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RESEARCH ARTICLE
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The Role of Cannabinoids in Cancer Therapy: Mechanisms, Therapeutic Potential, and Challenges."

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Abstract

Cannabis sativa L. (pot) has been beneficial for a point in time in medicinal and related to sports frameworks, with attraction pharmacological trends attributed to cannabinoids. Amongst almost 108 cannabinoids provided by way of this plant, delta-9-tetrahydrocannabinol (THC) is final forceful and enormous. THC mimics endocannabinoids within the manner that anandamide and 2-arachidonoylglycerol (2-AG), stimulating precise receptors, containing CB1 and CB2. CB1 is especially determined in the crucial fearful system, intervening many cannabinoids' effects, since CB2 became first of all categorized in invulnerable tissues however has due to the truth that existed determined in diverse container kinds. Rising studies focus on the presence of CB1 and CB2 receptors in miscellaneous malignancy cells, sparking interest in the recovery potential of cannabinoids in oncology. Cannabinoids show off antagonistic-tumor characteristics, containing inducing apoptosis, stopping ideas, and impeding angiogenesis, making office work promising bidders for tumor remedy. Moreover, they have comfort advantages, consisting of pain relaxation, fondness stimulation, and the decline of negative agent-induced revulsion and disgorging. No matter those advances, challenges remain in translating preclinical judgments into dispassionate exercises because of limited files from randomized managed troubles and capability affecting the thoughts which will produce wonderful visions outcomes manual THC. This evaluation explores the microscopic manner underlying cannabinoid operation in malignancy, emphasizing restoration uses and barriers. Information on the endocannabinoid plan's act in oncology may additionally moreover open streets for evolving cannabinoid-primarily based situations, weigh efficacy securely to increase affected person outcomes.

Keywords: *Cannabis sativa*, cannabinoids, arm of the sea-9-tetrahydrocannabinol (THC), endocannabinoid arrangement, CB1 receptor, CB2 receptor, cancer healing, apoptosis, angiogenesis, palliative care, oncology, anandamide, 2-arachidonoylglycerol (2-AG), cannabinoid receptors, antagonistic-lump effects, a destructive agent, microscopic mechanisms, malignancy containers, THC psychoactivity, randomized controlled tests, cannabinoid-located treatments, CB2 verbalization, cannabinoid research rebirth, TRPV1 receptor, GPR55 receptor, immune scheme, central nervous system, therapeutic belongings, receptor incitement, cancer container conception, tumor microenvironment, cannabinoid disadvantages, cancer relief belongings.

Introduction

Developments from *Cannabis sativa* L. (grass) had existed used for oodles point in time both physician- finally and recreationally. However, the synthetic systems of their particular forceful preservatives— the cannabinoids—were immediately not elucidated till the 1960s. Three decades later the basic strong clues on cannabinoid microscopic flow were attached,

which generated an outstanding growth of plain cannabinoid research and a renaissance in the study of the healing effects of cannabinoids in various fields, in addition to oncology. Today it's far widely knowledgeable that, in a group the approximately. 108 cannabinoids caused by way of *C. sativa*, delta-nine-tetrahydrocannabinol (THC) is the maximum rel- event deducible to allure high effectiveness and plethora in plant readiness (Gaoni et al. 1964; Pertwee 2008). THC expends a monstrous sort of basic results by using mocking inner materials— the endocannabinoids anandamide (Devane and others. 1992) and referring to a specifically known amount of-arachidonoylglycerol (2-AG) (Mechoulam and others. 1995; Sugiura et al. 1995) that have interplay particular travelling-floor cannabinoid receptors (Pertwee et al. 2010) earlier, the main cannabinoid-exact receptors - CB1 and CB2 - have been cloned and distinguished from carnal tissues (Matsuda et al. 1990; Munro and others. 1993). also, additional receptors that involve the provisional receptor potential cation channel subfamily V appendage 1 (TRPV1) and the child without parents G protein-coupled receptor GPR55 had happened projected to properly as endocannabinoid receptors (Pertwee *et al.* 2010). Most of the belongings created by way of cannabinoids inside the startled device and in non-affecting animate nerve organ tissues depend on CB1 receptor activation. In evaluation, the CB2 receptor curve at the beginning outlined to be talent inside the immune tool (Pertwee and others. 2010), however extra now it's proved to be meant also in cells from various inceptions (Atwood et al. 2010; Fernandez-Ruiz and others. 2007). Of discussion, expression of CB1 and CB2 receptors has happened situated in innumerable forms of cancer containers, which does now not inevitably equate with the verbalization of those receptors in the fabric sort of inception (Fernandez-Ruiz and others. 2007; Guzmán and others. 2006; Sarfaraz et al. 2008).

The endocannabinoids, together accompanying their receptors and the proteins accountable for their syn- belief, transportation, and degradation, show the endocannabinoid device. Other than its important neuromodulatory interest (Katona and others. 2008), the endocannabinoid machine applies added regulatory physiognomy inside the party such as the control of cardiovascular color, substance absorption, immunity, and duplication (Pacher and others. 2006; Pertwee 2009). This miscellaneous exercise from the pharmacological manipulation of the endocannabinoid maneuver is a hopeful arrangement for the management of many particular disease. Mainly, cannabinoids are widely acknowledged to wield palliative effects in malignancy patient (Pacher et al. 2006; Pertwee 2009). The phenomenal-backed use is the hindrance of chemotherapy-provoked disease in the stomach and vomiting (Guzmán 2003; Pertwee 2009). Existing, drug of THC (Marinol®) and allure synthetic parallel nabilone (Cesamet®) are granted for this motive. Cannabinoids again prevent pain, and so a standardized marijuana extract (Sativex®) has already been approved in Canada and is presently in the position of enormous-scale section 3 dispassionate troubles for directing most cancers-associated pain. Some different potential palliative impact of cannabinoids in oncology, situated utilizing section three dispassionate tests, includes demand provocation and debilitation of wasting. In conditions of this Marinol® can now be prescribed for eating disorders to guide weight decline in AIDS patients the healing volume of cannabinoids in oncology won't be forced to their foremen-tioned relief actions. Therefore, several studies have determined evidence that THC and different cannabinoids reveal antitumor results on a big draft of animal models of most cancers (Guzmán 2003; Sarfaraz and others. 2008; Velasco and others. 2012). moreover, these remarks managed to the improvement of a ship dispassionate study to investigate the antitumor action of THC in glioma victims. Although research has shown that, beneath certain conditions, cannabinoid situation can excite cancer cellular conception artificial (Cudaback et al. 2010; Hart and others. 2004), and obstruct the Cancer- suppressor position of the immune novelty (McKallip and others. 2005; Zhu et al. 2000). Likewise, skilled are contradictory reviews regarding the part (swelling-suppressor or oncogenic) of the endocannabinoid machine in tumor (Malfitano and others. 2011) (BOX.1).

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Box 1 Biological role of the endocannabinoid system in tumor generation and progression

To date, little is known about the biological role of the endocannabinoid system in cancer physiopathology. Although there are some exceptions that may be tumor type-specific, both cannabinoid receptors and their endogenous ligands are generally upregulated in tumor tissue compared with non-tumor tissue (Caffarel et al. 2006; Guzmán 2003; Malfitano et al. 2011; Sánchez et al. 2001). Additionally, different studies have associated the expression levels of cannabinoid receptors, endocannabinoids, and/or endocannabinoid-metabolizing enzymes with tumor aggressiveness (Malfitano et al. 2011; Nomura et al. 2010; Thors et al. 2010), which suggests that the endocannabinoid system may be overactivated in cancer and hence protumo- rigenic (Malfitano et al. 2011). In support of this, in mouse models of cancer, genetic ablation of CB_1 and CB_2 receptors reduces ultraviolet light-induced skin carcinogenesis (Zheng et al. 2008), and CB_2 receptor overexpression enhances the predisposition to leukemia after leukemia virus infection (Joosten et al. 2002).

Conversely, and in line with the evidence supporting the hypothesis that pharmacological activation of cannabinoid receptors reduces tumor growth (Guzmán 2003; Sarfaraz et al. 2008), the upregulation of endocannabinoid-degrading enzymes has been observed in aggressive human tumors and cancer cell lines (Nomura et al. 2010; Thors et al. 2010), indicating that endocannabinoid signaling can also have a tumor-suppressive role. In support of this, deletion of CB_1 receptors accelerates intestinal tumor growth in a genetic mouse model of colon can- cer (Wang et al. 2008), increased endocannabinoid levels diminish azoxymethane-induced precancerous lesions in the mouse colon (Izzo et al. 2008), and a reduction in the expression of the endocannabinoid-degrading enzyme monoacylglycerol lipase reduces tumor growth in xenografted mice (Nomura et al. 2010).

Further studies, including those analyzing the activation of the precise signaling mechanisms involved in the regulation of cannabinoid-induced cell death or cell proliferation upon genetic or pharmacological manipulation of the endocannabinoid system, are therefore needed to clarify which are the contextual determinants for this system to act as either a guardian or an inducer of tumorigenesis or tumor progression.

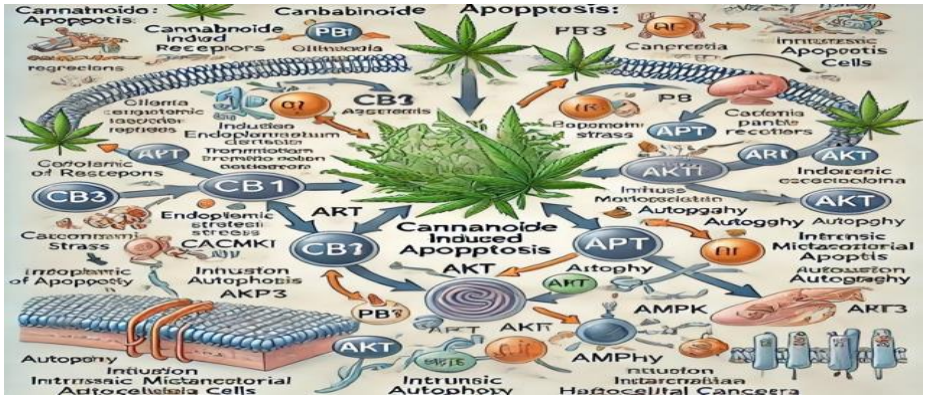

Fig.1 Cannabinoid-inferred apoptosis depends on the stimulation of ER stress and autophagy. Scheme describing the machine of cannabinoid-induced apoptosis in glioma, pancreatic, and hepatocellular malignant growth containers. This indicating route may establish the main means of cannabinoid-induced container dying, accompanying some differences hereditary to different types of malignancy containers.

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Cannabinoid agonists bind to CB1 and/or CB2 receptors (CBR) to provoke a de novo combination of ceramide (Carracedo and others. 2006b; Galve-Roperh et al. 2000; Gomez del Pulgar and others. 2002; Herrera and others. 2006; Salazar and others. 2009) which brings about the inference of an endoplasmic reticulum (ER) stress-connected answer that advances the upregulation of the transcription determinant p8 and variousof its coming after goals, containing the pseudokinase Treble's 3 (TRIB3) (Carracedo et al. 2006a; Salazar and others. 2009). This favors the interplay of TRIB3 with AKT (Du and others. 2003; Salazar and others. 2009), thus superior to the hindrance of the AKT–the mechanistic aim of rapamycin C1 (mTORC1) axis and the after inference of autophagy (Salazar et al. 2009). Autophagy is hard to do because of inborn mitochondrial apoptosis while cannabinoid-induced container oblivion. The importance of this road is emphasized by the skill of various chemical and hereditary manipulations to block cannabinoid-inferred container death. In hepatocellular malignant growth containers, the cannabinoid-evoked and ER stress-weak incitement of calcium/calmodulin-reliant protein kinase kinase 2-beta (CaCMKKβ) and AMP-stimulated protein kinase (AMPK) leads, in addition to the p8–TRIB3 pathway, to autophagy and apoptosis (Vara and others. 2011). The cannabinoid-stimulated hindrance of AKT could advance era arrest in breast tumor and melanoma containers, in addition to apoptosis, this study epitomizes these notes and provides a joined view of the microscopic means responsible for cannabinoid antitumor endeavor. It too discusses the experiment- babble evidence advocating the life of mechanisms of opposition to the container death-advancing conduct of THC in certain types of cancer containers, the attainable strategies that may start to overcome aforementioned resistance, and the preclinical dossier upholding that the combined presidency of cannabinoids and different drugs may be useful in anticancer analyses.

2. Preclinical antitumor exercise

Since the late 1990s, a big body of evidence has grown professed that miscellaneous cannabis- noids apply antitumor effects in an expansive difference of exploratory models of cancer, varying from can- cer container lines in sophistication to innately engineered rodent (inspected by Velasco and others. 2012). Multiple cannabinoids have shown this endeavor, containing THC, the endocannabinoids 2-AG and anandamide, and various artificial cannabinoid receptor agonists that have either comparable similarity for CB1 and CB2 receptors (like, WIN 55212-2 or HU-210), larger similarity for CB1 (e.g., methananda- mode), or bigger similarity for CB2 (such as, JWH-133). These findings powerfully support that, apart from the part performed by the inside cannabinoid order in tumors, pharmacological stimulation of CB receptors is private cases antitumorigenic. Nonetheless, many reports have projected a Cancer-promoting effect of cannabinoids (Cudaback and others. 2010; Hart and others. 2004; McKallip and others. 2005; Zhu et al. 2000) these contradictory notes are debated in later sections.

Cannabinoids hinder carcinoma progress at different levels. Their most prevailing effect is the initiation of malignancy container death by apoptosis and the restriction of tumor container proliferation. At least one individual of these conduct has existed and explained in virtually all malignancy container types proven (Velasco et al. 2012). In addition, in vivo experiments have proved that cannabinoids harm lump angiogenesis and block attack and metastasis.

3. Mechanisms of antitumor belongings

3.1 Induction of malignancy container oblivion

A significant amount of the research administered up until now on the machine of cannabinoid antitumor activity has attracted on glioma containers. Initial studies accompanied that THC and additional cannabinoids induce the apoptotic obliteration of glioma containers by way of CB1- and CB2-dependent provocation of the again combination of the proapoptotic sphingolipid ceramide (Blazquez and others. 2004; Galve-Roperh et al. 2000; Gomez del Pulgar and others. 2002; Sánchez and others. 2001). Further studies, established the analysis of the deoxyribonucleic acid verbalization sketch of

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THC-impressionable and -resistant glioma containers, presenting further

FIg. 1 (continued) supplementary mechanisms, containing the curtailed phosphorylation of the proapoptotic protein BCL2-befriended agonist of container death (BAD) (Ellert-Miklaszewska and others. 2005) and the incitement of the cyclin-weak kinase (CDK) inhibitory proteins p21 and p27 (Blazquez and others. 2006; Caffarel et al. 2008; Caffarel and others. 2006). This would bring about the after-decreased phosphorylation of the retinoblastoma protein (pRB), which so hopefully alive to arrest the cell phase. ATF4: stimulating copy determinant 4; CHOP: C/EBP homology protein; eIF2α: eukaryotic interpretation introduction determinant 2 beginning; SPT: serine palmitoyltransferase. Reproduced from Nature Reviews Cancer, 12(6) Velasco G., Sánchez C. and Guzmán M., towards the use of cannabinoids as antitumor agents, pp. 436–44, © 2012, Nature Publishing Group.

Awareness of the particular signaling occurrences coming after ceramide that are activated in malignancy containers by cannabinoids (Carracedo et al. 2006b). THC sharply upregulates the verbalization of the stress-regulated protein p8 (more chosen NUPR1), a transcriptional manager that has been involved in the control of tumorigenesis and carcinoma progression (Encinar and others. 2001), in addition to several of allure coming after goals such as the endoplasmic web (ER) stress-accompanying transcription determinants ATF4 and CHOP, and the pseudokinase tribbles-complement 3 (TRIB3) (Carracedo et al. 2006b) (Fig. 1).

ER stress, as persuaded by various anticancer agents, can again lead through various methods (Verfaillie et al. 2010) to the provocation of autophagy, an essential basic process participating in any of corporal functions within the container (Mizushima and others. 2008; Verfaillie et al. 2010). During autophagy organelles and added cytoplasmic elements are overwhelmed within double-sheet vesicles named autophagosomes. The maturation of these vesicles includes their mixture with lysosomes, which leads in the proper sequence to the depravity of the autophagosome components by lysosomal enzymes (Mizushima et al. 2008). Autophagy is generally a cytoprotective means, although allure incitement can also bring about container death (Eisenberg-Lerner and others. 2009; Mizushima and others. 2008). Indeed, THC-sparked stimulation of the p8-controlled road enhances the inhibitory interplay of TRIB3 accompanying a prosurvival kinase, AKT which leads to the restriction of the beastlike target of rapamycin complex 1 (mTORC1), and the after provocation of autophagy-interfered cell extinction (Salazar and others. 2009) (Fig. 1). Cannabinoids induce autophagy indifferent types of tumor cells in civilization, and pharmacological or historical restriction of autophagy prevents cannabinoid antitumor operation indifferent animal models of cancer (Fig. 1), so professed that autophagy is important for cannabinoid antineoplastic exercise (Salazar and others. 2009; Vara et al. 2011). Moreover, the autophagy barrier hinders cannabinoid-inferred apoptosis and cell decrease when in fact apoptosis blockade avoids cannabinoid-inferred cell demise but not autophagy (Salazar and others. 2009; Vara et al. 2011). This displays that autophagy is hard on someone of apoptosis in the system of cannabinoid-induced container oblivion (Fig. 1).

The direct participation of the p8-intervened autophagy road in the antitumor action of cannabinoids has been positively showed in glioma cells and pancreatic and hepatic malignancy containers (Carracedo et al. 2006a, 2006b; Salazar and others. 2009; Vara and others. 2011). At least part of this indicating route has to be established expected upregulated on cannabinoid situation in other types of tumor containers. This suggests that accompanying few variations this could be an inexact method by which activation of CB1 and CB2 receptors advances malignancy cell passing.

Additional methods may nevertheless consent the p8-mediated autophagy road to induce tumor cell obliteration (Fig. 1). For example, in hepatocellular abnormal growth in animate being cells, cannabinoids can produce an ER stress-helpless activation of AMPK that cooperates accompanying the TRIB3- interfered inhibition of the AKT–mTORC1 point around which

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something revolves in the provocation of autophagy-arbitrated cell afterlife (Vara and others. 2011). In melanoma (Blazquez et al. 2006), feelings malignant growth (Caffarel et al. 2006, 2012), and prostate malignant growth (Sarfaraz and others. 2006) containers cannabinoids can induce container phase arrest in concert with accompanying apoptosis (Blazquez and others. 2006; Caffarel et al. 2006; Sarfaraz and others. 2006). Of note, cannabinoid antiproliferative operation—at least in melanoma (Blazquez and others. 2006) and conscience malignancy (Caffarel et al. 2006) containers—likewise relies on AKT hindrance.

Likewise, the effect of cannabinoids in birth control method-dependent tumors can bank, at least incompletely, on their strength to obstruct the activation of tumor determinant receptors (Guzmán 2003; Sarfaraz et al. 2008). Some of these and added machines (Guindon et al. 2011) concede the possibility take part in the cytotoxic operation of cannabinoids in different types of tumor containers together with the autophagy-interceded container death road. However, further case is required to purify this issue (Box 2).

Box 2. Mechanism of cannabinoid receptor-mediated cancer cell death: some important unanswered questions

Research conducted during the last few years has shed light onto the intracellular signaling mechanisms underlying cannabinoid anticancer action. However, a number of important observations—in particular ones related to the role played by cannabinoid receptors in the triggering of these signals—remain to be clarified. For example:

- Unlike the cell death-promoting action of cannabinoids on cancer cells, the viability of nor- mal (non-transformed) cells is unaffected or—under certain conditions—even enhanced by cannabinoid challenge (Carracedo *et al*. 2006b; Galve-Roperh *et al*. 2000, 2008; Gomez del Pulgar *et al.* 2002; Salazar *et al.* 2009). For example, THC treatment of astrocytes (a cell type that expresses functional CB_1 receptors) does not trigger the activation of ER stress, the upregulation of the p8 pathway, the inhibition of the AKT–mTORC1 axis or the stimulation of autophagy and apoptosis, even when concentrations of THC higher than those that promote glioma cell death are used (Carracedo *et al*. 2006b; Salazar *et al.* 2009). Similar results were obtained with primary embryonic fibroblasts (Carracedo *et al*. 2006a; Salazar *et al*. 2009) and other types of nontransformed cells expressing functional can- nabinoid receptors when compared with their transformed counterparts (Blazquez *et al.* 2006; Caffarel *et al.* 2006; Casanova *et al.* 2003; Chan *et al.* 1996). Thus, stimulation of can- nabinoid receptors seems to be coupled to the activation of different signaling mechanisms in transformed and nontransformed cells. The precise molecular reasons for this different behavior remain as an important open question in the cannabinoid field.
- Another intriguing observation is that, in some types of cancer cells, such as glioma cells, pharmacological blockade of either CB_1 or CB_2 receptors prevents cannabinoid-induced cell death with similar efficacy (Galve-Roperh *et al.* 2000; Lorente *et al.* 2011), while in other types of cancer cells, for example, pancreatic (Carracedo *et al.* 2006b), breast (Caffarel *et al.* 2006), or hepatic (Vara et al. 2011) carcinoma cells, antagonists of CB_2 but not of CB_1 receptors inhibit cannabinoid antitumor actions. Why the receptor type through which cannabinoids produce their antitumor action depends on the type of cancer cell studied has yet to be established.
- Some cannabinoid receptor agonists promote cancer cell death more efficiently than other agonists that exhibit similar or even higher affinity for CB_1 or CB_2 receptors. For example, THC promotes cancer cell death in a CB_1- and/or CB_2-dependent manner at lower concentrations than the synthetic cannabinoid receptor agonist WIN 55,212-2, although the latter agent displays significantly higher affinity for CB_1 and CB_2 receptors in binding assays (Pertwee *et al.* 2010).

Further work aimed at investigating, for example, CB receptor homo or hetero-oligomerization in response to different cannabinoid agonists, their association with specific domains in the plasma membrane such as lipid rafts, changes in the subcellular location of CB receptors, and the selective coupling to different G proteins and other signaling proteins will be essential to answer these questions and precisely define the role played by each cannabinoid receptor type as an anticancer signaling platform.

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Of note, cannabidiol (CBD), a phytocannabinoid accompanying reduced affinity for cannabinoid receptors (Pertwee 2009), and different grass-derivative cannabinoids (Ligresti and others. 2006) have also been projected to advance the apoptotic death of malignancy containers acting alone of CB1 and CB2 receptors. The mechanism by which CBD produces this effect has not existed entirely explained as yet but appears to rely—not completely incompletely—on its capability to improve the result of sensitive oxygen species in tumor containers (Massi and others. 2008; Shrivastava *et al.* 2011). It has still been projected that CBD may stimulate TRPV2 receptors to advance glioma container passing (Nabissi et al. 2012).

2. Inhibition of angiogenesis, encroachment, and often major

In tumor cells, cannabinoids block the incitement of the vascular endothelial development determinant (VEGF) road, an inducer of angiogenesis. Specifically, different components concerning this cascade, to a degree the main ligand (VEGF) and the active forms of allure main receptors (VEGFR1 and VEGFR2), are downregulated on cannabinoid situation of skin carcinomas (Casanova and others. 2003), gliomas (Blazquez *et al.* 2003, 2004), and thyroid carcinomas (Portella and others. 2003). In vascular endothelial containers, cannabinoid receptor incitement restricts proliferation and movement and induces apoptosis (Blazquez and others. 2003; Pisanti and others. 2007). These and perhaps added cannabinoid-induced conduct influence a normalized tumor vasculature; namely, tinier and/or minority vessels that are more differentiated and less punctured.

Likewise, cannabinoids humble the composition of distant lump crowd in animal models of two together persuaded and spontaneous change and restrict attachment, migration, and invasiveness of glioma (Blazquez and others. 2008), feelings (Grimaldi and others. 2006; Qamri and others. 2009), lung (Preet and others. 2008; Ramer and others. 2008), and cervical (Ramer and others. 2008) cancer containers in education. These belongings depend, not completely incompletely, on the timbre of extracellular proteases (in the way that matrix metalloproteinase 2 (MMP2)) (Blazquez and others. 2008) and their inhibitors (to a degree fabric inhibitor of origin metalloproteinases 1 (TIMP1)) (Ramer and others. 2008).

Of note, the pharmacological restriction of ceramide biosynthesis abrogates the antitumor and antiangiogenic effect of cannabinoids in glioma xenografts and decreases VEGF production by glioma containers artificial and in vivo (Blazquez and others. 2004). Likewise, hindrance of MMP-2 expression and glioma container attack is obviated by blocking ceramide biosynthesis and by knocking-unhappy p8 verbalization (Blazquez and others. 2008). Although further research is still unavoidable to precisely delimit the microscopic means responsible for the conduct of cannabinoids, these observations signify that the ceramide/p8-controlled pathway plays an accepted function in the antitumor activity of cannabinoids that guide CB1 and CB2 receptors.

It is value noting that CBD, by acting alone of CB1 and CB2 receptors, produces an extraordinary antitumor effect—including decline of invasiveness and metastasis—in various animal models of malignancy. This effect of CBD appears to rely—not completely in part—on the downregulation- of the loop-loop-loop copy factor prevention of DNA binding-1 (ID-1) (McAllister and others. 2011; Soroceanu and others. 2012).

3 Regulation of antitumor exemption

Of course, the provocation of cannabinoid receptors may result in important modifications inside the processes that organize antitumor exemption. For this reason, as an instance, the situation of rodents accompanying THC triggers a shift (from Th1 to Th2) in the cytokine characterization (Lu and others. 2006; McKallip and others. 2005; Newton and others. 2009; Steffens et al. 2005) and induces group of myeloid-derivative suppressor containers (Hegde et al. 2010), two occurrences that play a fault-finding act inside the abolition of antitumor immunity. In agreement at this moment idea, the provocation of CB2 receptors has been projected in a few reviews to decorate tumorigenesis

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through obstructing tumor following for one invulnerable machine (McKallip and others. 2005; Zhu and others. 2000). By comparison, cannabinoids provide permission nevertheless enhance invulnerable approach-intervened carcinoma surveillance in a few situations: the antitumor operation of WIN 55212-2 (a CB1/CB2-blended agonist) or JWH-133 (a CB2-discriminating agonist) changed into greater awesome in cancer xenografts produce in immunocompetent rodent in comparison accompanying the ones in immunodeficient rodent (Blazquez and others. 2006). This also presents that, now not completely in this vicinity model, provocation of CB2 receptors often prevents most cancer development through direct consequences on malignancy packing containers instead in reality interfering with the sane antitumor function of the invulnerable arrangement. In line with this concept, the state of affairs for 2 age immunocompetent rats accompanying very excessive doses (50 mg/kg/day 5 periods a temporal duration of occasion or entity's life) of THC curtailed the occurrence of diverse styles of tumors and decorated the overall continuation of these mammals (Chan et al. 1996). Those notes may have reference to the ability of THC to defeat swelling (Burstein and others. 2009; Liu and others. 2010), an impact which could halt certain styles of cancer (Liu and others. 2010). For cannabinoid use to be clinically worthwhile, antitumor belongings will want to triumph over immunosuppressive (conceivably swelling-promoting) assets. Extra studies undergo explain this problem. For example, it can be reasonable to examine the impact of cannabinoid administration in the era and development of tumors offering distinctive feeling to cannabinoids and creation in immunocompetent or immunodeficient rodents in which the verbalization of CB1 and/or CB2 receptors in packing containers from the invulnerable method has been innately maneuvered.

4 Resistance gadgets

Numerous research has supplied our appreciation of the sort of malignancy, by way of which each subtype of most cancers, or even every individual cyst, well-known shows an order of microscopic characteristics that comes to a decision its conduct and, enormously, allure responsiveness to various anticancer drugs. In agreement with this presentation of argument, a contemporary file examined the molecular countenance manual for the fighting of a set of human glioma container traces and basic breedings to cannabinoid antitumor operation (Lorente et al. 2011). This takes a look at granted that, even though the apoptotic effect of THC on glioma bins trusted the provocation of cannabinoid receptors and the incitement of the p8-intervened autophagy avenue, the differences in the subtlety to THC-inferred field demise compared accompanying the decorated verbalization of a particular set of genes inside the THC-opposing glioma bins rather with the region of numerous verbalization stages of CB1 or CB2 receptors (Lorente and others. 2011). Of hobby, upregulation of this kind of gene, midkine (MDK), encodes a tumor determinant that has passed off previously guide raised malign- jump and opposition to anticancer treatment plans in various sorts of tumors (Kadomatsu 2005; Mirkin and others. 2005), compares with a decrease ordinary endurance of cases accompanying glioblastoma (Lorente and others. 2011). moreover, MDK performs an immediate function in combating THC operation by using a manner of stimulation of the anaplastic lymphoma kinase (ALK) (Palmer and others. 2009). As a result, the provocation of ALK through MDK restricts the THC-brought-about autophagy-mediated field afterlife avenue. Further studies ought to explain whether this device contends with also arranging the combating of malignancy packing containers expressing severe stages of MDK to extra remedies. Curiously, in vivo, silencing of MDK or pharmacology- U.S state restriction of ALK in a rodent xenograft version abolishes the prevention of THC remedy of settled tumors arising cannabinoid-opposing glioma cells (Lorente and others. 2011).

Taken collectively, those verdicts aid the plan that provocation of the MDK–ALK axis assisting- motes opposition to THC antitumor operation in gliomas and will help to set the action for the potential dispassionate use of THC

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collectively accompanying inhibitors of this spindle (Fig. 35.2). In step with this plan, ALK inhibitors have begun to be secondhand in dispassionate checks for the administration of non-small-box

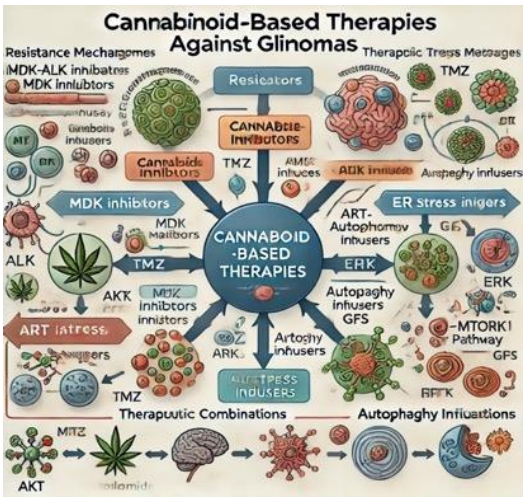

Fig. 35.2 (See further color plate portion.) Possible strategies proposed for optimizing cannabinoid-located remedies against gliomas. Glioblastoma is well-resistant to current anticancer medicines (Lonardi and others. 2005; Nieder and others. 2006; Purow et al. 2009).

Specifically, fighting glioma containers Cannabinoid-inferred cell demise relies, not completely incompletely, on the embellished expression of the development determinant midkine (MDK) and the after-activation of the anaplastic lymphoma receptor tyrosine kinase (ALK) (Lorente and others. 2011). Likewise, reinforced verbalization of the heparin-bound EGFR-ligand amphiregulin (AREG) can promote fighting to THC antitumor operation by way of ERK provocation (Lorente et al. 2009). A combination of THC accompanying pharmacological inhibitors of ALK (or hereditary hindrance of MDK) enhances cannabinoid operation in opposing tumors, which provides the action for the design of address healings fit increasing cannabinoid antineoplastic project (Lorente and others. 2011). Combinations of cannabinoids accompanying classical chemotherapeutic drugs to a degree the alkylating power temozolomide (TMZ; the standard power for the management of glioblastoma (Lonardi and others. 2005; Stoop and others. 2005)) have been shown to produce a forceful anticancer operation in animal models (Torres and others. 2011). Combining cannabinoids and TMZ is thus a very appealing feasibility for dispassionate studies proposed to investigate cannabinoids' antitumor belongings in glioblastoma. Other conceivably appealing strategies to reinforce cannabinoid anticancer operation (still needing additional exploratory support from dossier acquired utilizing preclinical models) could be joining cannabis- noids accompanying endoplasmic mesh (ER) stress and/or autophagy inducers or with inhibitors of the AKT–mechanistic aim of rapamycin C1 (mTORC1) pivot. Abs: antibodies; EGFR: epidermal tumor factor receptor; ERK: extracellular signal-controlled kinase; GF: development determinants; RTK: receptor tyrosine kinase; TRIB3: tribbles 3; VEGF: vascular endothelial progress factor. Reproduced from Nature Reviews Cancer, 12(6) Velasco G., Sánchez C. and Guzmán M., Towards the use of cannabinoids as antitumor powers, pp. 436–44, © 2012, Nature Publishing Group. Body part malignancy and other types of tumors (de Bono and others. 2010; Grande and others. 2011). Future research endures explaining whether this method of opposition to cannabinoid operation operates in added types of tumors. In agreement with this feasibility, MDK muzzling enhanced the sympathy of cannabinoid-opposing pancreatic tumor containers to THC-induced container dying (Lorente and others. 2011).

The release by cancer containers of added tumor determinants has also existed involved in the means of resistance to cannabinoid antitumor operation. Thus, raised verbalization of the heparin-bound epidermal growth determinant receptor (EGFR) ligand amphiregulin is guide reinforced as opposed-ance to THC antitumor action in glioma xenografts (Lorente and others. 2009). Of note, illustrating that the application of cannabinoids may be crucial for their optimum healing effect, depressed (submicromo- lar) concentrations of THC or additional synthetic cannabinoid agonists reinforce the increase of various cancer container lines. This effect depends on the activation of the protease ADAM17, the peeling of heparin-bound EGFR ligands, containing amphiregulin, and the

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after-provocation of the extracellular signal-regulated kinase (ERK) and AKT pathways (Hart and others. 2004). In line with this plan, a current report has shown that the situation accompanying the artificial cannabinoid, CP-55,940, increases the increase of murine glioma containers devised to express CB1 or CB2 receptors only when these receptors were connected to AKT activation (Cudaback and others. 2010). Although a protumorigenic effect has not been noticed on the growth of lump xenografts create accompanying glioma containers and treated accompanying depressed doses of THC (Torres and others. 2011), increased verbalization of amphiregulin advances opposition to THC antitumor operation through a mechanism that includes the EGFR-weak provocation of ERK and the subsequent restriction of p8 and TRB3 verbalization. Likewise, pharmacological restriction of EGFR, ERK (Lorente et al. 2009) or AKT (authors' classified remarks) improves the container death-advancing operation of THC in the education of glioma cells. These remarks imply that point or direct at a goal EGFR and the AKT and ERK pathways take care of enhancing the antitumor effect of cannabinoids.

5 Cannabinoid-located producing combinations therapies

The use of producing combinations of anticancer analyses has theoretical benefits over sole-power-based plans as they admit the concurrent targeting of carcinoma development, progress, and spreading at various levels. In line with this plan, current observations desire that the linked presidency of cannabinoids with different anticancer drugs acts synergistically to humble cyst growth. For example, the presidency of THC and temozolomide (the standard power for the management of glioblastoma) utilizes a powerful antitumor operation in glioma xenografts, an effect that is likewise clear in temozolomide-opposing tumors (Torres et al. 2011). Of interest, no toxicity was noticed in rodents treated accompanying consolidations of THC and temozolomide (Torres and others. 2011). As most patients accompanying glioblastoma have temozolomide situation, these findings display that the linked presidency of temozolomide and cannabinoids could be therapeutically used for the administration of glioblastoma (Fig. 2).

Likewise, another study has currently shown that the linked presidency of gemcitabine (the yardstick agent for the situation of pancreatic tumors) and various cannabinoid ago- lists synergistically reduce the being of pancreatic malignancy containers (Donadelli et al. 2011). Other reports display that anandamide and HU-210 concede the possibility again to enhance the anticancer venture of paclitaxel (Miyato and others. 2009) and 5-fluorouracil (Gustafsson and others. 2009), respectively.

A supplementary approach has existed to integrate THC with CBD, a phytocannabinoid that reduces—even though to a lower magnitude than THC—the tumor of several types of Cancer xenografts through a still poorly delineated device (Massi et al. 2006; McAllister and others. 2007; Shrivastava and others. 2011). Combined presidency of THC and CBD enhances the anticancer exercise of THC and reduces the doses of THC to encourage its swelling progress-preventing activity (Marcu and others. 2010; Torres and others. 2011). Moreover, the consolidation of THC and CBD together with temozolomide produces an extraordinary decline in the tumor of glioma xenografts even when low doses of THC are secondhand (Torres and others. 2011). Of note, CBD has also been proven to lessen a few of the undesired belongings of THC presidency, to a degree convulsions, discoordination, and psychotic occurrences, and then improves the tolerability of marijuana-located cures (Pertwee 2009). As mentioned earlier, *Cannabis sativa* produces nearly 108 various cannabinoids, and, other than CBD, some of the added cannabinoids present in pot ability to attenuate the affecting the mind to produce vivid vision reactions of THC or even produce added therapeutic benefits (Pertwee 2009). Thus, we judge that dispassionate studies proposed at analyzing the efficiency of cannabinoids as antitumor powers concede the possibility to be based on the use two together of clean elements, such as THC and CBD, and of marijuana extracts holding reserved amounts of THC, CBD, and other cannabinoids.

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6. Clinical antitumor belongings of cannabinoids

Although the dispassionate authorization of cannabinoids is largely limited to relief uses in differing diseases, following a hopeful preclinical dossier, the antitumor belongings of cannabinoids are begun- complain expected clinically determined. In a pilot Phase 1 dispassionate study, nine sufferers accompanying actively increasing repeating glioblastoma that had earlier failed standard remedy experienced intracranial THC presidency (Guzmán et al. 2006). Under these conditions, cannabinoid transfer was dependable and may achieve outside important undesirable effects. In addition, even though no statistically important ends can be elicited from a follower of nine sufferers, the results obtained because the study submitted that few patients responded—at slightest partially—to THC situation in terms of dropped lump tumor rate, as evaluated by drawing reverberation depict (Guzmán

Box .3 Different pharmacological approaches to target cancer cells with cannabinoids

Cannabinoid agonists or enhancers of endocannabinoid tone?

Administration of endocannabinoids or inhibitors of endocannabinoid-degrading enzymes has been shown to reduce the growth of different types of tumor xenografts (Bifulco et al. 2001; Ligresti et al. 2003) and, therefore, could be a reasonable strategy for targeting can- nabinoid receptors for anticancer purposes. However, as discussed in Box 35.1, the role of the endocannabinoid system, including the endocannabinoid-degrading enzymes, in the control of tumor generation and progression is not well understood. Since enhancing endocannabinoid tone only has mild antitumor effects in mice and since no inhibitor of endocannabinoid degradation has been approved as yet for use in humans, clinical studies aimed at analyzing the efficacy of cannabinoids as antitumor agents should be based on the use of plant-derived or synthetic agonists of cannabinoid receptors rather than on endocannabinoids or inhibitors of endocannabinoid degradation.

Cannabis extracts or pure cannabinoids?

The long-known therapeutic properties of *Cannabis sativa*—including amelioration of symptoms associated with cancer and its chemotherapy—have led to the authorization

Box .3 Different pharmacological approaches to target cancer cells with cannabinoids

medical use of this plant and its extracts in several countries. As mentioned in the text, *C. sativa* produces about 108 different cannabinoids, including THC and CBD. Some of the other cannabinoids present in marijuana may contribute to the attenuation of THC psychoactive side effects or even to the production of other therapeutic benefits (Pertwee 2009). However, pure drugs are more prone to standardization than complex molecular cocktails. Thus, it would be ideal that studies aimed at investigating the anticancer actions of cannabinoids in patients were performed comparatively with both pure substances and cannabis extracts con- taining controlled amounts of THC, CBD, and other cannabinoids.

Which routes of cannabinoid administration?

The most widely used route of administration of recreational and self-medicated marijuana is smoking. Although THC and other phytocannabinoids are rapidly absorbed by inhalation, smoking is an unattractive clinical option. Preclinical work in animal models has typically administered cannabinoids intra peritumorally. Likewise, in the only clinical trial in which a cannabinoid has been assayed as an antitumor agent, THC was administered locally (intracra- nial delivery to GBM

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patients) (Guzmán et al. 2006). Nevertheless, this route of administration has many obvious limitations. Currently available cannabis-based medicines are administered as capsules or using an oromucosal spray (Pertwee 2009). Preclinical animal models have yielded data indicating that systemic (oral or intraperitoneal) administration of cannabinoids effectively reduces tumor growth (authors' unpublished observations), so it seems reasonable that future clinical studies directed at determining the efficacy of cannabinoids as antitumor agents use oral or oromucosal routes of administration. and others. 2006). Importantly, studies of samples acquired from two patients in this place study before and subsequently THC presidency display that the microscopic mechanism of cannabinoid antitumor operation outlined in the prior portions, that is to say p8 and TRIB3 upregulation (Carracedo et al. 2006b; Salazar and others. 2009), mTORC1 restriction (Salazar and others. 2009), provocation of autophagy and apoptosis (Carracedo and others. 2006a; Guzmán and others. 2006; Salazar et al. 2009), hindrance of container conception(Guzmán and others. 2006), declined VEGF signaling (Blazquez and others. 2004), and MMP-2 downregulation (Blazquez and others. 2008), likewise keep in tumor patients. These judgments were bright and supported the interest in the potential use of cannabinoids in malignancy analyses. However, they also emphasize the need for further research proposed to optimize the use of-cannabinoids in conditions of patient selection, mixture with different anticancer powers, and use of different routes of presidency (visualize Box 3).

Research Methodology

To investigate the position of cannabinoids in most cancer remedies, a mixed-approach method was used, integrating experimental research, systematic reviews, and meta-analyses of existing literature. Preclinical experiments applied in vitro and in vivo models that specialize in glioblastoma and different resistant cancers. Databases inclusive of PubMed, Scopus, and the Internet of Technological know-how were searched for research published between 2000 and 2023 with the use of keywords like "cannabinoids," "most cancers remedy," "mechanisms," and "clinical trials."

Information was gathered on:

Molecular mechanisms of cannabinoids' antitumor pastime.

Combination remedies involving cannabinoids and traditional anticancer sellers.

Limitations and demanding situations in cannabinoid therapy for most cancers.

Consequences

Mechanisms of Antitumor pastime:

Cannabinoids, in the main tetrahydrocannabinol (THC) and cannabidiol (CBD), show off antitumor residences through diverse mechanisms, consisting of:

Induction of apoptosis through cannabinoid receptor activation.

Inhibition of angiogenesis and tumor proliferation.

Modulation of the tumor microenvironment to suppress immune evasion.

Resistance pathways were diagnosed, along with MDK-ALK and AREG-ERK signaling.

Mixture treatment plans:

THC mixed with temozolomide (TMZ) showed more advantageous anticancer consequences in glioblastoma fashions.

Capability synergy between cannabinoids and inhibitors of AKT-mTORC1 and ER stress pathways.

Improved consequences whilst combined with traditional chemotherapy agents like cisplatin and doxorubicin.

Therapeutic capability and demanding situations:

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Promising preclinical results highlight cannabinoids' function in overcoming resistance in most cancer types.

Challenges include variability in cannabinoid formulations, dosing regimens, and a shortage of sturdy clinical trials.

Discussion

Mechanisms of action

They have looked at confirmed cannabinoids' ability to goal a couple of hallmarks of cancer, which include cellular proliferation, apoptosis, and metastasis. By binding to CB1 and CB2 receptors, cannabinoids impact key signaling pathways together with PI3K/AKT and MAPK. However, resistance mechanisms, including MDK-mediated ALK activation and AREG-brought-on ERK signaling, necessitate mixture strategies to optimize healing effects.

Combination techniques

Proof supports that combining cannabinoids with chemotherapy enhances efficacy. As an example, in glioblastoma fashions, the THC-TMZ aggregate ended in tremendous tumor size discount as compared to monotherapies. Moreover, targeting pathways like mTORC1 or inducing ER strain along with cannabinoids ought to gift novel avenues for research.

Therapeutic demanding situations

At the same time as cannabinoids show off sizable ability, their therapeutic utility faces huge hurdles, such as:

Restrained standardization of cannabinoid merchandise.

Insufficient scientific proof due to small-scale studies and lack of randomization.

Regulatory challenges and societal stigma surrounding cannabinoid use.

Destiny guidelines

To maximize the healing advantages of cannabinoids, similarly, research has to recognition on:

Large-scale, randomized clinical trials to establish safety and efficacy.

Improvement of standardized cannabinoid formulations and shipping systems.

Exploration of biomarkers to identify patients most probably to gain from cannabinoid-based cures.

Research into the function of cannabinoids in aggregate with immune checkpoint inhibitors and different rising cancer treatments.

7. Conclusions and future directions

Cannabinoids provide a promising street for cancer remedies by focusing on various pathways associated with tumor growth and resistance. However, the entire capability of cannabinoids remains unrealized due to limited scientific evidence and demanding situations in standardization and transport. Addressing those gaps through rigorous research and medical trials will be essential to advancing cannabinoids as viable anticancer marketers.

It is widely trusted that plans proposed at lowering death from malignancy should involve sullying- got remedies worthy of providing an ultimate efficacious and discriminating situation for each carcinoma and patient. Thus, the important focus of anticancer-drug development has to a greater extent transported from remiss chemotherapies to molecularly point or direct goal inhibitors. However, despite the huge amount of preclinical research on by what method these sensibly created compounds work, the advance in the use of most of these drugs in the dispassionate practice is still limited.

How do cannabinoid-located cures fit into this ongoing synopsis? Let us deem gliomas, the type of malignancy on which ultimate itemized cannabinoid research has been conducted to date. As argued former, the date of a molecular goal (CB receptors) by a classification of discriminating drugs (THC and other cannabinoid agonists) prevents Cancer tumors in animal models through a traditional mechanism of operation that appears to be managed in patients. Moreover, cannabinoids potentiate the antitumor efficiency of

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temozolomide and ALK inhibitors in rodent-protecting gliomas. These findings determine preclinical evidence-of-idea that "cannabinoid sensitizers" could help the dispassionate efficiency of classical cytotoxic drugs in glioblastoma (Fig. 35.2) and possibly added well malignant tumors to a degree pancreatic malignancy, melanoma, and hepatocellular carcinoma. However, further research is necessary to define the exact microscopic cross-talk middle from two points cannabinoids and chemotherapeutic drugs, and to optimize the pharmacology of preclinical cannabinoid-located producing combinations cures.

Regarding patient stratification, we concede the possibility of definitely deciding that particular individuals- also are potentially active to cannabinoid presidency. For this purpose, extreme-throughput approaches should be executed to find cannabinoid medicine-mixed biomarkers in tumor biopsies or, wonderfully, in surely-seized fluids containing flowing malignancy containers or enhanced levels of fighting determinants that have been freed by tumor containers. These biomarkers would conceivably have a connection with cannabinoid pharmacodynamics—namely verbalization and venture of cannabinoid receptors and their downstream container cessation-encouraging effectors. This would be similar to the biochemical judgment of estrogen and ERBB2 receptors that predict the benefit from endocrine remedies and trastuzumab, individually, in conscience malignancy. Predictive markers to delineate the sympathy of the tumor to cannabinoid-located medicines also involve the rank of progress factors, in the way that MDK in gliomas, in addition to their receptors and indicating partners.

In conclusion, cannabinoids encourage swelling container death and restrict cyst angiogenesis and invasion in animal models of tumors and there are clues that they do so also in subjects with glioblastoma. As cannabinoids show a satisfactory security description, clinical troubles experiment bureaucracy as alone drugs or, ideally, together cures in glioblastoma and different types of cancer are two together authorized and insistently needed.

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Announcement of interest

I at this moment declare that :

I have no pecuniary or other personal hobby, direct or oblique, in any rely that raises or may additionally boost a battle with my obligations as a supervisor of my workplace management.

Conflicts of interest: The authors claim that they've no conflicts of interest.

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