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TOPIC REVIEW

Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas

Francisco Carlos Machado Rocha · Jair Guilherme dos Santos Júnior · Sergio Carlos Stefano · Dartiu Xavier da Silveira

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Abstract To evaluate, through a systematic review of the literature, the antitumoral effects of cannabinoids on gliomas. Research included the following electronic databases: PUBMED, EMBASE, LILACS and The Cochrane Collaboration Controlled Trials Register. All published studies involving the antitumoral effects (cellular and molecular mechanisms) of cannabinoids were considered for this review. The bibliography search strategy included all publications of each of these databases until December 31, 2012. From 2,260 initially identified articles, 35 fulfilled the inclusion criteria for this review. All the studies included in this systematic review were experimental (in vivo and/or in vitro), except for one pilot clinical trial phase I/II involving humans. In all experimental studies included, cannabinoids exerted antitumoral activity in vitro and/or antitumoral evidence in vivo in several models of tumor cells and tumors. The antitumor activity included: antiproliferative effects (cell cycle arrest), decreased viability and cell death by toxicity, apoptosis, necrosis, autophagy, as well as antiangiogenic and antimigratory effects. Antitumoral evidence included: reduction in tumor size, antiangiogenic, and antimetastatic effects. Additionally, most of the studies described that the canabinnoids exercised selective antitumoral action in several distinct tumor models. Thereby, normal cells used as controls were not affected. The safety factor in the cannabinoids' administration has also been demonstrated in vivo. The various cannabinoids tested in multiple tumor models showed antitumoral effects both in vitro and in vivo. These findings indicate that cannabinoids are promising compounds for the treatment of gliomas.

Keywords Gliomas · Cannabinoids · Apoptosis · Cell cycle arrest · Anti-angiogenesis · Anti-metastasis

F. C. M. Rocha (✉) · S. C. Stefano · D. X. da Silveira
Paulista School of Medicine, Federal University of São Paulo, Av. Ascendino Reis, 763, Vila Clementino, São Paulo, SP 04027-000, Brazil
e-mail: franciscocmrocha@uol.com.br

S. C. Stefano
e-mail: scstefano@uol.com.br

D. X. da Silveira
e-mail: dartiu@terra.com.br

J. G. dos Santos Júnior
Faculty of Medical Sciences of Santa Casa of São Paulo, Rua dos Otonis, 628, Vila Clementino, São Paulo, SP 04025-001, Brazil
e-mail: guilherme.stos.jr@gmail.com

Introduction

The antineoplastic activity of THC and its analogues was first observed in the 1970s [1] prior to the discoveries of cannabinoid and endocannabinoid receptors. Nevertheless, more in-depth research on the subject was pursued only in the 1990s.

Cannabinoids present two well established endocannabinoids: anandamide (AEA), first described by Dr. Mechoulam's group [2] and 2-arachidonoylglycerol (2-AG) [3, 4]. To date, endocannabinoids have been described as interacting with five receptors: receptor CB1, CB2, vanilloid receptor 1 (TPRV1), GPR55 and PPARα (although little is known about the functional role of endocannabinoids' interactions with the last two receptors in the list) [5].

The so-called endocannabinoid system is constituted by endogenous cannabinoids, their receptors and their synthesis, reuptake and degradation processes [6]. Many of the pharmacological actions of the endocannabinoid system are a result of its modulatory properties with other neurotransmission systems [7], which offers great potential for

the discovery of therapeutic drugs that act within the system.

In addition to endocannabinoids, there are three primary structural classes of cannabinoid agonist ligands: (i) classical cannabinoid analogues of THC; (ii) (bicyclic and tricyclic) nonclassical cannabinoid analogues of THC; and (iii) aminoalkylindoles [8]. Synthetic agonists [8] and antagonists [9] were created for the CB1 and CB2 receptors through the selected modification of the chemical structures of the cannabinoid molecules.

Several studies suggest that drugs that mimic the endocannabinoid system can be used to hinder or block cancer development [10, 11]. Other studies show the effects of cannabinoids on various cellular and molecular mechanisms directly related to the control of cell proliferation and survival.

The objective of this systematic review was to find all the scientific information available on the antitumor effects of cannabinoids in international literature and then to group these results in order to provide an overview of the medicinal effects of cannabinoids in the treatment of gliomas.

Methodology (systematic review)

Inclusion criteria for this review

Types of studies

All published studies involving the antitumor effects (cellular and molecular mechanisms) of cannabinoids were included:

Methodologically appropriate, randomized and non-randomized clinical trials involving human beings who used cannabis (and/or cannabinoids) as antitumor treatment of gliomas.
Experimental studies that assessed the antitumor mechanisms of cannabinoids in any type of gliomas in laboratory animals as well as the use of cannabinoids in these tumor cells.

Types of participants (sample)

Patients with gliomas, independent of sex, age and area of treatment.
Laboratory animals with any type of glioma.
Glioma cells in in vitro experiments.

Types of intervention

Pharmacological interventions based on derivatives of cannabis (cannabinoids) and/or smoked cannabis, independently of the duration of intervention and independently of the association with other types of antitumor therapy in the following cases: (i) in patients with gliomas; (ii) in laboratory animals with gliomas; (iii) in tumor cells (gliomas) in vitro experiments.

Search strategy for study identification

Searches were conducted using the electronic databases of MEDLINE (PUBMED), EMBASE, LILACS and the Cochrane Collaboration Controlled Trials Register. Initially, a bibliographic search was conducted across all databases through December 2012. A further search of all references from the relevant articles found (which included review articles) was also performed in order to select items that might have been overlooked during the initial electronic search. There was no language restriction, but only complete papers published in peer-reviewed journals were considered. Data not related to the cellular and molecular effects of the antitumor actions of cannabinoids were not considered. There was no need to contact the authors of the included studies for clarification of the their study data. The search was based on the following Medical Subject Heading terms and categories: "cannabis", "cannabinoids", "endocannabinoids", "cannabinoid receptors", "gliomas", "cultured tumor cells", "antineoplastic drugs", "fatty acid synthesis inhibitors", "antimitotic drugs", "cancer treatment protocol". Adjustments were made to the terms used according to the electronic database consulted.

Methodological quality of the studies included

This systematic review did not find any randomized studies for the outcomes proposed. The only study included on the antitumor effects of cannabinoids in human beings was a pilot phase I/II clinical trial. All other studies included were experimental. Consequently, the methodological quality was intrinsic since the authors included a detailed description of all the experimental procedures carried out. Thus, the methodological assessment criteria contained in the Cochrane Collaboration Manual [12, 13] were not used to assess methodological quality.

Based on the inclusion criteria, the authors of this review included all published studies that, despite the limitations inherent to experimental studies, currently comprehend the body of scientific evidence regarding these outcomes.

Study selection process

2,260 articles were identified using the aforementioned search strategy. The titles of these articles were then sifted

Table 1 Summary of the included studies

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
End et al. [58]	in vitro	Rat C6 glioma cells	Delta-9-THC	Cell death
Sánchez et al. [59]	in vitro	C6.9 glioma cells; human astrocytoma U373MG cells	Delta-9-THC	Apoptosis (not mediated by CB1R) increase of ceramide
Galve-Roperh et al. [15]	in vitro and in vivo	in vitro: C6.9 and C6.4 in vivo: C6 glioma tumors	in vitro: delta-9-THC in vivo: delta-9-THC and WIN 55,212-2	Apoptosis (merely C6.9) CB1R, CB2R Accumulation of ceramide ERK activation in vivo: significant decrease of tumor volume compared to control
Retch et al. [16]	in vitro and in vivo	in vitro: C6 cells (rats) and U87 cells (human) in vivo: U87 tumor-bearing rats	in vitro: AJA versus delta-8-THC in vivo: AJA versus delta-8-THC versus control	Cytostatic action of AJA (CB2R) Delta-8-THC action (CB1R and CB2R) in vivo: significant decrease of tumor volume compared to control
Jacobsson et al. [33]	in vitro	C6 cells	AEA. 2-AG, PEA, meAEA, JWH015, CP 55,940, WIN 55,212-2	Apoptosis Mediation of CB and VR receptors by endogenous cannabinoids, with the contrary occurring with synthetic cannabinoids. Possible mediation of ceramide
Sánchez et al. [17]	in vivo	C6 and GBM tumor-bearing rats (immmunodeficient)	Intratumoral injection of JWH-133 versus vehicle (control)	Apoptosis Synthesis of ceramide de novo—ERK activation CB2R in vivo: significant decrease of tumor volume compared to control
Gómez del Pulgar et al. [38]	in vitro	C6.9 and C6.4 cells	Delta-9-THC	Apoptosis only C6.9 cells Event sequence: ceramide de novo, ERK activation and decrease of PKB
Macarrone et al. [60]	in vitro	C6 cells	SEA and HU-210	Apoptosis Mediation via activation of the arachidonic acid cascade
Blázquez et al. [18]	in vitro and in vivo	in vitro: vascular endothelial cells in vivo: biopsies obtained from C6 and GBM tumors-bearing immunodeficient rats	in vitro: JWH-133, WIN 55,212-2, HU-210 and delta-9-THC in vivo: intratumoral injection of JWH-133 versus vehicle	Apoptotic (ERK activation) and antimigratory effect through JWH-133 (CB2) and WIN (CB1 and CB2) in vivo: decrease of VEGF, Agn2 and MMP2 expression by JWH

Table 1 continued

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
Fowler et al. [61]	in vitro	C6 glioma cells	AEA, meAEA, 2-AG, 1-AG	Antiproliferative effects CBRs and VRs Increase of AA did not affect proliferation
Massi et al. [20]	in vitro and in vivo	in vitro: human U87 and U373 glioma cells in vivo: U87 tumor-bearing rats	in vitro: CBD in vivo: peritumoral administration of CBD versus control	Apoptosis CB2R Oxidative stress in vivo: significant decrease of tumor volume compared to control
Blázquez et al. [19]	in vitro and in vivo Phase I/II clinical trial	in vitro: C6 cells in vivo: biopsies obtained from C6 tumor-bearing immunodeficient rats Biopsies obtained from 2 patients with recurrent GBM	in vitro: WIN-55,212-2, anandamida and JWH-133 in vivo: intratumoral administration of JWH-133 and/or fumonisina In humans biopsies: delta-9-THC	Inhibitory effect on the VEGF (VEGF and VEGFR-2) mechanism, mediated by ceramide in vitro, in vivo and in humans Involvement of CB1 and CB2 (WIN 55,212-2) receptors and by CB2 (JWH-133)
Contassot et al. [62]	in vitro	U87 and U251cells Primary human leukocytes (control)	AEA	Apoptosis VR1R (and not CBRs)
Hinz et al. [35]	in vitro	Human H4 glioma cells	meAEA, AEA and delta-9-THC	Apoptosis meAEA and AEA: receptor-independent mechanism and mediated by COX-2 activation (with the same not occurring with THC) PGE2 (product of meAEA), induced by COX-2 activation,also induced apoptosis
Vaccani et al. [36]	in vitro	U87 cells	CBD	Antimigratory effect No mediation by the cannabinoid, vanilloid or protein G-coupled receptors
Goncharov et al. [63]	in vitro	C6 glioma cells	Delta-9-THC under oxidative stress and absence of glucose.	Increased cellular damage (CB1) Oxidative stress Decrease of glucose intake
McAllister et al. [64]	in vitro	GBM cells: U251-MG, U87-MG, U373-MG,SF126, SF188 Normal human glial cells (control)	Delta-9-THC versus WIN 55,212-2 versus control	Antiproliferative effect and cell death; THC > WIN Partial mediation of the CB1 and CB2 receptors (SF126 cells)

Table 1 continued

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
Ellert-Miklaszewsk et al. [65]	in vitro	C6 cells	WIN 55,212-2	Apoptosis Cell cycle arrest (sub-G1 phase) Down-regulation of Akt and ERK 1/2 Decrease of Bad phosphorylation Decrease of mitochondrial membrane potential Activation of caspase cascade
Bari et al. [34]	in vitro	C6 glioma cells	AEA AEA + MCD	Apoptosis Decrease of MAPK and PI3K Release of cytochrome c Mediation by VR1 and by the cholesterol membrane (additive antagonistic effect)
Eichele et al. [66]	in vitro	Human H4 glioma cells	meAEA	Mitochondrial apoptosis mediated by caspase 9, 3 and PARP activation, which were mediated through the increase of COX-2
Massi et al. [32]	in vitro	U87 cells Normal glial cells (control)	CBD (25 μM) versus CBD (10 μM)	Apoptosis just with the dosage of 25 μM: mitochondrial apoptosis and 'death-receptor'; oxidative stress
Duntsch et al. [21]	in vitro and in vivo	in vitro: U87 cells, U373, C6 and F98 Normal glial cells (control) in vivo: U87 tumor-bearing rats	in vitro: KM-233 versus control, delta-8-THC and BCNU in vivo: KM-233 intratumoral injection versus intraperitoneal injection	Cytotoxicity (not apoptosis):all cells U87 cells: Potency: KM-233 (CB2) = delta-8-THC (CB1 and CB2) > BCNU in vivo: safety (independent of via of administration); significant decrease of tumor volume compared to control

Table 1 continued

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
Carracedo et al. [22]	in vitro and in vivo	in vitro: C6.9, C6.4, U87, Gos3 cells in vivo: U87 tumors-bearing rats Human cells: biopsies from patients with GBM treated with delta-9-THC	in vitro: delta-9-THC in vivo: delta-9-THC	Apoptosis (exception: C6.4) Sequence of events in vitro: THC activated CB1 and CB2 receptors and induced an increase in ceramide; activation of p8 with consequent up regulation of ATF4 and TRB3 (and also CHOP in U87 cells); decrease of mitochondrial membrane potential and caspase-3 activation; apoptosis. in vivo: increase of p8 mRNA and TRB3; increase of apoptotic cells; significant decrease of tumor volume compared to control Human biopsies: apoptosis and immunoreactivity of p8
Guzmán et al. [14]	Pilot phase I clinical trial	9 patients with recurrent GBM who showed no success with standard treatment; KPS = 81; average tumor volume = 64 cm^3	Intracranial administration of delta-9-THC beginning 3–6 days following surgery	in vivo (material extracted from biopsies): apoptosis; CBRs Delta-9-THC reduced cell proliferation (Ki67) in 2 patients (1 and 2) Delta-9-THC tended to decrease tumor vascularization (CD31) in 2 patients (1 and 2), but effect was not statistically significant. Administration of the cannabinoid was safe and produced no excessive side effects
Galanti et al. [42]	in vitro	U251-MG and U87-MG cells	Delta-9-THC	Apoptosis Cell cycle arrest (G0/1 phase): decrease of the E2F1 protein expression through mediation of the proteasome; decrease of cycline A; increase of p16INK4A
Massi et al. [23]	in vitro and in vivo	in vitro: U87 cells in vivo: tumors removed from U87 tumor-bearing rats	in vitro: CBD in vivo: peritumoral administration of CBD versus vehicle	Antiproliferative effect (in vitro) and antitumor effect (in vivo) through modulation (and not mediation) of the LOX system CBD regulates endogenous tone of AEA through the increase of FAAH and decrease of AEA

Table 1 continued

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
Widmer et al. [51]	in vitro	U373 cells Primary astrocyte cells	Delta-9-THC, HU-210	Cannabinoids induced apoptosis in U373 cells, but under high dosages Mediation of the CB1R Activation of caspase 3/7 Both cannabinoids induced ERK and JNK1/2 phosphorylation (not mediation) Non-selective action of cannabinoids
Blázquez et al. [24]	in vitro and in vivo Phase I clinical trial	in vitro: C6.9, C6.4, SW1088, T98 G, U87 MG and U118 MG (GBM) cells in vivo: biopsies from C6.9 and C6.4 tumor-bearing rats Biopsies from 2 patients with GBM	in vitro: THC in vivo: peritumoral administration of THC, JWH-133 and/or fumonisina B1 Intratumoral administration of THC	in vitro: THC (1.5 μM) did not decrease the viability of C6.9 cells, but decreased the migration of C6.9 and U87 cells; Decrease of TIMP-1 expression All effects through the mediation of ceramide and p8 in vivo: significant decrease of tumor growth and of TIMP-1(C6.9, but not C6.4) through cannabinoids via mediation of ceramide In human biopsies: decrease of TIMP-1
Blázquez et al. [25]	in vitro and in vivo	in vitro: C6.9, C6.4, SW1088, T98G, U87MG, U118MG, normal glial cells and HUVECs in vivo: biopsies from C6.9 and C6.4 tumor-bearing rats Biopsies from 2 patients with recurrent GBM treated with THC	in vitro: delta-9-THC, AEA in vivo: Peritumoral administration of delta-9-THC or JWH-133 with/without fumonisina B1 versus control	THC (in vitro): inhibited invasiveness (exception: C6.4) and decreased MMP-2 mRNA levels (exception: HUVECS); mediation through CBRs, ceramide and p8 AEA (decreased MMP-2 levels by receptor-independent mechanism) in vivo: THC and JWH significantly inhibited C6.9 tumor growth (but not C6.4 tumor growth) as well as MMP-2 levels; effects mediated by ceramide Humans: reduced MMP-2 levels

Table 1 continued

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
Salazar et al. [26]	in vitro and in vivo	in vitro: U87MG, T98G, U373MG and normal astrocyte cells in vivo: U87 tumors-bearing rats Human cells: biopsies from 2 pacients with GBM treated with THC	in vitro: delta-9-THC in vivo: peritumoral administration of THC Human cells: THC	in vitro: autophagy and endoplasmatic reticulum stress mediated apoptosis induced by THC Event sequence in vitro: THC activated the CB1 receptor and induced endoplasmatic reticulum stress; increase in ceramide; increase in phosphorylation of eIF2α; up regulation of p8, with consequent up regulation of ATF4, CHOP and TRB3; inhibition of AKT/mTORC1 mechanism; autophagy; caspase-3 and Bax/Bak activation; apoptosis in vivo: THC significantly decreased tumor growth through autophagy; human biopsies: increase of autophagic cells
Marcu et al. [52]	in vitro	U251 e SF126 cells	in vitro: CBD and delta-9-THC isolated and associated	Synergistic effect (cell cycle arrest and apoptosis; not verified for invasiveness) Mediation: pERK down-regulation CB2 receptor ROS generation Specific modulation of the caspase activity (increased 3, 7, 9 e PARP) Increased p8 (not specific from synergism)
Torres et al. [27]	in vitro and in vivo	in vitro: U87, T98G, U373, A172, SW1783, SW1088, LN 405 cells in vivo: U87 and T98 tumor-bearing rats	in vitro: TMZ + THC, THC, THC-BDS, CBD, CBD-BDS, THC-BDS:CBD-BDS (1:1) in vivo: peritumoral injection: TMZ + THC, TMZ + THC + CBD, TMZ + SAT-L, THC + CBD, THC-BDS = CBD-BDS, vehicle	Synergistic effect in vitro (autophagy and apoptosis) and in vivo The glioma cells' resistance to the antitumor effects upon use of both temozolomide as well as delta-9-THC was overcome.

Table 1 continued

Study	Methods (system)	Tumor sample	Therapeutic intervention (cannabinoid used)	Effects on cell fate (cellular and molecular mechanisms)
Gurley et al. [29]	in vitro and in vivo	in vitro: U87MG in vivo: U87 tumor-bearing rats	in vitro: KM-233 in vivo: intraperitoneal injection versus control	in vitro: Autophagy (mediated by mitochondria mechanism) and apoptosis CB1R Down-regulation AKT; ERK activation; decrease of BAD phosphorylation Decrease of mitochondrial membrane potential; activation of caspase 3; cytochrome c release in vivo: Significant decrease of tumor volume compared to control Safety (any evidence of toxicity—histopatholic analysis of organs)
Nabissi et al. [57]	in vitro	U87MG and MZC glioma cells (expressTRPV2—transient receptor potential vanilloid type 2)	CBD CBD plus (TMZ or BCNU or DOXO) CBD plus (TMZ + BCNU + DOXO)	CBD acts as selective TRPV2 agonist (increase of calcium influx) CBD increases TRPV2 expression (mRNA and protein levels) CBD potentiates the cytotoxicity (apoptosis) of chemotherapeutic agents (mediation: increase of TRPV2) (CBD increase the drug intake and retention into glioma cells)
Soroceanu et al. [28]	in vitro and in vivo	in vitro: U251 cells (expressed gene Id-1) in vivo: U251 tumor-bearing rats	in vitro: CBD in vivo: intraperitoneal injection of CBD versus vehicle	in vitro: CBD inhibited Id-1 gene expression correlated with inhibition of U251 cell invasion CBD modulated the phosphorylation of several phosphor-kinases: increase of cJun, p27 and p38; decrease of Akt and pERK1/2 in vivo: Significant downregulation of Id-1 expression (and of Ki67) Significant reduction of tumor volume compared to control

to exclude all articles that did not meet the objectives of this review. Subsequently, 735 abstracts were assessed in detail. Up to this point, assessment was conducted by a single reviewer. Complete articles detailing randomized clinical trials for possible inclusion in this review were assessed by two independent reviewers (co-reviewer: JGSJr). The reviewers were not blind to the authors' names, institutions and publication journals. Finally, 81 complete articles were assessed. Bear in mind that the bibliographic references in all of the articles deemed important for this review (articles as well as reviews) were searched. The assessment was carried out in accordance with the inclusion criteria, and 35 articles met the inclusion criteria for this review. There was no disagreement between the reviewers regarding article inclusion.

Results

Of the 2,260 articles initially identified, 35 met all of the inclusion criteria for this review. Table 1 of the included studies and the section entitled "Discussion" describe the cellular and molecular mechanisms involved in cannabinoids' antitumor action. It is noteworthy that when researchers conducted more specific experiments, the sequence of events mediators of these antitumor action compounds was described.

Characteristics of the included studies in the systematic review

This review covered 35 studies on the antitumor effects of cannabinoids in gliomas. Only one study has been carried out on humans [14]. The remaining studies were experimental. Sixteen studies covered the antitumor effects of cannabinoids in vivo [14–29]. Different dosages of cannabinoids as well as different types of glioma cells were used in the studies. Furthermore, some studies used immunodeficient rats to assess the effect of cannabinoids on immunity [15, 17–19].

The studies in this review covered the effects of cannabinoids on the death of tumor cells. The angiogenesis–inhibitor and metastasis-inhibitor effects on the different types of cells investigated were also analyzed.

Discussion

Gliomas

Gliomas are classified as primary tumors originating in the glial cells, and astrocytomas are their most frequent representation (being approximately half of all brain tumors) [30]. Astrocytomas are considered highly aggressive, generally with a tumor mass exhibiting a high grade of heterogeneity and significant microvascular proliferation.

The WHO classifies astrocytomas as having either a low grade (I or II) or high grade (III and IV) of malignancy, depending on the location and rate of growth. Anaplastic astrocytomas (grade III) and glioblastoma multiforme (GBM—grade IV) represent the most aggressive primary tumors in the central nervous system and are responsible for one-third of all brain tumor diagnoses [31].

Cellular mechanisms and cannabinoid receptors

The antitumor action verified occurs through different mechanisms depending on the cannabinoid compound used and the tumor cells investigated [32]. Though a number of these actions involve the activation of receptors (e.g. cannabinoids, vanilloids) [19, 33, 34], many studies show that these effects occur through a receptor-independent mechanism [35, 36].

Apoptosis, or programmed cell death, was the most commonly described mechanism in the studies. Secondarily, cell cycle arrest through cannabinoid action was described as an important antiproliferative mechanism in tumor cells. In fact, this mechanism has been an important target in cancer management since molecular analyses of human tumors have shown that cell-cycle regulators suffer frequent mutations in the majority of common malignancies [37]. Finally, a recent study [26] showed that autophagy precedes apoptosis through delta-9-THC action in various tumor cells.

It is important to emphasize that all studies in vivo that evaluated cannabinoids action decreasing tumor size resulted in statistically significant reductions of the tumors' volumes when comparing to controls.

Molecular mechanisms and intracellular signaling pathways

This review described some mechanisms underlying cannabinoids' apoptotic effects and the cell cycle arrest. Galve-Roperh et al. [15] stressed the importance of the sustained activation of Raf1 and the accumulation of ceramide in apoptosis induced by delta-9-THC in cells C6.9. Raf1 is extremely important for controlling cell fate and involves activation of the biochemical cascade mediated by extracellular signal-regulated kinases (ERKs).

The accumulation of ceramide, in turn, leads to the sustained inhibition of Akt [38] and of other protein kinases, such as c-Jun N-terminal kinase (JNK) and p38 MAPK (mitogen-activated protein kinase) [15]. In his study, Gómez Del Pulgar et al. [39] proved a direct relationship between the accumulation of ceramide and ERK

activation as a result of exposure to delta-9-THC in C6 cells. The sphingomyelin cycle has been shown to be critically important in regulating cell function as it is associated with apoptosis through the increase in intracellular ceramide levels [40] in tumor cells in both the central [15, 26] and the peripheral nervous systems [41].

Massi et al. [20], in turn, shows that the apoptotic effect of CBD in human glioma cells (U87 and U373) was not mediated by accumulation of ceramide, but, at least in part, by oxidative stress (ROS) [20]. Additional mechanisms involved in CBD action include lipoxygenase (LOX) modulation [23].

Other important cannabinoid mechanisms involve cyclooxygenase-2 (COX-2) activity [35] and the lipid transport mechanism [34]. Indeed, this review showed that these mechanisms were exclusive to the endocannabinoids action and of their synthetic analogues.

In terms of the mechanisms involved in cell cycle arresting, intrinsic characteristics occur in the cells depending on the phase of the cycle in which this block occurs. In a study of human astrocytoma cells (U251MG and U87MG), Galanti et al. [42] shows that delta-9-THC decreased E2F1 and cyclin A in cells, both being proteins that promote the progression of the cell cycle. Furthermore, there was an increase in the levels of p16INK4A, a cell cycle inhibitor [43], which is inactivated in gliomas in more than 50 % of cases [43].

We know that early mechanisms that precede deregulation of cell survivor mechanisms as well as other mechanisms that lead to tumor cell death are important targets of the cannabinoid action. Salazar et al. [26] showed the importance of endoplasmatic reticulum stress and of the up-regulation of the p8-TRB3 mechanism (through delta-9-THC action) in inducing autophagia and subsequent apoptosis of human glioma cells (U87MG, T98G and U373MG). The various experiments conducted in Salazar's study [26] elucidate the sequential events involved in tumor cell death induced by delta-9-THC, which are listed in Table 1. An analysis of rat tumors marked with U87MG tumor cells as well as biopsies of GBM patients were consistent with the foregoing findings [26] suggesting an effetive action of delta-9-THC cannabinoid in human tumors.

It is important to highlight a recent study [28] showing the action of CBD (in vitro and in vivo) in the inhibition of Id-1 gene expression, which is related to the aggressiveness of some tumors, including GBM.

Inhibition of tumor angiogenesis

Vascular endothelial growth factors (VEGFs) and Ang2 (angiopoietin-2) are essential to generate new blood vessels in a number of tumors, including gliomas [44]. Inhibiting tumor angiogenesis via cannabinoids involves at least two mechanisms: (i) direct inhibition of migration and survival of endothelial cells; (ii) suppression of pro-angiogenic (VEGF and Ang2) factors [18] and expression of matrix metalloproteinase (MMP, primarily MMP-2) in tumors [18]. We must keep in mind that endothelial cells express functional CB1 [45] and CB2 [18] receptors and that these receptors modulate essential functions of these cells, such as migration and proliferation [18]. We know that ceramide also inhibits both VEGF production as well as activation of its receptor, which indicates that ceramide plays a central role in the anti-angiogenic action of cannabinoids [10, 19].

The migration-inhibitor (metastasis-inhibitor) effect

The action of MMPs and their inhibitors tissue inhibitors of metalloproteinases (TIMPs) play a central role in the migration and invasiveness of tumor cells [24]. A number of studies show that the majority of human cancers present an increase in the expression and activation of MMPs, including MMP-2 [46] and that this increase is associated with a poor prognosis [47]. In addition, the most proeminent TIMP, TIMP-1 [24], is being studied to determine if inhibition of the MMP, induced by the cannabinoid, is related to inhibition of the glioma cell migration, induction of cell death and inhibition of tumor angiogenesis [24].

In vitro (human astrocytomas cells) and in vivo experiments (biopsies of both rats and humans with gliomas) demonstrated the antitumor action of delta-9-THC through mediation of ceramide and stress protein p8, including the decrease of TIMP-1 and MMP-2 [24, 25]. Furthermore, they showed that expression thereof preceded apoptosis evoked through the cannabinoid. Migration-inhibitor effects were also observed in experiments involving other cannabinoids, such as AEA, JWH-133 and WIN 55,212-2 [24, 25].

Finally, we must describe that this cannabinoids' effect has been reported in other types of tumor cells, such as SW480 colon cancer cells [48] and in thyroid cancer cells in rats [49].

Cannabinoids, immunity and the biphasic effect

Some studies in this review [15, 17–19] used immunodeficient rats that were deficient in mature T-cells and B-cells in order to assess the effect of the immunity in antitumor action of the cannabinoids. We know that, under certain circunstances, cannabinoids act as immunosuppressants on account of stimulation of CB2 receptors in immunological cells and organs. This action can inhibit antitumor immunity [17, 50] and, consequently, increase tumor growth [50]. However, in studies included in this review, the host's antitumor immunity did not impact the in vivo experiments. It is possible that immunity inhibition has not been enough to minimize the cannabinoids' antitumor effect.

Selectivity of cannabinoids in antitumor acticity

All of the studies in this review, except one [51], showed that cannabinoids are capable of selectively killing tumor cells. In contrast to its pro-apoptotic and antitumor effect in various types of tumors, cannabinoids protect normal cells from apoptosis.

One of the possible explanations for this paradoxical behavior in glia cells may owe itself to the different capacities of tumor and non-tumor cells to synthesize ceramide in response to cannabinoids [10]. This would act in addition to the different characteristics of their respective intracellular mechanisms and/or differences in the functionality of their cannabinoid receptors [10].

Cannabinoids, side effects and treatment strategies

Cannabinoid activation of the CB1 receptor is the main factor responsible for the known side effects of these substances. However, in some clinical situations, such as cancer patients who undergo chemotherapy, patients may consider some possible side effects tolerable.

Various non-psychoactive cannabinoids are potentially useful as antitumor agents in gliomas, including ajulemic acid [16], cannabidiol [20, 23, 32, 36] and JWH-133 [17–19]. Many experiments showed that cannabinoids acting in CB2 receptors are not psychoactive. In relation to gliomas, we must consider that not all human glioblastoma multiforme and types of glioma cells express functional CB2 receptors [17].

Studies also show that CBD and delta-9-THC differ in terms of the mechanisms of action in inducing apoptosis of tumor cells. As such, the combined treatment with these cannabinoids could significantly increase the efficacy of the cannabinoids as antitumor agents. This was shown in recent studies in which CBD and delta-9-THC had a greater effect when used in conjunction than separate use of them in inhibiting the viability of glioma cells in vitro [27, 52] and in the tumor growth in vivo [27]. Moreover, preliminary reports showed that the combination of these phytocannabinoids was better tolerated than the isolated use of delta-9-THC [53].

Another potential strategy for treatment of neoplasia would be to increase concentrations of the endocannabinoid AEA. In some types of tumors, the use of substances capable of increasing the level of endogenous AEA have shown promising results. This strategy is possible with drugs that inhibit reuptake or the intracellular degradation of AEA. In addition, use of these substances would be particularly useful in tumor tissues that superexpress AEA, 2-AG or both [54]. Other types of tumor cells that are especially sensitive to AEA action would be those that superexpress COX-2 given that, in these cells, the antiproliferative effects of AEA are mediated by COX-2 catabolism of prostaglandins [35, 55].

Finally, the concomitant use of ceramide and cannabinoids may be an interesting strategy in some types of tumors in order to maximize efficacy and minimize the side effects of some cannabinoids in some tumor models [15, 39, 41]. This association with ceramide is already being carried out in some treatment approaches together with conventional chemotherapies [56]. These ones, in turn, together with cannabinoids, could bring interesting antitumoral effects, as shown in two recent studies [27, 57]. As such, the ROS mediated anti-tumor effects of cannabinoids [20, 52], for example, make them good adjuvant therapy candidates.

In this sense, this review shows that cannabinoids can be considered an excellent treatment option, specifically on account of the present scarcity of effective resources to treat some types of cancers in medicine.

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