is one of the earliest mechanisms identified by which CBD induces tumor cell death, primarily via the mitochondrial pathway and the activation of the caspase cascade.[28] CBD can induce a significant increase in intracellular ROS levels, disrupt mitochondrial membrane potential, trigger the release of cytochrome c, and subsequently activate Caspase-9 and Caspase-3, leading to classical apoptosis.[70] CBD-induced apoptosis appears to involve coordinated mitochondrial perturbation, ROS accumulation, cardiolipin oxidation, depletion of glutathione, release of cytochrome c, and activation of initiator caspases (including caspase-9 and, in some settings, caspase-8), ultimately converging on caspase-3-dependent apoptosis.[25,70,71] Simultaneously, CBD downregulates the anti-apoptotic protein Bcl-2 and upregulates the pro-apoptotic protein Bax, disrupting their balance and amplifying the apoptotic cascade. In various colorectal cancer cell lines, CBD also induces the expression of other pro-apoptotic proteins, such as caspase-3 and p53, while suppressing anti-apoptotic proteins, such as Bcl-xL, IAP-1, and survivin.[27] In multiple tumor cell types, CBD induces apoptosis in a dose-dependent manner.[24,26,27,72]

Autophagy

Autophagy is a primary mechanism that mediates the delivery of various intracellular materials to lysosomes for degradation and recycling, and it also participates in diverse physiological processes such as maintaining cellular homeostasis, adapting to nutrient deprivation and metabolic stress, regulating cell development and differentiation, and controlling aging.[73] However, autophagy plays a dual role in cancer, with its mechanisms exhibiting stage-dependent effects. In the early stages of tumorigenesis, autophagy suppresses tumor transformation by clearing damaged organelles and protein aggregates, thereby maintaining genomic stability. In established tumors, cancer cells exploit autophagy to recycle metabolic substrates under stress conditions thereby supporting anabolic metabolism, proliferation, and therapy resistance.[74] Furthermore, accumulating evidence indicates that CBD can induce autophagy through multiple and context-dependent mechanisms.[72,75] In some cancer models, CBD has been reported to suppress AKT/mTOR signaling, thereby facilitating activation of the ULK1 complex and initiation of the autophagic program.[72] This process is subsequently associated with the involvement of key autophagy regulators, including the Beclin-1/VPS34 complex, as well as conversion of LC3-I to LC3-II during autophagosome formation.[72,76] However, CBD-induced autophagy does not appear to be uniformly mediated through canonical mTORC1 inhibition. In other experimental settings, CBD has been shown to promote autophagy through ERK1/2 activation and AKT suppression in a ULK1-dependent but mTORC1-independent manner.[75] Collectively, these findings suggest that CBD-induced autophagy may contribute to tumor cell death directly or may interact with apoptotic signaling, depending on the cellular context.[26,72] Some studies

have found that CBD-induced autophagy exhibits a synergistic relationship with the CHOP-dependent endoplasmic reticulum stress pathway.[49] In glioblastoma (GBM) and colorectal cancer, CBD can enhance the expression of autophagy markers (LC3-II) and upregulate autophagy-related proteins such as Atg-7 and Beclin-1.[26,27]

Ferroptosis

Ferroptosis is a regulated, non-apoptotic form of cell death characterized by iron-dependent accumulation of membrane lipid peroxides.[77] Mechanistically, it reflects a coordinated failure of cellular redox defense, typically involving reactive oxygen species (ROS) accumulation, glutathione (GSH) depletion, increased labile iron, and impaired detoxification of phospholipid peroxides through the System Xc^-–GSH–GPX4 axis.[78] Current evidence suggests that CBD may promote ferroptosis in selected tumor contexts rather than uniformly across cancers. In glioblastoma cells, CBD induced ERK activation, increased ROS production, endoplasmic reticulum stress, and intracellular iron load, reduced GSH levels, and modulated ferroptosis-related proteins including GPX4, SLC7A11, and TFRC.[26] These effects were partially attenuated by N-acetyl-cysteine or ERK inhibition, supporting a role for ROS/ERK-driven ferroptotic signaling. However, because direct evidence remains limited and ferroptosis inhibition provides only partial rescue in available models, ferroptosis should presently be regarded as an emerging, context-dependent complementary mechanism of CBD-induced antitumor activity rather than a universally established pathway.

Regulation of Cell Cycle-Mediated Death

In estrogen receptor-positive and triple-negative breast cancer cells, CBD has been reported to downregulate mTOR and cyclin D1 signaling while enhancing PPARγ activity, thereby suppressing proliferation and promoting cell death.[24] In addition to these effects, available evidence suggests that CBD-mediated cell cycle arrest involves broader regulation of the G1/S checkpoint. In gastric cancer cells, CBD induces G0/G1 arrest accompanied by reduced CDK2 and cyclin E expression together with increased p53 and p21 signaling.[28] Similarly, in colorectal cancer cells harboring wild-type p53, CBD has been shown to trigger G0/G1 arrest, reduce CDK2 expression, and engage p53-dependent checkpoint signaling.[79] Given that progression through early G1 and the G1/S transition is primarily governed by the cyclin D-CDK4/6 and cyclin E-CDK2 axes and is negatively regulated by the p53-p21 checkpoint pathway, these findings collectively suggest that CBD exerts antiproliferative effects by modulating multiple nodes of cell-cycle control rather than isolated regulators alone.[80–82]

Pyroptosis

Pyroptosis is a lytic form of regulated cell death mediated by gasdermin family proteins. In the canonical inflammasome pathway, inflammatory caspases cleave gasdermin D (GSDMD), leading to membrane pore formation and release of pro-inflammatory mediators.[83,84] However, current evidence suggests that CBD-related pyroptosis in cancer is more accurately explained by a distinct caspase-3/gasdermin E (GSDME) axis rather than the classical GSDMD pathway.[36,85] In hepatocellular carcinoma cells, CBD has been reported to induce integrated stress response- and mitochondrial stress-associated signaling, culminating in caspase-3 activation, GSDME cleavage, and pyroptotic cell death.[36] By contrast, direct evidence for CBD-induced pyroptosis in other tumor types remains limited, and findings derived from experiments using Necrosulfonamide (NSA) should therefore be interpreted cautiously.[65,86–88] Collectively, these findings indicate that pyroptosis may represent an emerging but still relatively underexplored component of CBD-induced tumor cell death, with the strongest mechanistic support currently centered on caspase-3/GSDME-dependent signaling in hepatocellular carcinoma.[36,89]

CBD Simultaneously Induces Multiple Modes of Cell Death

CBD can simultaneously or sequentially engage multiple regulated cell death pathways within the same tumor model. Rather than activating a single downstream program, CBD appears to induce a broader stress-response network in which different forms of cell death may coexist or interact in a context-dependent manner. In colorectal cancer cells, CBD activates MAPK signaling, including JNK, p38, and ERK, and thereby induces apoptosis, paraptosis, and autophagy concurrently.[27] In glioblastoma cells, CBD has been shown to promote ERK activation and ROS accumulation, leading

to increased LC3-II expression and downregulation of ferroptosis-suppressive proteins such as GPX4, consistent with the induction of both autophagy and ferroptosis.[26] In addition, mitophagy has also emerged as a relevant component of CBD-induced tumor cell death. In human glioma models, CBD directly perturbs mitochondrial function and triggers TRPV4-dependent lethal mitophagy, thereby contributing to autophagic cell death.[90] Collectively, these findings indicate that the cell death mechanisms triggered by CBD are highly tumor-context dependent and may be co-regulated by intracellular metabolic state, genetic background, and microenvironmental conditions. Further studies are still needed to clarify the hierarchy and crosstalk among these pathways and to determine whether they can be therapeutically leveraged in combination strategies.

Therapeutic Implications and Future Perspectives

Potential Clinical Value of CBD

The apoptosis induced by CBD shows some selectivity, with a significantly stronger cytotoxic effect on malignant cells than on normal cells.[34] Moreover, it even demonstrates protective effects on damaged normal cells. For example, CBD has been shown to alleviate alcohol-induced liver injury by modulating the NLRP-3 pyroptosis pathway,[91] mitigate erastin-induced ferroptosis in non-cancerous skin cell lines (HaCaT cells),[92] and reduce LDH levels to protect human skin keratinocytes from oxidative stress-induced pyroptosis.[93] These findings suggest that CBD may exhibit a certain degree of tolerability and context-dependent selectivity in some non-cancerous cellular models. However, current evidence remains predominantly preclinical and derived from specific experimental settings, and therefore does not yet allow definitive conclusions regarding its therapeutic selectivity or safety in cancer treatment. Further pharmacological evaluation and well-designed clinical studies are still required to clarify the safety profile, optimal dosing, and therapeutic window of CBD in oncology. In addition, CBD can be administered through multiple routes, including oral, sublingual, inhalational, and transdermal delivery, which may facilitate its use in different clinical settings. CBD has a high plasma protein binding rate, primarily binding to albumin and lipoproteins, this characteristic helps prolong its half-life but also implies that patients with hypoalbuminemia or severe liver disease may experience an increased proportion of free drug in the body.[13,14] Multiple preclinical studies have shown that CBD, when combined with certain antitumor agents, may produce synergistic effects and enhance antitumor efficacy.[94–96] However, CBD has also been reported to suppress key mediators of T-cell activation and proliferation, including IL-2 and IFN-γ, which play important roles in antitumor immunity.[97–99] This apparent paradox suggests that the therapeutic impact of CBD in combination settings is likely to be context dependent. While CBD may sensitize tumor cells to chemotherapeutic or targeted agents in some preclinical models, its immunomodulatory effects could, in certain settings, attenuate beneficial T-cell- or NK-cell-mediated antitumor responses.[96,100] Therefore, the net therapeutic outcome of CBD-based combination strategies should be interpreted cautiously and requires further evaluation in immunocompetent preclinical models and clinical studies.[96,101]

Pharmacokinetics and Dosage Issues

Population and clinical pharmacokinetic studies indicate that orally administered CBD exhibits low and variable bioavailability, largely owing to poor aqueous solubility, erratic gastrointestinal absorption, and extensive first-pass metabolism.[102–104] After repeated oral administration, CBD shows a relatively prolonged apparent elimination and marked interindividual variability, which are influenced by formulation, food intake, sex, body composition, and hepatic function.[105–108] Although a retrospective study in 119 patients with solid tumors reported no obvious side effects with pharmaceutical-grade synthetic cannabidiol, this uncontrolled observation did not establish the maximum tolerated dose or define the therapeutic window.[109] Collectively, these findings indicate that the pharmacokinetic profile of CBD remains an important translational challenge, and further dose-optimization, interaction-focused, and controlled clinical studies are required before CBD-based therapies can be more confidently integrated into oncology.[102,109,110]

Future Research Directions

Based on current understanding of CBD-induced tumor cell death, future research should advance along three interconnected dimensions—mechanistic elucidation, precision application, and clinical translation—each corresponding to distinct stages of drug development.

At the mechanistic level, genetic and pharmacological tools can be employed to generate tumor models deficient in specific cell death pathways, enabling systematic dissection of the synergistic and compensatory relationships among CBD-induced apoptosis, autophagy, and ferroptosis. For instance, it remains to be determined whether inhibition of apoptotic signaling enhances the activation of alternative death programs, such as ferroptosis, in response to CBD. Elucidating the plasticity and hierarchy of these death pathways will provide a mechanistic foundation for the rational design of CBD-based combination therapies.

For precision application, the identification and validation of biomarkers associated with CBD-responsive cell death pathways will be essential for patient stratification. For example, immunohistochemical or molecular assays targeting ferroptosis-related regulators, such as GPX4 or components of System Xc^-, may help identify tumor subtypes more likely to benefit from CBD-based therapy.

At the level of clinical translation, a priority strategy is to evaluate CBD in combination with conventional chemotherapeutic agents or targeted therapies. Given that CBD can sensitize tumor cells through endoplasmic reticulum stress and oxidative damage pathways, its potential to overcome therapeutic resistance warrants investigation, particularly in chemotherapy-resistant or recurrent tumors. Additionally, leveraging the multitarget nature of CBD, low-dose combination regimens incorporating CBD with other anticancer agents may represent a "gentler" therapeutic strategy. Such approaches may be particularly suitable for elderly patients or individuals with poor performance status, in whom treatment tolerability and quality of life are critical considerations.

At the same time, several translational challenges must be addressed before CBD can be more confidently advanced in oncology. Its low and variable oral bioavailability, extensive first-pass metabolism, and marked interindividual pharmacokinetic variability remain important barriers to clinical application. Future studies should therefore place greater emphasis on dose optimization, formulation improvement, and delivery strategies that enhance systemic exposure and pharmacological consistency. In addition, because CBD may alter CYP450-mediated metabolism, potential drug-drug interactions should be carefully evaluated, particularly in patients receiving multidrug anticancer regimens. Moreover, despite encouraging preclinical findings, well-designed clinical trials demonstrating clear anticancer efficacy are still lacking. Further controlled studies are needed to define the therapeutic window, optimal formulation, dosing schedule, and safety profile of CBD in different oncologic settings.

Another important direction for future study is the role of CBD in modulating the tumor microenvironment and antitumor immunity. Because CBD has been reported to influence cytokine signaling, immune cell function, and stromal components of the tumor niche, its impact on tumor progression may extend beyond direct cytotoxicity. In particular, whether CBD enhances or attenuates immune-mediated antitumor responses under different conditions remains to be clarified. Addressing these context-dependent effects will be especially important for evaluating the rational use of CBD in combination with immune-based cancer therapies.

Notably, the ability of CBD to engage multiple cell death pathways suggests potential utility in suppressing tumor recurrence. Preclinical minimal residual disease models may be used to evaluate whether sustained low-dose administration of CBD can suppress tumor regrowth by maintaining continuous cell death pressure. If validated, this strategy could provide new avenues for the long-term management of malignancies and support the repositioning of cannabidiol as a mechanism-driven anticancer therapeutic.

Conclusion

In conclusion, current evidence indicates that cannabidiol exerts antitumor effects through pleiotropic and context-dependent regulation of multiple cell death programs, including apoptosis, autophagy, ferroptosis, pyroptosis, and cell cycle arrest. By integrating oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, calcium imbalance, and diverse signaling networks, CBD reshapes tumor cell fate and provides a mechanistic basis for potential anticancer

intervention. Nevertheless, most available evidence remains preclinical, and further studies are required to clarify its pharmacological properties, optimize therapeutic strategies, and support its clinical translation in oncology.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Hanahan D. Hallmarks of Cancer: new Dimensions. *Cancer Discov*. 2022;12(1):31–46. doi:10.1158/2159-8290.CD-21-1059
3. Ożarowski M, Karpiński TM, Zielińska A, Souto EB, Wielgus K. Cannabidiol in neurological and neoplastic diseases: latest developments on the molecular mechanism of action. *Int J Mol Sci*. 2021;22(9):4294. doi:10.3390/ijms22094294
4. Melo ESA, Asevedo EA, Duarte-Almeida JM, et al. Mechanisms of cell death induced by cannabidiol against tumor cells: a review of preclinical studies. *Plants*. 2025;14(4):585. doi:10.3390/plants14040585
5. Ma L, Liu M, Liu C, et al. Research progress on the mechanism of the antitumor effects of cannabidiol. *Molecules*. 2024;29(9):1943. doi:10.3390/molecules29091943
6. Nahler G. Cannabidiol and Other Phytocannabinoids as Cancer Therapeutics. *Pharmaceut Med*. 2022;36(2):99–129. doi:10.1007/s40290-022-00420-4
7. Mould RR, Botchway SW, Parkinson JRC, et al. Cannabidiol modulates mitochondrial redox and dynamics in MCF7 cancer cells: a study using fluorescence lifetime imaging microscopy of NAD(P)H. *Front Mol Biosci*. 2021;8:630107. doi:10.3389/fmolb.2021.630107
8. Moniruzzaman M, Wong KY, Janjua TI, et al. Cannabidiol targets colorectal cancer cells via cannabinoid receptor 2, independent of common mutations. *ACS Pharmacol Transl Sci*. 2025;8(2):543–556. doi:10.1021/acsptsci.4c00644
9. Gross C, Ramirez DA, McGrath S, Gustafson DL. Cannabidiol induces apoptosis and perturbs mitochondrial function in human and canine glioma cells. *Front Pharmacol*. 2021;12:725136. doi:10.3389/fphar.2021.725136
10. Jung B, Lee JK, Kim J, et al. Synthetic strategies for (-)-cannabidiol and its structural analogs. *Chem Asian J*. 2019;14(21):3749–3762. doi:10.1002/asia.201901179
11. Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and anti-inflammatory properties of cannabidiol. *Antioxidants*. 2019;9(1):21. doi:10.3390/antiox9010021
12. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol*. 2002;42(S1):11S–19S. doi:10.1002/j.1552-4604.2002.tb05998.x
13. Martinez Naya N, Kelly J, Corna G, et al. Molecular and cellular mechanisms of action of cannabidiol. *Molecules*. 2023;28(16):5980. doi:10.3390/molecules28165980
14. Ibeas Bih C, Chen T, Nunn AVW, et al. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics*. 2015;12(4):699–730. doi:10.1007/s13311-015-0377-3
15. Mb V, Pea DA, D E, Da R, Gsb V. Cannabis sativa and cannabidiol: a therapeutic strategy for the treatment of neurodegenerative diseases? *Med cannabis cannabinoids*. 2022;5(1):207–219.
16. Turner SE, Williams CM, Iversen L, Whalley BJ. Molecular pharmacology of phytocannabinoids. *Prog Chem Org Nat Prod*. 2017;103:61–101. doi:10.1007/978-3-319-45541-9_3
17. S M, Kl T, M A-S. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365(6441):61–65.
18. Seltzer ES, Watters AK, MacKenzie D, Granat LM, Zhang D. Cannabidiol (CBD) as a promising anti-cancer drug. *Cancers*. 2020;12(11):3203. doi:10.3390/cancers12113203
19. Cooray R, Gupta V, Suphioglu C. Current aspects of the endocannabinoid system and targeted THC and CBD phytocannabinoids as potential therapeutics for parkinson's and Alzheimer's diseases: a review. *Mol Neurobiol*. 2020;57(11):4878–4890. doi:10.1007/s12035-020-02054-6
20. Milian L, Monleon-Guinot I, Sancho-Tello M, et al. In vitro effect of Δ9-tetrahydrocannabinol and cannabidiol on cancer-associated fibroblasts isolated from lung cancer. *Int J Mol Sci*. 2022;23(12):6766.
21. Golub V, Reddy DS. Cannabidiol therapy for refractory epilepsy and seizure disorders. *Adv Exp Med Biol*. 2021;1264:93–110.
22. Reddy DS. The utility of cannabidiol in the treatment of refractory epilepsy. *Clin Pharmacol Ther*. 2017;101(2):182–184. doi:10.1002/cpt.441
23. Mashabela MD, Kappo AP. Anti-cancer and anti-proliferative potential of cannabidiol: a cellular and molecular perspective. *Int J Mol Sci*. 2024;25(11):5659. doi:10.3390/ijms25115659
24. Sultan AS, Marie MA, Sheweita SA. Novel mechanism of cannabidiol-induced apoptosis in breast cancer cell lines. *Breast*. 2018;41:34–41. doi:10.1016/j.breast.2018.06.009

25. Massi P, Vaccani A, Bianchessi S, et al. The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells. *Cell Mol Life Sci*. 2006;63(17):2057–2066. doi:10.1007/s00018-006-6156-x
26. Kim NY, Shivanne Gowda SG, Lee S-G, Sethi G, Ahn KS. Cannabidiol induces ERK activation and ROS production to promote autophagy and ferroptosis in glioblastoma cells. *Chem Biol Interact*. 2024;394:110995. doi:10.1016/j.cbi.2024.110995
27. Kim NY, Mohan CD, Sethi G, Ahn KS. Cannabidiol activates MAPK pathway to induce apoptosis, paraptosis, and autophagy in colorectal cancer cells. *J Cell Biochem*. 2024;125(4):e30537. doi:10.1002/jcb.30537
28. Zhang X, Qin Y, Pan Z, et al. Cannabidiol induces cell cycle arrest and cell apoptosis in human gastric cancer SGC-7901 cells. *Biomolecules*. 2019;9(8):302. doi:10.3390/biom9080302
29. Lyu P, Li H, Wan J, et al. Bipiperidinyl derivatives of cannabidiol enhance its antiproliferative effects in melanoma cells. *Antioxidants*. 2024;13(4):478. doi:10.3390/antiox13040478
30. Bansal S, Ladumor MK, Paine MF, Unadkat JD. A Physiologically-based pharmacokinetic model for cannabidiol in healthy adults, hepatically-impaired adults, and children. *Drug Metab Dispos*. 2023;51(6):743–752. doi:10.1124/dmd.122.001128
31. Beers JL, Fu D, Jackson KD. Cytochrome P450-catalyzed metabolism of cannabidiol to the active metabolite 7-hydroxy-cannabidiol. *Drug Metab Dispos*. 2021;49(10):882–891. doi:10.1124/dmd.120.000350
32. Ho JJY, Goh C, Leong CSA, Ng KY, Bakhtiar A. Evaluation of potential drug-drug interactions with medical cannabis. *Clin Transl Sci*. 2024;17(5):e13812. doi:10.1111/cts.13812
33. Lamonarca J, Mintz I, Bayarres L, Kochen S, Oddo S. Psychiatric comorbidities before and after cannabidiol treatment in adult patients with drug resistant focal epilepsy. *Epilepsy Behav*. 2024;160:110032. doi:10.1016/j.yebeh.2024.110032
34. Paduch R, Szwaczko K, Dziuba K, Wiater A. Exploring the potential of synthetic cannabinoids: modulation of biological activity of normal and cancerous human colon epithelial cells. *Cells*. 2024;13(19):1616. doi:10.3390/cells13191616
35. Eskandari N, Delisi D, Vakili Saatloo M, et al. TRPA1 activation prompts lysosome-mediated Nrf2 degradation enhancing the killing of colorectal cancer cells. *Redox Biol*. 2025;88:103942. doi:10.1016/j.redox.2025.103942
36. Shangguan F, Zhou H, Ma N, et al. a novel mechanism of cannabidiol in suppressing hepatocellular carcinoma by inducing gsdme dependent pyroptosis. *Front Cell Dev Biol*. 2021;9:697832. doi:10.3389/fcell.2021.697832
37. Elbaz M, Nasser MW, Ravi J, et al. Modulation of the tumor microenvironment and inhibition of EGF/EGFR pathway: novel anti-tumor mechanisms of Cannabidiol in breast cancer. *Mol Oncol*. 2015;9(4):906–919. doi:10.1016/j.molonc.2014.12.010
38. Sies H, Berndt C, Jones DP. Oxidative Stress. *Annu Rev Biochem*. 2017;86(1):715–748. doi:10.1146/annurev-biochem-061516-045037
39. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. *Curr Biol*. 2014;24(10):R453–R462. doi:10.1016/j.cub.2014.03.034
40. Ray PD, Huang B-W, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cell Signal*. 2012;24(5):981–990. doi:10.1016/j.cellsig.2012.01.008
41. Sanz-Pérez A, Anaya BJ, Fraguas-Sánchez AI, et al. Oxidative stress and mitochondrial dysfunction in neuronal cells induced by commercial CBD products. *Chem Biol Interact*. 2025;421:111785. doi:10.1016/j.cbi.2025.111785
42. Narayanasamy B, Helmueller S, Zhang Y, et al. DZ-1-artesunate induces apoptosis via a bid-, bax-, and bak-independent caspase-3 activation pathway. *J Oncol Res Ther*. 2025;10:10301.
43. Bernardi P, Rasola A, Forte M, Lippe G. The mitochondrial permeability transition pore: channel formation by F-ATP synthase, integration in signal transduction, and role in pathophysiology. *Physiol Rev*. 2015;95(4):1111–1155. doi:10.1152/physrev.00001.2015
44. Lim MP, Devi LA, Rozenfeld R. Cannabidiol causes activated hepatic stellate cell death through a mechanism of endoplasmic reticulum stress-induced apoptosis. *Cell Death Dis*. 2011;2(6):e170. doi:10.1038/cddis.2011.52
45. Zhang Y, Gao Z, Li Y, et al. Cannabidiol reprograms glucose metabolism in colorectal adenocarcinoma by targeting HIF-1α/LDHA pathway. *Am J Chin Med*. 2025;53(08):2561–2578. doi:10.1142/S0192415X25500958
46. Ryan D, Drysdale AJ, Lafourcade C, Pertwee RG, Platt B. Cannabidiol targets mitochondria to regulate intracellular Ca2+ levels. *J Neurosci*. 2009;29(7):2053–2063. doi:10.1523/JNEUROSCI.4212-08.2009
47. Jeon K-H, Park S-H, Bae WJ, et al. Cannabidiol, a regulator of intracellular calcium and calpain. *Cannabis Cannabinoid Res*. 2023;8(1):119–125. doi:10.1089/can.2021.0197
48. Stammers AN, Susser SE, Hamm NC, et al. The regulation of sarco(endo)plasmic reticulum calcium-ATPases (SERCA). *Can J Physiol Pharmacol*. 2015;93(10):843–854. doi:10.1139/cjpp-2014-0463
49. Pongking T, Thongpon P, Intuyod K, et al. Cannabidiol exhibits potent anti-cancer activity against gemcitabine-resistant cholangiocarcinoma via ER-stress induction in vitro and in vivo. *BMC Complement Med Ther*. 2024;24(1):325. doi:10.1186/s12906-024-04610-2
50. Farrimond JA, Whalley BJ, Williams CM. Cannabinol and cannabidiol exert opposing effects on rat feeding patterns. *Psychopharmacology*. 2012;223(1):117–129. doi:10.1007/s00213-012-2697-x
51. De Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol*. 2011;163(7):1479–1494. doi:10.1111/j.1476-5381.2010.01166.x
52. O'Sullivan SE, Sun Y, Bennett AJ, Randall MD, Kendall DA. Time-dependent vascular actions of cannabidiol in the rat aorta. *Eur J Pharmacol*. 2009;612(1–3):61–68. doi:10.1016/j.ejphar.2009.03.010
53. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res*. 2005;30(8):1037–1043. doi:10.1007/s11064-005-6978-1
54. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A*. 2006;103(20):7895–7900. doi:10.1073/pnas.0511232103
55. Ghovanloo M-R, Shuart NG, Mezeyova J, et al. Inhibitory effects of cannabidiol on voltage-dependent sodium currents. *J Biol Chem*. 2018;293(43):16546–16558. doi:10.1074/jbc.RA118.004929
56. Dávila EM, Patricio F, Rebolledo-Bustillo M, et al. Interacting binding insights and conformational consequences of the differential activity of cannabidiol with two endocannabinoid-activated G-protein-coupled receptors. *Front Pharmacol*. 2022;13:945935. doi:10.3389/fphar.2022.945935
57. Falasca M, Ferro R. Role of the lysophosphatidylinositol/GPR55 axis in cancer. *Adv Biol Regul*. 2016;60:88–93. doi:10.1016/j.jbior.2015.10.003

58. Tan S, Zaman QU, Fahad S, Deng G. Cannabidiol reverts the malignant phenotype of hepatocellular carcinoma cells via the GPR55/TP53/MAPK axis. *Biochim Biophys Acta Gen Subj*. 2024;1868(8):130651. doi:10.1016/j.bbagen.2024.130651
59. Calvillo-Robledo A, Cervantes-Villagrana RD, Morales P, Marichal-Cancino BA. The oncogenic lysophosphatidylinositol (LPI)/GPR55 signaling. *Life Sci*. 2022;301:120596. doi:10.1016/j.lfs.2022.120596
60. Andradas C, Blasco-Benito S, Castillo-Lluva S, et al. Activation of the orphan receptor GPR55 by lysophosphatidylinositol promotes metastasis in triple-negative breast cancer. *Oncotarget*. 2016;7(30):47565–47575. doi:10.18632/oncotarget.10206
61. Likar R, Koestenberger M, Stutschnig M, Nahler G. Cannabidiol μay prolong survival in patients with glioblastoma multiforme. *Cancer Diagn Progn*. 2021;1(2):77–82. doi:10.21873/cdp.10011
62. Khodadadi H, Salles ÉL, Alptekin A, et al. Inhalant cannabidiol inhibits glioblastoma progression through regulation of tumor microenvironment. *Cannabis Cannabinoid Res*. 2023;8(5):824–834. doi:10.1089/can.2021.0098
63. Reis EVDS, Lopes-Ribeiro Á, Moraes TDFS, et al. Cannabidiol promotes fine-tuning of natural killer and monocytic cells subsets as well as cytokine storm during chikungunya virus exposure in vitro: insights for putative therapeutic interventions. *Biomed Pharmacother*. 2025;193:118900. doi:10.1016/j.biopha.2025.118900
64. Salles ÉL, Naeini SE, Khodadadi H, et al. Inhalant cannabidiol impedes tumor growth through decreased tumor stemness and impaired angiogenic switch in NCI-H1437-induced human lung cancer model. *Hum Cell*. 2023;36(3):1204–1210. doi:10.1007/s13577-023-00869-8
65. Yang F, Duan S, Liu J, et al. Antitumor effects of cannabidiol (CBD) on osteosarcoma by targeting TNF-α/NF-κB/CCL5 signaling axis. *Phytomedicine*. 2025;145:157066. doi:10.1016/j.phymed.2025.157066
66. Li J, Gu T, Hu S, Jin B, Lupo G. Anti-proliferative effect of Cannabidiol in Prostate cancer cell PC3 is mediated by apoptotic cell death, NFκB activation, increased oxidative stress, and lower reduced glutathione status. *PLoS One*. 2023;18(10):e0286758. doi:10.1371/journal.pone.0286758
67. Mangal N, Reebye V, Habib N, Sodergren MH. Cannabidiol's cytotoxicity in pancreatic cancer is induced via an upregulation of ceramide synthase 1 and ER stress. *J Cannabis Res*. 2024;6(1):22. doi:10.1186/s42238-024-00227-x
68. Marinelli O, Morelli MB, Annibali D, et al. The effects of cannabidiol and prognostic role of TRPV2 in human endometrial cancer. *Int J Mol Sci*. 2020;21(15):5409. doi:10.3390/ijms21155409
69. Hamad H, Olsen BB. Cannabidiol induces cell death in human lung cancer cells and cancer stem cells. *Pharmaceuticals*. 2021;14(11):1169. doi:10.3390/ph14111169
70. Wu H-Y, Huang C-H, Lin Y-H, Wang -C-C, Jan T-R. Cannabidiol induced apoptosis in human monocytes through mitochondrial permeability transition pore-mediated ROS production. *Free Radic Biol Med*. 2018;124:311–318. doi:10.1016/j.freeradbiomed.2018.06.023
71. Wu H-Y, Chu R-M, Wang C-C, et al. Cannabidiol-induced apoptosis in primary lymphocytes is associated with oxidative stress-dependent activation of caspase-8. *Toxicol Appl Pharmacol*. 2008;226(3):260–270. doi:10.1016/j.taap.2007.09.012
72. Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther*. 2011;10(7):1161–1172. doi:10.1158/1535-7163.MCT-10-1100
73. Debnath J, Gammoh N, Ryan KM. Autophagy and autophagy-related pathways in cancer. *Nat Rev Mol Cell Biol*. 2023;24(8):560–575.
74. Du M, Yu Y, Wang J, Ji C. Autophagy-lysosome pathway dysfunction in neurodegeneration and cancer: mechanisms and therapeutic opportunities. *Int J Mol Sci*. 2025;27(1):366. doi:10.3390/ijms27010366
75. Vrechi TAM, Leão AHFF, Morais IBM, et al. Cannabidiol induces autophagy via ERK1/2 activation in neural cells. *Sci Rep*. 2021;11(1):5434. doi:10.1038/s41598-021-84879-2
76. Russell RC, Tian Y, Yuan H, et al. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. *Nat Cell Biol*. 2013;15(7):741–750. doi:10.1038/ncb2757
77. Dixon SJ, Lemberg K, Lamprecht M, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072. doi:10.1016/j.cell.2012.03.042
78. Dai E, Chen X, Linkermann A, et al. A guideline on the molecular ecosystem regulating ferroptosis. *Nat Cell Biol*. 2024;26(9):1447–1457. doi:10.1038/s41556-024-01360-8
79. Wang F, Dezfouli AB, Khosravi M, et al. Cannabidiol-induced crosstalk of apoptosis and macroautophagy in colorectal cancer cells involves p53 and Hsp70. *Cell Death Discov*. 2023;9(1):286. doi:10.1038/s41420-023-01578-9
80. Topacio BR, Zatulovskiy E, Cristea S, et al. Cyclin D-Cdk4,6 drives cell-cycle progression via the retinoblastoma protein's C-terminal helix. *Mol Cell*. 2019;74(4):758–770.e4. doi:10.1016/j.molcel.2019.03.020
81. Fassl A, Geng Y, Sicinski P. CDK4 and CDK6 kinases: from basic science to cancer therapy. *Science*. 2022;375(6577):eabc1495. doi:10.1126/science.abc1495
82. Li Y, Jenkins CW, Nichols MA, Xiong Y. Cell cycle expression and p53 regulation of the cyclin-dependent kinase inhibitor p21. *Oncogene*. 1994;9(8):2261–2268.
83. Xia S, Hollingsworth LR, Wu H. Mechanism and regulation of gasdermin-mediated cell death. *Cold Spring Harb Perspect Biol*. 2020;12(3):a036400. doi:10.1101/cshperspect.a036400
84. Man SM, Kanneganti T-D. Gasdermin D: the long-awaited executioner of pyroptosis. *Cell Res*. 2015;25(11):1183–1184. doi:10.1038/cr.2015.124
85. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature*. 2017;547(7661):99–103. doi:10.1038/nature22393
86. Rathkey JK, Zhao J, Liu Z, et al. Chemical disruption of the pyroptotic pore-forming protein gasdermin D inhibits inflammatory cell death and sepsis. *Sci Immunol*. 2018;3(26):eaat2738. doi:10.1126/sciimmunol.aat2738
87. Leem Y-H, Kim D-Y, Park J-E, Kim H-S. Necrosulfonamide exerts neuroprotective effect by inhibiting necroptosis, neuroinflammation, and α-synuclein oligomerization in a subacute MPTP mouse model of Parkinson's disease. *Sci Rep*. 2023;13(1):8783. doi:10.1038/s41598-023-35975-y
88. Valenti C, Billi M, Pancrazi GL, et al. Biological effects of cannabidiol on human cancer cells: systematic review of the literature. *Pharmacol Res*. 2022;181:106267. doi:10.1016/j.phrs.2022.106267
89. Kong Q, Zhang Z. Cancer-associated pyroptosis: a new license to kill tumor. *Front Immunol*. 2023;14:1082165.

90. Huang T, Xu T, Wang Y, et al. Cannabidiol inhibits human glioma by induction of lethal mitophagy through activating TRPV4. *Autophagy*. 2021;17(11):3592–3606.
91. Jiang X, Gu Y, Huang Y, et al. CBD alleviates liver injuries in alcoholics with high-fat high-cholesterol diet through regulating NLRP3 inflammasome-pyroptosis pathway. *Front Pharmacol*. 2021;12:724747. doi:10.3389/fphar.2021.724747
92. Li H, Puopolo T, Seeram NP, Liu C, Ma H. Anti-ferroptotic effect of cannabidiol in human skin keratinocytes characterized by data-independent acquisition-based proteomics. *J Nat Prod*. 2024;87(5):1493–1499. doi:10.1021/acs.jnatprod.3c00759
93. Liu C, Li H, Xu F, et al. Cannabidiol protects human skin keratinocytes from hydrogen-peroxide-induced oxidative stress via modulation of the Caspase-1-IL-1β axis. *J Nat Prod*. 2021;84(5):1563–1572. doi:10.1021/acs.jnatprod.1c00083
94. Alsherbiny MA, Bhuyan DJ, Low MN, Chang D, Li CG. Synergistic interactions of cannabidiol with chemotherapeutic drugs in MCF7 cells: mode of interaction and proteomics analysis of mechanisms. *Int J Mol Sci*. 2021;22(18):10103. doi:10.3390/ijms221810103
95. Soroceanu L, Singer E, Dighe P, et al. Cannabidiol inhibits RAD51 and sensitizes glioblastoma to temozolomide in multiple orthotopic tumor models. *Neurooncol Adv*. 2022;4(1):vdac019. doi:10.1093/noajnl/vdac019
96. Buchtova T, Lukac D, Skrott Z, Chroma K, Bartek J, Mistrik M. Drug-drug interactions of cannabidiol with standard-of-care chemotherapeutics. *Int J Mol Sci*. 2023;24(3):2885.
97. Kaplan BLF, Springs AEB, Kaminski NE. The profile of immune modulation by cannabidiol (CBD) involves deregulation of nuclear factor of activated T cells (NFAT). *Biochem Pharmacol*. 2008;76(6):726–737. doi:10.1016/j.bcp.2008.06.022
98. Maraskovsky E, Chen WF, Shortman K. IL-2 and IFN-gamma are two necessary lymphokines in the development of cytolytic T cells. *J Immunol*. 1989;143(4):1210–1214. doi:10.4049/jimmunol.143.4.1210
99. Piersma SJ, Pak-Wittel MA, Lin A, Plougastel-Douglas B, Yokoyama WM. Activation receptor-dependent IFN-γ production by nk cells is controlled by transcription, translation, and the proteasome. *J Immunol*. 2019;203(7):1981–1988. doi:10.4049/jimmunol.1900718
100. Wang F, Bashiri Dezfouli A, Multhoff G. The immunomodulatory effects of cannabidiol on Hsp70-activated NK cells and tumor target cells. *Mol Immunol*. 2024;174:1–10. doi:10.1016/j.molimm.2024.07.008
101. Twelves C, Sabel M, Checketts D, et al. A Phase 1b randomised, placebo-controlled trial of nabiximols cannabinoid oromucosal spray with temozolomide in patients with recurrent glioblastoma. *Br J Cancer*. 2021;124(8):1379–1387. doi:10.1038/s41416-021-01259-3
102. Perucca E, Bialer M. Critical aspects affecting cannabidiol oral bioavailability and metabolic elimination, and related clinical implications. *CNS Drugs*. 2020;34(8):795–800. doi:10.1007/s40263-020-00741-5
103. Knaub K, Sartorius T, Dharsono T, et al. A novel Self-Emulsifying Drug Delivery System (SEDDS) based on vesisorb® formulation technology improving the oral bioavailability of cannabidiol in healthy subjects. *Molecules*. 2019;24(16):2967. doi:10.3390/molecules24162967
104. Lim SY, Sharan S, Woo S. Model-based analysis of cannabidiol dose-exposure relationship and bioavailability. *Pharmacotherapy*. 2020;40(4):291–300. doi:10.1002/phar.2377
105. Schultz HB, Hosseini A, McLachlan AJ, Reuter SE. Population pharmacokinetics of oral-based administration of cannabidiol in healthy adults: implications for drug development. *Cannabis Cannabinoid Res*. 2023;8(5):877–886. doi:10.1089/can.2021.0202
106. MacNair L, Kulpa J, Hill ML, et al. Sex differences in the pharmacokinetics of cannabidiol and metabolites following oral administration of a cannabidiol-dominant cannabis oil in healthy adults. *Cannabis Cannabinoid Res*. 2024;9(4):e1170–e1178. doi:10.1089/can.2022.0345
107. Jang J-H, Jeong J-H, Jeong S-H. Quantitative summary on the human pharmacokinetic properties of cannabidiol to accelerate scientific clinical application of cannabis. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;397(11):8285–8309. doi:10.1007/s00210-024-03185-6
108. Taylor L, Crockett J, Tayo B, Morrison G. A Phase 1, Open-Label, Parallel-Group, Single-Dose Trial of the Pharmacokinetics and Safety of Cannabidiol (CBD) in subjects with mild to severe hepatic impairment. *J Clin Pharmacol*. 2019;59(8):1110–1119. doi:10.1002/jcph.1412
109. Kenyon J, Liu W, Dalgleish A. Report of objective clinical responses of cancer patients to pharmaceutical-grade synthetic cannabidiol. *Anticancer Res*. 2018;38(10):5831–5835. doi:10.21873/anticanres.12924
110. Lacroix C, Guilhaumou R, Micallef J, Blin O. Cannabidiol and pharmacokinetics drug-drug interactions: pharmacological toolbox. *Therapie*. 2024;79(3):351–363. doi:10.1016/j.therap.2023.05.003