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(54) Title: USE OF TETRAHYDROCANNABINOL AND/OR CANNABIDIOL FOR INCREASING RADIOSENSITIVITY IN THE TREATMENT OF A BRAIN TUMOUR

(57) Abstract: The present invention relates to the use of phytocannabinoids for increasing radiosensitivity in the treatment of cancer. Preferably the phytocannabinoids used are either tetrahydrocannabinol (THC) and / or cannabidiol (CBD). Preferably the type of cancer to be treated is glioma.

USE OF TETRAHYDROCANNABINOL AND/OR CANNABIDIOL FOR INCREASING RADIOSENSITIVITY IN THE TREATMENT OF A BRAIN TUMOUR

[0001] The present invention relates to the use of phytocannabinoids for increasing radiosensitivity in the treatment of cancer. Preferably the phytocannabinoids used are either tetrahydrocannabinol (THC) and / or cannabidiol (CBD).

BACKGROUND TO THE INVENTION

[0002] Cancer is a disease in which a group of cells display the traits of uncontrolled growth. This means that the cells grow and divide beyond the levels of normal limits. The cells are also able to invade and destroy surrounding tissues. In addition cancer cells sometimes also metastasize, meaning that they spread to other locations in the body via the blood or lymph.

[0003] Most cancers are caused by abnormalities in the genetic material of the cells. These abnormalities may be due to the effects of carcinogens. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication, or are inherited, and thus present in all cells from birth.

[0004] Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting oncogenes are often activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments.

[0005] Tumour suppressor genes are often inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.

[0006] There are many different types of cancer and the cancer is usually classified according to the type of tissue from which it originated.

[0007] Cancer is usually treated by one or more of the following: surgery, chemotherapy, radiation therapy, immunotherapy and monoclonal antibody therapy. The type of therapy depends upon the location and grade of the tumour and the stage of the disease.

[0008] Complete removal of the cancer without damage to the rest of the body is the goal of treatment. Sometimes this can be accomplished by surgery, but the propensity of cancers to invade adjacent tissue or to spread to distant sites by microscopic metastasis often limits its effectiveness. The effectiveness of chemotherapy is often limited by toxicity to other tissues in the body. Radiation can also cause damage to normal tissue.

[0009] Cancers are known to affect many areas of the body with the most common types of cancers including: cancer of the bile duct, cancer of the bladder, cancer of the bone, cancer of

the bowel (including cancer of the colon and cancer of the rectum), cancer of the brain, cancer of the breast, cancer of the neuroendocrine system (commonly known as a carcinoid), cancer of the cervix, cancer of the eye, cancer of the oesophagus, cancer of the head and neck (this group includes carcinomas that start in the cells that form the lining of the mouth, nose, throat, ear or the surface layer covering the tongue), Kaposi's sarcoma, cancer of the kidney, cancer of the larynx, leukaemia, cancer of the liver, cancer of the lung, cancer of the lymph nodes, Hodgkin's lymphoma, non-Hodgkin's lymphoma, melanoma, mesothelioma, myeloma, cancer of the ovary, cancer of the pancreas, cancer of the penis, cancer of the prostate, skin cancer, soft tissue sarcomas, cancer of the spinal cord, cancer of the stomach, testicular cancer, cancer of the thyroid, cancer of the vagina, cancer of the vulva and cancer of the uterus.

[0010] A tumour that develops in the brain can destroy or damage brain cells by producing inflammation, compressing other parts of the brain, inducing cerebral oedema (brain swelling) and can cause increases in intracranial pressure (pressure within the skull).

[0011] Each year, approximately 4300 people in the UK are diagnosed with a brain tumour. A primary brain tumour is a mass created by the growth or uncontrolled proliferation of cells in the brain. Malignant primary brain tumours are most likely to cause problems by spreading into the normal brain tissue which surrounds them and causing pressure and damage to the surrounding areas of the brain. These tumours rarely spread outside the brain to other parts of the body. However, secondary brain tumours occur when cancer cells from other parts of the body, such as the lung or breast spread to the brain.

[0012] Surgery is the treatment option of choice for many brain tumours. Some may be completely excised, but those that are deep or that infiltrate brain tissue may be debulked rather than removed.

[0013] Radiation therapy and / or chemotherapy may be recommended depending on the type of tumour involved.

[0014] Glioma cell tumours can often be lethal. The characteristic diffuse infiltrative tumour growth of gliomas often makes the surgical removal of them impossible and this profoundly complicates the clinical management of these patients.

[0015] Glioblastoma multiforme (GBM) is the most common and most aggressive type of primary brain tumour and accounts for 52% of all primary brain tumour cases and 20% of all intracranial tumours.

[0016] Different approaches are being researched in order to improve the mortality rate of patients diagnosed with a glioma. These include therapies that target the glioma cells but leave normal cells unharmed, methods that limit the spread of the cancer cells and treatments that block the tumours life-sustaining molecules.

[0017] One such area of research involves the use of phytocannabinoids as anti-tumoural agents.

[0018] Phytocannabinoids are the active constituents of cannabis plants and they have been found to demonstrate numerous pharmacological properties.

[0019] For example EP1177790 (Guzman *et al*.) describes the treatment of cerebral tumours by the administration of a natural or synthetic cannabinoid, specifically THC. It is claimed that activation of specific receptors leads to selective death of the transformed cells.

[0020] Recently the phytocannabinoid CBD has been shown to possess anti-tumoural properties (Massi *et al*. 2004). The work described by this paper describes anti-proliferative effects both *in-vitro* using U87 and U373 human glioma cell lines and *in-vivo* using U87 human glioma cells subcutaneously implanted to nude mice.

[0021] Malignant gliomas are highly infiltrative and proliferative tumours, which follow a characteristic pattern of growth. Glioma cells invade the adjacent normal brain structures and surrounding large blood vessels.

[0022] In addition the applicant's earlier patent EP1802274 describes the use of the cannabinoid CBD to impede the progress of cancer cells migrating from their primary tumour location to a secondary site.

[0023] Furthermore the patent applications WO 2009/147439 and WO 2009/147438 respectively describe the use of a combination of the phytocannabinoids THC and CBD and the combination of the phytocannabinoids THC and CBD with chemotherapeutic agents in the treatment of glioma.

BRIEF SUMMARY OF THE DISCLOSURE

[0024] In accordance with a first aspect of the present invention there is provided the use of the phytocannabinoids (tetrahydrocannabinol) THC and / or (cannabidiol) CBD to increase radiosensitivity in the treatment of a brain tumour.

[0025] Preferably the brain tumour is a glioma tumour. More preferably the brain tumour is a glioblastoma multiforme (GBM).

[0026] Preferably the phytocannabinoids are in the form of an extract or botanical drug substance. Alternatively the phytocannabinoids are in an isolated or pure form.

[0027] The ratio of THC to CBD used may be in the range of from 99:1 to 1:99 (THC:CBD). Preferably the ratio of THC:CBD is from 20:1 to 1:20 (THC:CBD). More preferably the ratio of THC:CBD is from 5:1 to 1:5 (THC:CBD). More preferably still the ratio of THC:CBD is substantially 1:1.

[0028] In accordance with a second aspect of the present invention there is provided the use of a combination of the phytocannabinoids tetrahydrocannabinol) THC and (cannabidiol) CBD to increase radiosensitivity in the treatment of a brain tumour.

[0029] In this specification the following terms are used and are intended to have the following meanings / definitions:

[0030] "Cannabinoids" are a group of compounds including the endocannabinoids, the phytocannabinoids and those which are neither endocannabinoids nor phytocannabinoids, hereafter "syntho-cannabinoids".

[0031] "Endocannabinoids" are endogenous cannabinoids, which are high affinity ligands of CB1 and CB2 receptors.

[0032] "Phytocannabinoids" are cannabinoids that originate in nature and can be found in the cannabis plant. The phytocannabinoids can be present in an extract including a botanical drug substance, isolated, or reproduced synthetically.

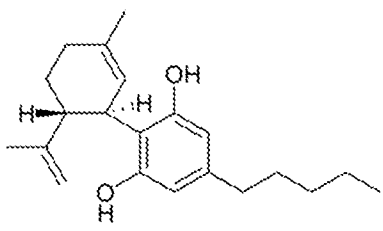
[0033] "Syntho-cannabinoids" are those compounds capable of interacting with the cannabinoid receptors (CB1 and / or CB2) but are not found endogenously or in the cannabis plant. Examples include WIN 55212 and SR141716 (rimonabant).

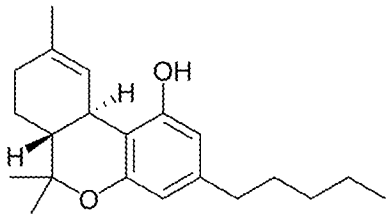
[0034] An "isolated phytocannabinoid" is one which has been extracted from the cannabis plant and purified to such an extent that substantially all the additional components such as secondary and minor cannabinoids and the non-cannabinoid fraction have been removed.

[0035] A "synthetic cannabinoid" is one which has been produced by chemical synthesis this term includes modifying an isolated phytocannabinoid, by for example forming a pharmaceutically acceptable salt thereof.

[0036] A "botanical drug substance" or "BDS" is defined in the Guidance for Industry Botanical Drug Products Guidance, June 2004, US Department of Health and Human Services, Food and Drug Administration Centre for Drug Evaluation and Research as: "A drug derived from one or more plants, algae, or microscopic fungi. It is prepared from botanical raw materials by one or more of the following processes: pulverisation, decoction, expression, aqueous extraction, ethanolic extraction or other similar processes." A botanical drug substance does not include a highly purified or chemically modified substance derived from natural sources. Thus, in the case of cannabis, BDS derived from cannabis plants do not include highly purified Pharmacopoeial grade cannabinoids

[0037] The structure of the phytocannabinoids, CBD and THC are as shown below:

CBD	Cannabidiol	

THC	Tetrahydrocannabinol	

[0038] The term "increase radiosensitivity" refers to the ability of the phytocannabinoids to enhance the activity of irradiation provided during treatment for cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

[0040] Figure 1 shows the radiosensitivity of glioma cell lines;

[0041] Figure 2 which shows the effect of CBD on the radiosensitivity of glioma cell lines;

[0042] Figure 3 which shows the effect of THC on the radiosensitivity of glioma cell lines; and

[0043] Figure 4 which show the effect of combining THC and CBD on the radiosensitivity of glioma cell lines.

DETAILED DESCRIPTION

[0044] The Example below describes the effect of using phytocannabinoids to increase radiosensitivity in glioma cells.

EXAMPLE 1: COMBINATION OF PHYTOCANNABINOIDS WITH RADIATION

Materials and Methods

Radiosensitivity of glioma cell lines

[0045] An initial dose response experiment was carried out to determine the radiosensitivity of the individual cell lines.

[0046] The human glioma cell lines T98G and U87MG were obtained from ATCC, and were lines derived from patients with a glioblastoma multiforme tumour and a glioblastoma astrocytoma respectively.

[0047] The mouse glioma cell line GL261, which is syngeneic to the C57BL/6 mouse was acquired from the NCI.

[0048] Cells were exposed to increasing doses of irradiation and then clonogenic cell survival assays were performed. The ability of the cells to survive an irradiation insult and go on and

divide indefinitely forming a colony was assessed in this manner and used as our read-out of radiosensitivity.

[0049] Cells were initially seeded into flasks and left to adhere overnight. The following day they were irradiated with increasing doses of radiation (0, 1, 2, 5, 10 and 20Gy) using Cs^{137} as a radiation source. Cells were then harvested, counted and seeded again at increasing densities in 6-well plates, adjusting the density appropriately for the radiation dose, and then incubated for approximately 14 days. At this time, plates were washed and fixed in 70% ethanol, and colonies were stained with 5% methylene blue. Colonies consisting of >50 cells were counted and calculated as a proportion of the number of cells initially seeded (surviving fraction). This value is then used to calculate the radiosensitivity of the cell line. Data represents mean ± SD of three independent experiments.

Effect of CBD on the radiosensitivity of glioma cell lines

[0050] Cells were treated with pure CBD for 24h prior to irradiation to determine whether the single phytocannabinoids were able to prime cells to irradiation.

[0051] Cells were initially seeded into flasks and left to adhere overnight. The following day they were treated with increasing concentrations of pure CBD and then left for 24 hours. Cells were then irradiated with increasing doses of radiation (0, 1, 2 and 5Gy) using Cs^{137} as a radiation source. Cells were then harvested, counted and seeded again at increasing densities in 6-well plates, adjusting the density appropriately for the radiation dose, and then incubated for approximately 14 days. At this time, plates were washed and fixed in 70% ethanol, and colonies were stained with 5% methylene blue. Colonies consisting of >50 cells were counted and surviving fraction was calculated. Data represents mean of three independent experiments except for GL261 which is only one data set.

Effect of THC on the radiosensitivity of glioma cell lines

[0052] Cells were treated with pure THC for 24h prior to irradiation to determine whether the single phytocannabinoids were able to prime cells to irradiation.

[0053] Cells were initially seeded into flasks and left to adhere overnight. The following day they were treated with increasing concentrations of pure THC and then left for 24 hours. Cells were then irradiated with increasing doses of radiation (0, 1, 2 and 5Gy) using Cs^{137} as a radiation source. Cells were then harvested, counted and seeded again at increasing densities in 6-well plates, adjusting the density appropriately for the radiation dose, and then incubated for approximately 14 days. At this time, plates were washed and fixed in 70% ethanol, and colonies were stained with 5% methylene blue. Colonies consisting of >50 cells were counted and surviving fraction was calculated. Data represents mean of three independent experiments.

Effect of combining THC and CBD on the radiosensitivity of glioma cell lines

[0054] The impact of using a combination of pure THC and pure CBD on the radiosensitivity of the cell lines was then assessed. The effect of drugs prior to exposure to irradiation was assessed; therefore the phytocannabinoids THC and CBD were combined at a ratio of 1:1, and applied to cells 24h prior to irradiation.

[0055] Cells were initially seeded into flasks and left to adhere overnight. The following day they were treated with increasing either pure THC, pure CBD or an equimolar 1:1 combination of both and then left for 24 hours. Cells were then irradiated with increasing doses of radiation (0, 1, 2 and 5Gy) using Cs^{137} as a radiation source. Cells were then harvested, counted and seeded again at increasing densities in 6-well plates, adjusting the density appropriately for the radiation dose, and then incubated for approximately 14 days. At this time, plates were washed and fixed in 70% ethanol, and colonies were stained with 5% methylene blue. Colonies consisting of >50 cells were counted and surviving fraction was calculated. Data from one data set only.

[0056] All phytocannabinoids reported here were used at molar concentrations, determined by masses of the substances received.

Results

[0057] Figure 1 shows that the GL261 cell line is the most radiosensitive and that the human glioma cell lines were equally as sensitive.

[0058] Figure 2 shows the impact of CBD on radiosensitivity, while Figure 3 shows data for the impact of THC on radiosensitivity. Results suggested that the phytocannabinoids, when used alone, did not appear to alter the radiosensitivity of the cell lines, as there is no dose dependent effect on the surviving fraction.

[0059] Figure 4 shows that a combination of THC and CBD at a final concentration of 20μM may enhance the activity of irradiation, compared to using the agents alone.

Conclusion

[0060] The combination of phytocannabinoids THC and CBD enhances the effect of the radiation and as such is a valuable treatment option in this difficult to treat disease.

CLAIMS

1. Use of the phytocannabinoids (tetrahydrocannabinol) THC and / or (cannabidiol) CBD to increase radiosensitivity in the treatment of a brain tumour.

2. Use of the phytocannabinoids THC and / or CBD as claimed in claim 1, wherein the brain tumour is a glioma tumour.

3. Use of the phytocannabinoids THC and / or CBD as claimed in claim 1 or claim 2, wherein the brain tumour is a glioblastoma multiforme (GBM).

4. Use of one or more phytocannabinoids as claimed in any of the preceding claims, wherein the phytocannabinoids are in the form of an extract or botanical drug substance.

5. Use of one or more phytocannabinoids as claimed in any of the preceding claims, wherein the phytocannabinoids are in an isolated or pure form.

6. Use of a combination of the phytocannabinoids tetrahydrocannabinol) THC and (cannabidiol) CBD to increase radiosensitivity in the treatment of a brain tumour.

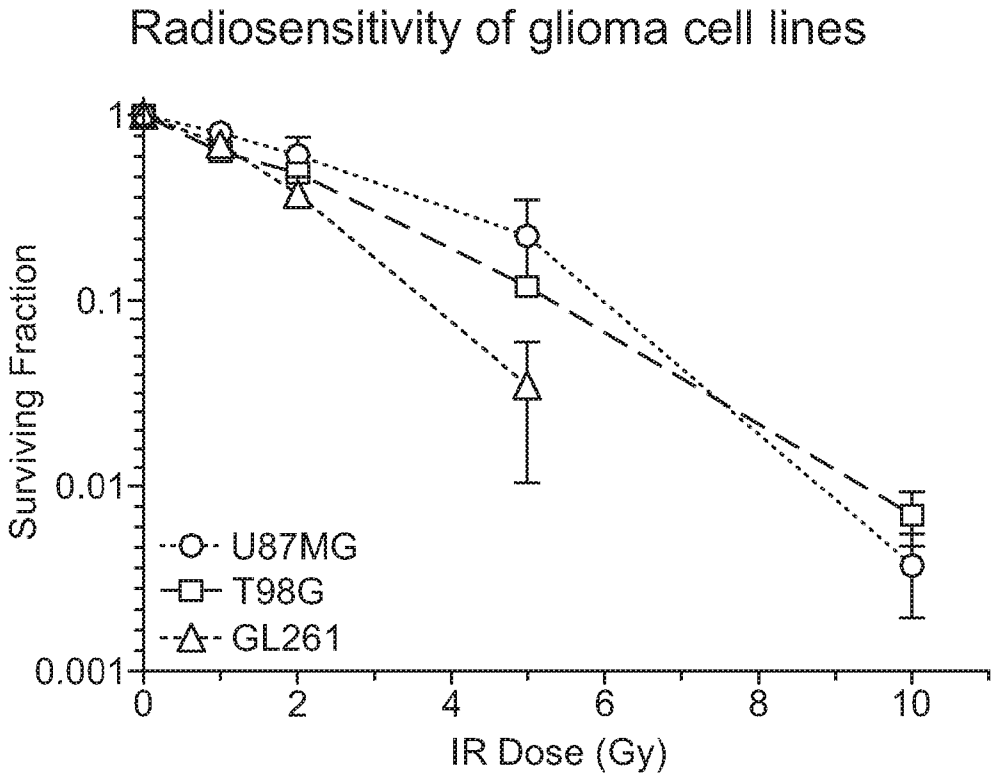

Radiosensitivity of glioma cell lines
Surviving Fraction
1
0.1
0.01
0.001
U87MG
T98G
GL261
0
2
4
6
8
10
IR Dose (Gy)

Fig. 1

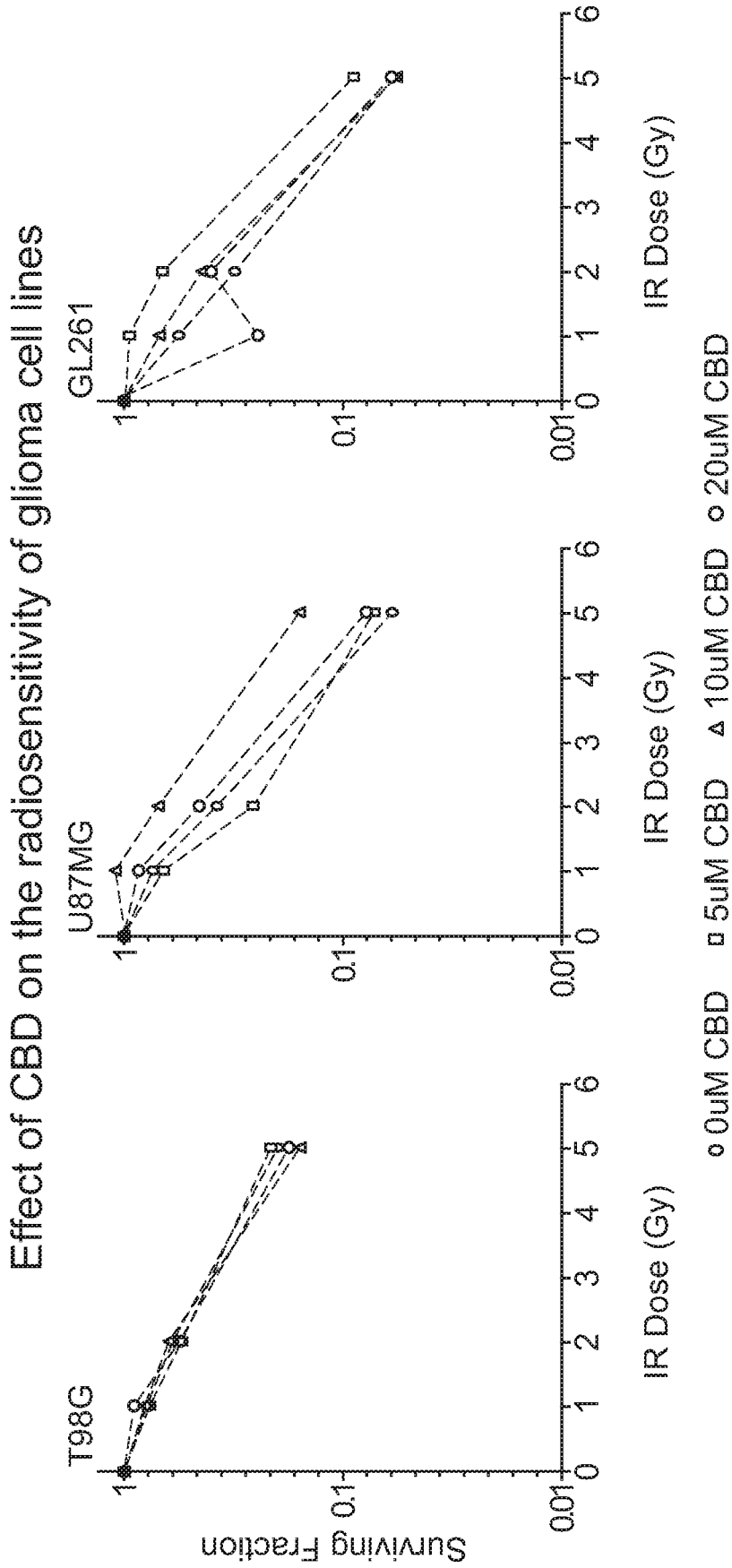

Effect of CBD on the radiosensitivity of glioma cell lines
T98G
U87MG
GL261
Surviving Fraction
1
0.1
0.01
0
1
2
3
4
5
6
IR Dose (Gy)
0uM CBD
5uM CBD
10uM CBD
20uM CBD

Fig. 2

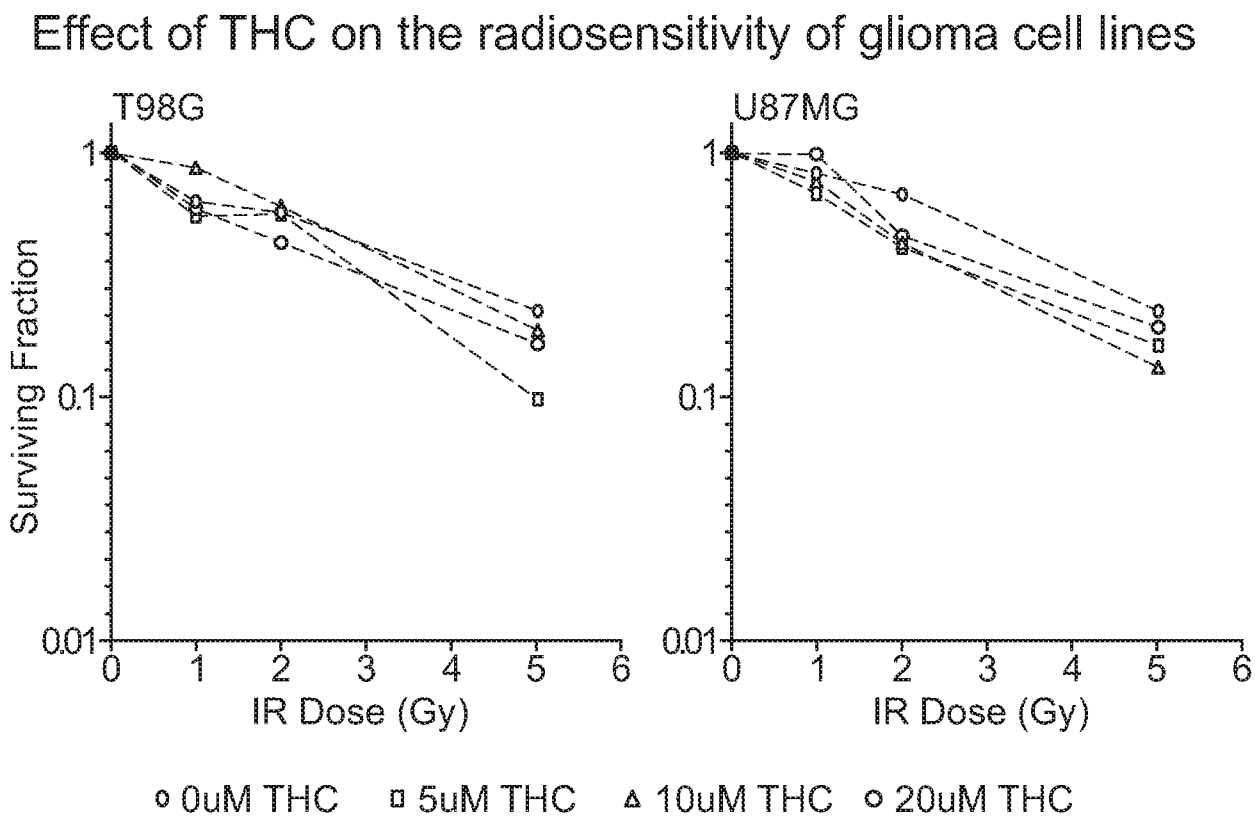

Effect of THC on the radiosensitivity of glioma cell lines
T98G
U87MG
Surviving Fraction
1
0.1
0.01
0
1
2
3
4
5
6
IR Dose (Gy)
0uM THC
5uM THC
10uM THC
20uM THC

Fig. 3

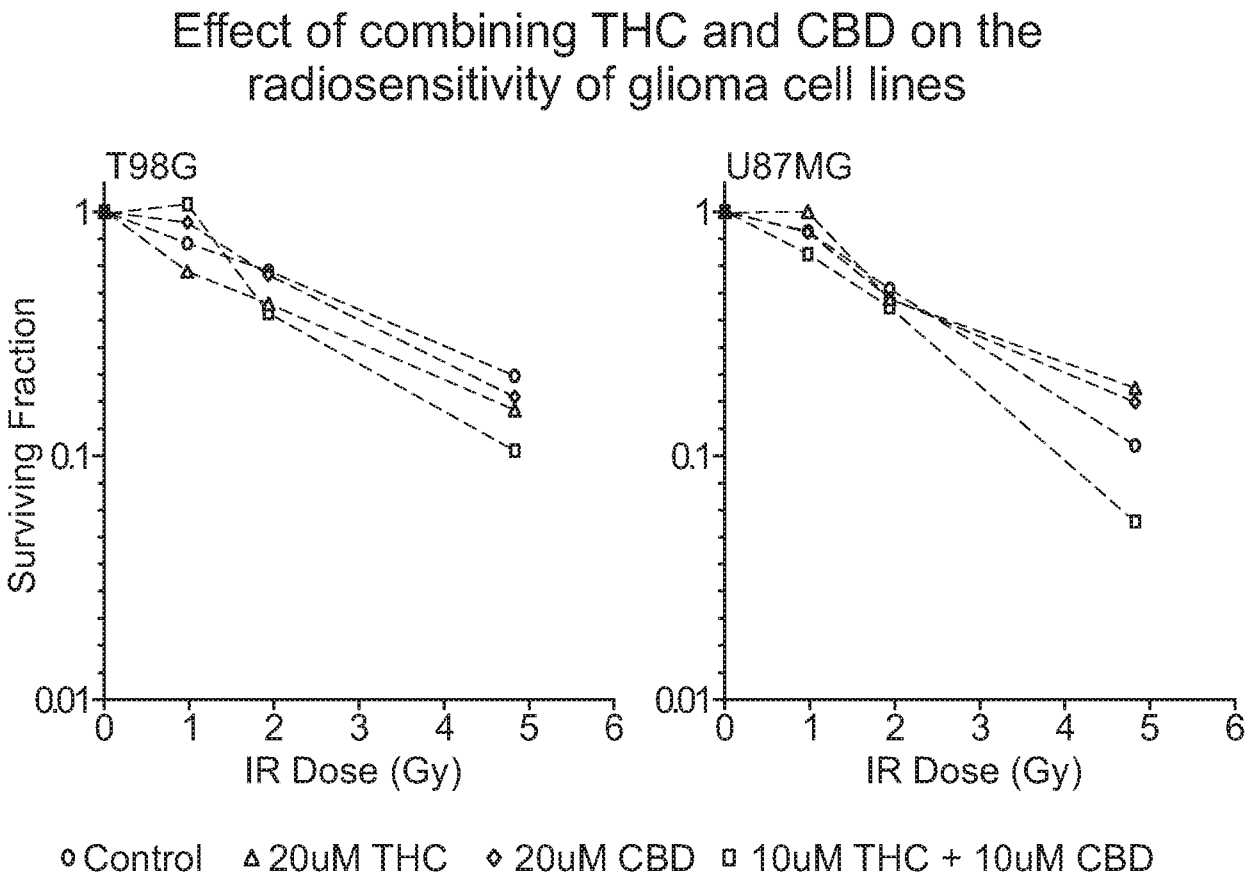

Effect of combining THC and CBD on the radiosensitivity of glioma cell lines
T98G
U87MG
Surviving Fraction
1
0.1
0.01
0
1
2
3
4
5
6
IR Dose (Gy)
Control
20uM THC
20uM CBD
10uM THC + 10uM CBD

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/051888

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61K36/185 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2014	01/08/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fey-Lamprecht, F

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/051888

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 2011/117216 A1 (VELASCO DIEZ GUILLERMO [ES] ET AL) 19 May 2011 (2011-05-19) paragraph [0001] paragraph [0034] claims	1-6
Y	WO 2008/144475 A1 (CALIFORNIA PACIFIC MED CENTER [US]; MCALLISTER SEAN D [US]; DESPREZ PI) 27 November 2008 (2008-11-27) claims	1-6
Y	WO 2009/147438 A1 (GW PHARMA LTD [GB]; OTSUKA PHARMA CO LTD [JP]; VELASCO DIEZ GUILLERMO) 10 December 2009 (2009-12-10) cited in the application claims	1-6
Y	US 2012/225136 A1 (WHITTLE BRIAN [GB] ET AL) 6 September 2012 (2012-09-06) cited in the application paragraph [0021] paragraph [0046] claims	1-6

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/051888

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