Review Article

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Medicinal Cannabis in Cancer Therapy: Targeting Ferroptosis as a Novel and Promising Axis

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ABSTRACT

Medicinal cannabis is attracting increasing attention for its therapeutic potential in cancer treatment due to its ability to modulate key signaling pathways associated with tumor progression and cell death. Among various mechanisms, cannabinoids have recently been shown to trigger ferroptosis that is a regulated, iron-dependent form of cell death characterized by lipid peroxidation and glutathione depletion. This review focuses on the emerging role of cannabinoids in inducing ferroptosis in cancer cells. Cannabinoids, particularly non-psychoactive compounds such as cannabidiol (CBD), have been shown to disrupt redox homeostasis by suppressing the cystine/glutamate antiporter system Xc^-, depleting intracellular glutathione, and inhibiting glutathione peroxidase 4 (GPX4) activity. These events lead to excessive lipid peroxidation and ultimately cause ferroptotic cell death. Furthermore, cannabinoids disrupt iron metabolism, promote ferritinophagy, and affect certain transcriptional regulators, making tumor cells more susceptible to ferroptosis. Cannabinoid-induced ferroptosis has been observed to be particularly selective in cancer cells, providing a strategic advantage in targeting treatment-resistant tumors. Despite encouraging preclinical evidence, studies directly linking cannabinoids to ferroptosis are still limited, and clinical data are lacking. Future research should focus on improving formulation strategies, identifying reliable ferroptosis biomarkers, and validating the clinical significance of these pathways in cannabinoid-based anticancer therapies.

Keywords: Apoptosis resistance, Cancer therapy, Ferroptosis, Medicinal cannabis, Redox imbalance

1. Introduction

Cancer is one of the leading causes of death worldwide, and treatment resistance and tumor recurrence present significant therapeutic challenges [1,2]. Avoiding programmed cell death, particularly apoptosis, a defining characteristic of cancer, has been extensively researched and targeted. However, the discovery of alternative, non-apoptotic regulated cell death pathways, such as ferroptosis, has created a promising new area of research in cancer treatment, especially in apoptosis-resistant tumors.

Feroptosis is an iron-dependent, regulated cell death mechanism triggered by excessive lipid peroxidation and oxidative damage to cellular membranes [3,4]. Unlike apoptosis, ferroptosis is caspase-independent and is controlled by specific metabolic and redox-regulatory processes such as the Xc^-/GSH/GPX4 axis, iron metabolism, and polyunsaturated fatty acid oxidation [5]. Due to its sensitivity to tumor-specific metabolic vulnerabilities and mechanistic differences, ferroptosis has become an increasingly important therapeutic target in malignancies such as glioblastoma [6], triple-negative breast cancer [7], and hepatocellular carcinoma [8].

Medicinal cannabis, derived from Cannabis sativa, has gained importance as an alternative agent in cancer treatment in recent years. Its bioactive components, particularly Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have demonstrated various pharmacological effects such as antiproliferative, pro-apoptotic, anti-inflammatory, and anti-angiogenic activities [9,10]. While the pro-apoptotic effects of cannabinoids are widely documented, new evidence suggests that some cannabinoids, particularly CBD, can also trigger ferroptosis in various cancer cell types through mechanisms such as glutathione depletion, GPX4 inhibition, and lipid ROS accumulation [11,12].

The need for effective treatment of apoptosis-resistant tumors and the drug-induced sensitivity of ferroptosis have brought cannabinoid-induced ferroptosis to the forefront as a novel strategy in cancer therapy. This review critically evaluates the biochemical interactions between medicinal cannabis and ferroptotic signaling pathways, highlights key preclinical findings, and explores the therapeutic implications of selective ferroptosis induction in cancer cells via phytocannabinoids.

Rather than merely summarizing current findings, this review proposes a mechanistic integrative framework in which cannabinoids act as agents modulating ferroptotic vulnerability in cancer through a coordinated signaling network. We conceptualize a cannabinoid–cAMP–ERK1/2–SLC7A11 regulatory axis that functionally links receptor-mediated signaling with redox homeostasis and iron-dependent lipid peroxidation. In this model, activation of cannabinoid receptors dynamically reshapes intracellular cAMP levels and ERK1/2 signaling; This also modulates the transcriptional and post-translational regulation of SLC7A11 (xCT) and downstream glutathione metabolism. Consequently, cystine uptake and changes in GPX4-dependent antioxidant capacity shift the cellular redox threshold in favor of ferroptotic susceptibility. Importantly, this axis mechanistically explains the binding-dependent pro-oxidant and anti-tumoral effects of cannabinoids observed in different cancer models. By integrating receptor signaling, metabolic control, and ferroptotic action pathways, this framework not only goes beyond a descriptive literature synthesis but also forms a testable mechanistic hypothesis that can guide combination strategies of cannabinoids with ferroptosis-inducing therapies.

2. Mechanisms and Regulation of Ferroptosis in Cancer

Ferroptosis is a unique and tightly regulated form of cell death, independent of apoptosis, characterized by iron-dependent lipid peroxide accumulation leading to irreversible membrane damage [13]. As shown in Figure 1, this process can be initiated and modulated through numerous interconnected biochemical pathways such as redox imbalance, iron metabolism, and lipid peroxidation. Unlike apoptosis or necroptosis, ferroptosis is defined by its own morphological and biochemical features and has emerged as a sensitive target, particularly in many cancer types that exhibit resistance to classical cell death mechanisms [14,15].

At the heart of ferroptosis lies an imbalance between oxidative stress and the cell's antioxidant defenses [16]. The most critical antioxidant defense mechanism against ferroptosis is the GPX4 enzyme, which converts toxic lipid hydroperoxides into non-reactive lipid alcohols using the GSH cofactor [17,18]. When GSH levels are reduced or GPX4 activity is

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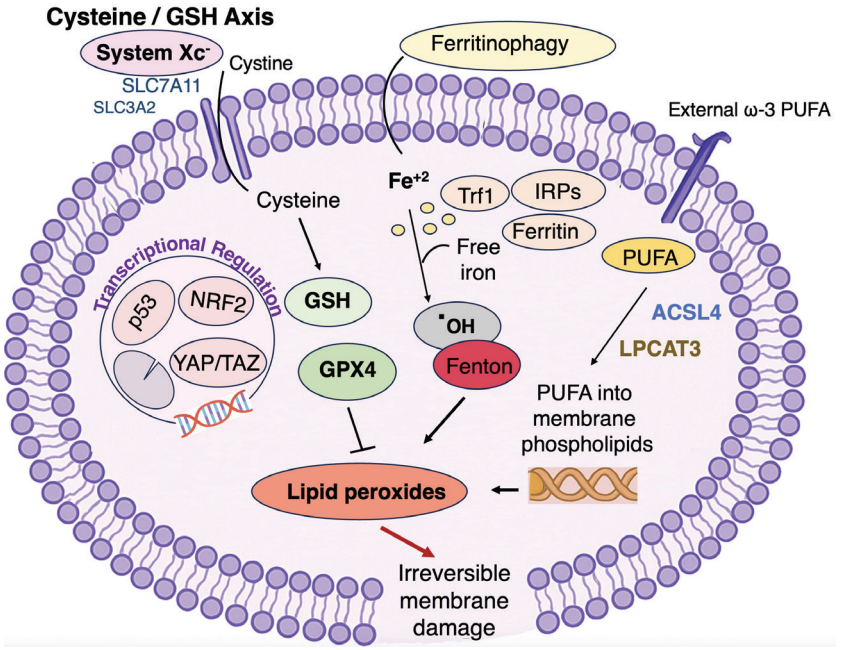

Figure 1. Integrated molecular pathways regulating ferroptosis in cancer cells. This figure illustrates the key regulatory mechanisms of ferroptosis in tumor biology. Cystine uptake via system Xc^- (comprising SLC7A11) allows for intracellular cysteine accumulation, promoting glutathione (GSH) synthesis and GPX4 activity, both essential for counteracting lipid peroxidation. Ferritinophagy releases free intracellular iron, enhancing reactive oxygen species (ROS) generation via the Fenton reaction, which in turn promotes the formation of lipid peroxides. The incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids by ACSL4 and LPCAT3 further sensitizes cells to ferroptosis. Transcriptional regulators such as NRF2 and YAP/TAZ modulate ferroptosis sensitivity by influencing antioxidant defense and lipid metabolism genes. Collectively, these interconnected pathways converge to promote irreversible membrane damage characteristic of ferroptotic cell death.

impaired, lipid peroxides accumulate, leading to ferroptotic cell death [19]. Particularly aggressive and treatment-resistant tumor cells are highly dependent on the GPX4-GSH axis for survival, making them highly susceptible to disruptions in this pathway [20,21].

GSH synthesis is dependent on cystine uptake via the system Xc^- transporter, which operates primarily through the SLC7A11 subunit. Inhibition of this transporter reduces intracellular cysteine levels, suppresses GSH synthesis, and indirectly disables GPX4 function [22]. Many cancer types overexpress SLC7A11 as an adaptation mechanism to oxidative stress; however, this overexpression paradoxically creates a dependency that can be therapeutically targeted [23]. Agents that inhibit system Xc^- or directly inactivate GPX4 can selectively induce ferroptosis in these cells [24].

In parallel, iron metabolism plays a fundamental role in ferroptosis. Free intracellular divalent iron (Fe^{2+}) catalyzes the formation of hydroxyl radicals via the Fenton reaction and leads to the formation of lipid reactive oxygen species (ROS), which increase membrane damage [25]. Cancer cells frequently exhibit increased iron uptake and storage through changes in the expression of transferrin receptors, ferritin, and iron regulatory proteins, which increases their susceptibility to ferroptosis [26]. Furthermore, the incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids via enzymes such as ACSL4 and LPCAT3 creates substrates highly susceptible to peroxidation and predisposes to ferroptotic cell death in cases where antioxidant defenses are insufficient [27].

Transcriptional regulation also influences susceptibility to ferroptosis. For example, NRF2, a major regulator of the antioxidant response, confers resistance by upregulating GPX4 and SLC7A11 [28]. In contrast, p53 has been shown to sensitize cells to

ferroptosis by suppressing SLC7A11 in some cases [29]. Frequently dysregulated YAP/TAZ transcriptional co-activators in cancer also modulate ferroptosis-related gene expression and may influence therapeutic response [30].

Importantly, the ferroptotic process is not isolated; it can intersect with other cell death pathways such as autophagy and apoptosis. A selective type of autophagy called ferritinophagy, which breaks down ferritin, can promote ferroptosis by increasing the intracellular iron pool [31]. Furthermore, although apoptosis is caspase-dependent and morphologically distinct, certain stress conditions, such as excessive ROS production, can lead to the co-activation of both ferroptosis and apoptosis [32]; this is particularly evident when triggered by compounds targeting multiple redox-sensitive pathways, such as cannabinoids [33].

Recent studies highlight that ferroptosis may be a strategic mechanism for overcoming treatment resistance, particularly in tumors exhibiting mesenchymal features, metabolic plasticity, or p53 pathway alterations. These tumor types can evade classical apoptotic stimulation while remaining susceptible to ferroptotic cell death; this makes ferroptosis a highly promising target for novel anticancer approaches [34].

Overall, ferroptosis is a redox-based sensitivity point in many malignancies. Its regulation involves complex interactions of iron homeostasis, lipid metabolism, cysteine availability, and antioxidant enzyme functions. Understanding these interconnected networks is critical for the use of ferroptosis as a therapeutic strategy in oncology, especially considering the potential of redox-active compounds such as cannabinoids to shift cellular equilibrium to ferroptotic cell death.

3. Cannabinoid Compounds and Their Redox-Modulatory Properties

Although the medicinal properties of Cannabis sativa have long been investigated in various disease contexts, its biochemical significance in cancer, particularly through the modulation of oxidative stress and the induction of ferroptosis, has only recently received focused attention. CBD and THC, the two most studied phytocannabinoids, exhibit remarkable anticancer properties through mechanisms that go beyond classical cannabinoid receptor (CB1/CB2) signaling [35]. As shown in Figure 2, these compounds can modulate cellular redox homeostasis, affecting critical processes that are key regulators of ferroptosis, such as glutathione balance, reactive oxygen species (ROS) production, and iron metabolism [36].

CBD, a non-psychoactive component of the plant, has been shown to exhibit pro-oxidant effects at high concentrations in tumor cells [37]. By disrupting mitochondrial respiration [38], increasing ROS accumulation, and leading to glutathione depletion, it shifts the redox balance in favor of oxidative cellular damage [39]. These effects are consistent with the biochemical requirements of ferroptotic cell death and have been validated in several cancer models, including breast cancer [40] and glioblastoma cells [12].

THC, the psychoactive component of cannabis, also affects redox-sensitive pathways; however, its role in ferroptosis is more indirect compared to CBD. THC can increase oxidative stress, disrupt mitochondrial membrane potential, and affect metabolic pathways associated with iron transport and lipid metabolism [41]. While the direct role of THC in ferroptosis induction has not yet been clearly established, its capacity to increase ROS production may synergize with ferroptotic processes [42], especially when used in combination with other agents [43].

In addition to CBD and THC, other less well-known cannabinoids such as cannabigerol (CBG) and cannabichromen (CBC) have also been reported to modulate oxidative stress pathways and exhibit antiproliferative effects [44,45]. However, the effects of these compounds on ferroptotic signaling have not yet been sufficiently investigated. These agents may hold potential as future ferroptosis modulators, particularly when used within the context of the “entourage” effect, where therapeutic efficacy is enhanced by the interaction of multiple cannabinoids.

It should also be emphasized that the pro-oxidant effects of cannabinoids are selective to cancer cells, which generally have high basal ROS levels and weakened antioxidant capacity [37]. This tumor-specific redox imbalance creates a favorable environment for cannabinoid-induced ferroptosis, while largely protecting normal, untransformed cells that maintain redox homeostasis. In general, the redox-modulatory properties of cannabinoids, particularly

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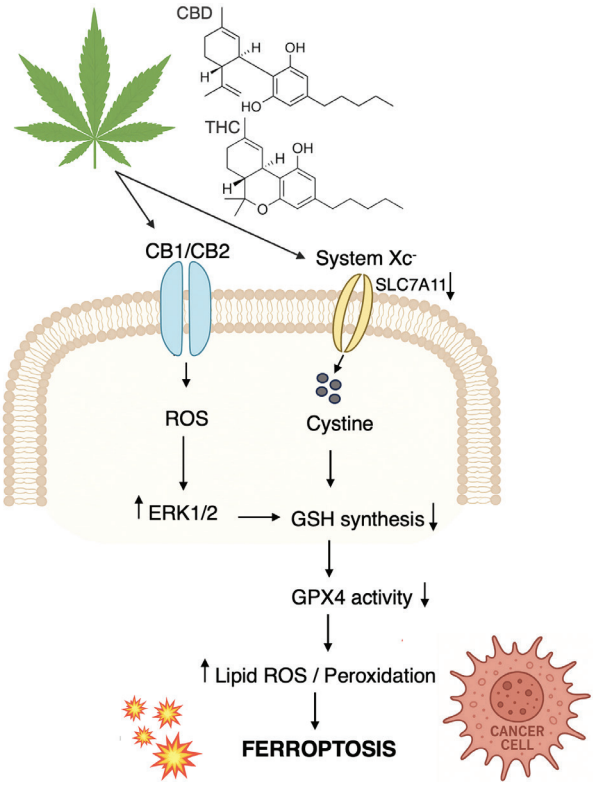

Figure 2. Proposed molecular pathway illustrating the ferroptosis-inducing effects of cannabinoids in cancer cells. This diagram summarizes the molecular mechanisms through which cannabinoids, particularly cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC), may promote ferroptosis in cancer cells. Upon interacting with cannabinoid receptors CB1 and CB2 on the cell membrane, downstream signaling pathways such as ERK1/2 are activated. These pathways modulate redox homeostasis and influence ferroptosis sensitivity. Cannabinoid-induced ERK activation leads to increased reactive oxygen species (ROS) production, which depletes intracellular glutathione (GSH) and enhances lipid peroxidation. Concurrently, modulation of the cystine/glutamate antiporter system Xc^-, especially via SLC7A11, reduces cysteine uptake and GSH synthesis. These pathways represent potential targets for ferroptosis-based therapeutic strategies involving cannabinoids.

CBD, make them promising agents that can trigger ferroptosis in cancer cells. By depleting glutathione stores, disrupting GPX4 function, and increasing lipid ROS accumulation, these compounds act on multiple pathways associated with ferroptosis, revealing their potential as unconventional ferroptosis inducers in cancer treatment.

4. Cannabinoid-Induced Ferroptosis: Preclinical Evidence

Recent preclinical studies have revealed that some cannabinoids, particularly cannabidiol (CBD), have the ability to selectively induce ferroptosis in cancer cells through multiple redox-sensitive mechanisms. These findings go beyond the previously known apoptotic effects of cannabinoids, pointing to a novel mechanism of action that could be critical in the treatment of apoptosis-resistant tumors.

In a remarkable study by Kim et al. [12] on glioblastoma cells, CBD was shown to induce ferroptosis and autophagy through ERK activation and increased ROS production, contributing significantly to cancer cell death. This study highlights the interaction between redox stress and autophagy in the regulation of ferroptosis and positions CBD as a promising dual-acting anticancer agent. Structural modifications of CBD to enhance its anticancer efficacy have also been investigated. It has been shown that bipiperidinyl derivatives of CBD enhance antiproliferative activity in melanoma cells, along with increased ROS production and impaired lipid metabolism, which may be associated with ferroptosis [46]. Furthermore, both natural and synthetic cannabinoids have been reported to exhibit cytotoxic effects in ovarian cancer models, and this effect is significantly enhanced in combination with cisplatin. Although ferroptosis was not directly measured, the synergistic increase in oxidative stress and antiproliferative effects suggests that redox-sensitive mechanisms, including ferroptosis, may play a role [33].

In addition, a study on triple-negative breast cancer (TNBC) showed that inhibition of cannabinoid receptor type 1 (CB1) modulated fatty acid metabolism, sensitizing cells to ferroptosis. Suppression of CB1 resulted in increased lipid peroxidation and decreased antioxidant capacity, predisposing TNBC cells to ferroptotic cell death [40].

It should also be noted that while some cannabinoids induce ferroptosis, others may exhibit protective effects against it. For example, cannabinol (CBN) has been shown to inhibit ferroptosis and oxytocin by directly targeting mitochondria, independently of classical cannabinoid receptors. This finding reveals that cannabinoids can both trigger and suppress ferroptosis depending on their molecular context [47]. Interestingly, CBD has also been reported to exhibit protective effects in non-cancer models, such as stress-induced liver damage, by modulating oxida-

tive stress and mitochondrial damage. This highlights its antioxidant properties in normal tissues while raising important questions regarding the selectivity of ferroptosis induction between cancer and normal cells [48].

Advanced nanoparticle-based drug delivery systems have also been developed to further enhance ferroptosis. In TNBC models, upcycled nanocarriers carrying microtubule inhibitors and ferroptosis inducers have been shown to selectively increase ferroptotic cell death in cancer cells. These findings support the feasibility of combination nanoformulations, including cannabinoids, in future oncological applications [49].

In summary, although there is strong evidence that some cannabinoids, particularly cannabidiol, can promote cell death in various cancer types by modulating redox homeostasis, data on whether cannabinoids directly and mechanistically induce ferroptosis are still limited. Most current studies suggest ferroptotic activity based on indirect indicators such as increased ROS, lipid peroxidation, and mitochondrial dysfunction; however, few studies explicitly demonstrate ferroptosis using gold standard tests or genetic validation methods. Furthermore, the bidirectional redox properties of cannabinoids, acting as pro-oxidants in malignant cells and antioxidants in normal tissues, further complicate their pharmacological interpretation. Despite these limitations, the synergy that cannabinoids demonstrate with established ferroptosis inducers and their capacity to influence key ferroptosis regulators such as GPX4, SLC7A11, and iron metabolism make them promising, yet insufficiently evaluated, agents in ferroptosis-targeted cancer therapy. In this context, further studies using ferroptosis-specific biomarkers and performing in vivo validations are necessary to reveal the precise role and therapeutic value of these compounds.

5. Therapeutic Potential and Selectivity of Cannabinoid-Induced Ferroptosis

The unique redox-dependent mechanism of ferroptosis presents an attractive therapeutic opportunity to target tumors resistant to apoptosis or other conventional treatments [13]. Cannabinoids, particularly CBD, have emerged as promising agents capable of selectively inhibiting the growth of cancer cells by targeting their metabolic and oxidative sensitivities [50]. This selectivity, combined with their relative safety and multifaceted (pleiotropic) effects, strengthens their potential role in next-generation cancer therapies.

One of the most striking features of cannabinoid-induced ferroptosis is its tumor selectivity. Cancer cells typically operate under increased oxidative stress and impaired iron metabolism, making them susceptible to ferroptosis. These cells often exhibit overexpression of SLC7A11, higher intracellular iron pools, increased polyunsaturated fatty acid (PUFA) levels in their membranes, and greater reliance on GPX4 activity for survival [51]. In contrast, normal epithelial or stromal cells tend to maintain stronger antioxidant systems and lower basal iron and PUFA levels, making them more resistant to ferroptotic stimuli [52]. This selectivity has also been demonstrated in studies comparing cancer cell lines with untransformed controls, where CBD has been observed to induce significant lipid peroxidation and cell death only in cancer cells [40]. This makes the strategy more selective than many conventional chemotherapeutics.

In addition to selectivity, the breadth of cancer types that respond to cannabinoid-induced ferroptosis is another indicator of the therapeutic potential. Studies have shown ferroptosis induction in various malignancies, including glioblastoma, ovarian cancer, triple-negative breast cancer (TNBC), and melanoma [12,33,40,46]. These tumors often share common features such as p53 mutations, metabolic reprogramming, or resistance to apoptosis, all of which are associated with increased susceptibility to ferroptosis [53]. CBD's multimodal effect can help overcome resistance mechanisms that develop via a single pathway, providing a broader cytotoxic effect across different tumor types.

The therapeutic applicability of CBD is further expanded by its ability to enhance ferroptosis in combination therapies. Preclinical findings reveal that CBD can enhance ferroptotic responses by exhibiting synergistic effects with erastin, sorafenib, or GPX4 inhibitors [54]. Such combinations can allow for dose reduction of toxic agents while maintaining or enhancing efficacy. For example, co-administration with CBD in erastin-resistant tumor models resulted in the resensitization of cells to ferroptosis [40]; this suggests that cannabinoids can help break resistance mechanisms or broaden the therapeutic window.

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Another promising approach is the development of cannabinoid-based drug delivery systems that enhance ferroptotic targeting. Nanoformulations of CBD or synthetic cannabinoids can be engineered to increase accumulation, bioavailability, and redox reactivity in tumor tissue [55,56]. Such approaches can optimize pharmacokinetics and enable tumor-specific targeted drug delivery, thereby increasing efficacy while reducing off-target effects. Furthermore, the potential of cannabinoid-based ferroptosis inducers to reduce systemic toxicity should not be overlooked. Unlike conventional chemotherapies that non-selectively damage proliferative cells, cannabinoids target metabolic weaknesses specific to malignancies; this can result in lower toxicity and better tolerability in a clinical setting [47,57]. This feature is of great importance, especially for fragile cancer patients with advanced stage or unsuitable for aggressive treatment.

Taking all these findings together, the therapeutic potential of cannabinoid-induced ferroptosis rests on three key elements: tumor selectivity, mechanistic complementarity to existing treatments, and favorable safety characteristics. These advantages make cannabinoids highly attractive, particularly in the context of personalized oncology where molecular markers such as GPX4 dependence, SLC7A11 expression, or iron loading phenotypes can guide treatment choices. However, translational research and clinical validation studies are necessary to fully realize this potential.

6. Challenges and Future Directions in Clinical Translation

Despite promising preclinical findings supporting the induction of ferroptosis by cannabinoids, translating these results into effective clinical treatments faces several significant challenges. One major obstacle is the pharmacokinetic profile of cannabinoids; their low water solubility, low bioavailability, and variable metabolism make it difficult to consistently deliver therapeutically effective concentrations to tumor sites [58]. To overcome these limitations, innovative drug delivery systems such as nanoparticle-based formulations and targeted delivery strategies are being actively investigated [59,60].

Another challenge is the heterogeneity of tumor responses to ferroptosis induction [61]. Variability in the expression of ferroptosis regulators such as GPX4, SLC7A11, and iron metabolism-related proteins among different cancer types and even within the same tumor [62] necessitates the identification and validation of reliable biomarkers to determine which patients would benefit most from cannabinoid-induced ferroptosis treatments. Personalized medicine approaches integrating molecular profiling can optimize patient selection and treatment efficacy.

Furthermore, dose optimization and safety profiles of cannabinoids should be elucidated in more detail. Although cannabinoids are generally well tolerated [63], high doses that may be necessary for inducing ferroptosis in tumors can produce unpredictable systemic toxicities or interact with other drugs. Comprehensive toxicological and pharmacodynamic studies are necessary to determine safe and effective dosing regimens.

The complexity of ferroptosis itself and its interaction with other cell death pathways and cellular stress responses [64] also presents a conceptual challenge. Clarifying how cannabinoids modulate these intertwined mechanisms in vivo and determining whether ferroptosis induction triggers compensatory survival pathways or inflammatory responses that could affect treatment outcomes is critical.

Finally, the lack of well-designed, large-scale clinical trials directly evaluating cannabinoid-induced ferroptosis in cancer patients constitutes a significant gap. Future research should focus on phase I/II clinical trials evaluating safety, pharmacokinetic properties, and preliminary efficacy; ideally incorporating biomarker-based patient stratification and combination therapy regimens with existing chemotherapeutics or targeted agents. In summary, addressing these challenges through interdisciplinary research efforts will be critical to unlocking the full therapeutic potential of medicinal cannabis in ferroptosis-targeted cancer therapy. Continuous advances in drug formulation, patient selection, and mechanistic understanding have the potential to pave the way for innovative, effective, and personalized cancer treatments that utilize cannabinoid-induced ferroptosis.

7. Conclusion

Inducing ferroptosis is emerging as a promising approach in cancer treatment, offering a novel strategy to overcome the resistance developing against

traditional apoptotic therapies. Medicinal cannabis, particularly its main phytocannabinoid, CBD, has emerged as a potent regulator of ferroptotic pathways. CBD exerts its effect by disrupting cellular redox balance, depleting glutathione, inhibiting cystine uptake, and increasing lipid peroxidation in cancer cells. This multi-targeted biochemical effect not only allows for the selective induction of ferroptosis in tumor cells but also suggests potential synergies with existing treatment methods. Overall, targeting ferroptosis through medicinal cannabis-derived compounds offers an innovative and multifaceted approach to cancer treatment. Future studies combining molecular-level findings with clinical evaluations could solidify the position of cannabinoid-induced ferroptosis as a viable and effective strategy in the treatment of resistant and aggressive cancers.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

Statement of Contribution of Researchers

Concept – F.B.A.; Design – F.B.A.; Literature Search – F.B.A.; Writing – F.B.A.; Critical Reviews – F.B.A.

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