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# The potential of cannabinoids in the treatment of lung cancer

**Małgorzata Drozd**
https://orcid.org/0000-0002-0710-2451
drozd.malg@gmail.com
Independent Public Clinical Hospital No. 4 in Lublin, Jaczewskiego 8, 20-954 Lublin

**Paweł Marzęda**
http://orcid.org/0000-0003-1697-5497
pawel.marzeda@onet.eu
Department of Pathophysiology, Medical University of Lublin, Jaczewskiego 8b, 20-090 Lublin, Poland

**Jakub Czarnota**
https://orcid.org/0000-0003-2783-0349
lek.jakub.czarnota@interia.pl
Specialist Hospital In Radom of the name Tytus Chałubiński, Adolfa Tochtermana 1, 26-610 Radom

**Michał Dobrzyński**
https://orcid.org/0000-0002-1416-6568
mdobrzyski4@gmail.com
1 Military Clinical Hospital with a Polyclinic in Lublin, Al. Racławickie 23, 20-904 Lublin

**Tomasz Skubel**
https://orcid.org/0000-0001-7572-401X
tomasz.wojciech.skubel@gmail.com
1 Military Clinical Hospital with a Polyclinic in Lublin, Al. Racławickie 23, 20-904 Lublin

**Iga Dudek**
https://orcid.org/0000-0002-8101-074X;
iga.dudek6@gmail.com
1 Military Clinical Hospital with a Polyclinic in Lublin, Al. Racławickie 23, 20-904 Lublin

**Natalia Rybak**
https://orcid.org/0000-0003-1437-7661
natalia.rybcia@gmail.com
Independent Public Clinical Hospital No. 4 in Lublin, Jaczewskiego 8, 20-954 Lublin

Abstract:
Introduction: Lung cancer is the number-one cause of death due to neoplasms worldwide. The 5-year overall survival rate is only 22%. In advanced stages, the therapeutic options are limited to chemotherapy, radiotherapy, molecularly targeted therapy and immunotherapy. Phytocannabinoids, the components of *Cannabis sativa*, their synthetic derivatives and endogenous cannabinoids have demonstrated anticancer activity in various common cancers - breast, prostate, colorectal and lung cancers, among others. The aim of this review was to assess the potential value of cannabinoids in the treatment of lung cancer.
State of knowledge: The majority of preclinical studies demonstrates that cannabinoids inhibit lung cancer cell viability both *in vitro* and *in vivo*. The main mechanism of anticancer activity is the induction of apoptosis, triggered by activation of CB1, CB2 and TRPV1 receptors or independently via other pathways. Cannabinoids influence the components of the tumour microenvironment - cancer associated fibroblasts, macrophages and lymphokine-activated-killer cells. Cannabinoids alter leukocyte infiltration into anti-cancer proportions, inhibit expression of EGFR and PAI-1 and increase the expression of TIMP-1. As a result they induce cytotoxicity, decrease proliferation, migration and invasive potential of lung cancer cells, suppress angiogenesis and metastasis forming. Patients with advanced lung cancer may also benefit from analgesic, antiemetic and appetite improving properties of cannabinoids.
Summary: Cannabinoids can be a supplementary agent in systemic anticancer therapeutic regimen in the future. The exact mechanisms of action, specific doses in anticancer treatment, routes of administration and interactions with other anticancer drugs has yet to be determined. Thus the clinical studies on cannabinoids in lung cancer should be performed in the future.

Keywords: cannabinoids; Cannabis; Δ9-tetrahydrocannabinol; cannabidiol; lung cancer

## 1. Introduction and purpose:

Lung cancer is the third most frequently diagnosed cancer in Europe and the number-one cause of death due to neoplasms in the world [1]. Lung cancers are divided into two major groups - non-small lung cancers (adenocarcinomas, squamous-cell cancers, large-cell cancers) and small-cell lung cancers (SCLC). Small-cell lung cancers (SCLC) represent 13% of all primary lung tumours. SCLC's uniqueness results from rapid proliferation rate, early metastasis, high chemosensitivity, relative radiosensitivity, and eventually worse prognosis than NSCLC.

The overall 5-year survival rate for lung cancer is 22% - 26% for NSCLC and 7% for SCLC. It is usually diagnosed in advanced stages. Only 24% of lung cancers are detected in the localised stage and even when they are detected early, the 5-year survival rate is only 60%. The main risk factor is active or second-hand smoking. Tobacco smoke components are responsible for up to 80% of lung cancers. The other risk factors are chemical environmental and occupational factors (e.g. asbestos, certain metals, painting, rubber manufacturing), radiation, air pollution, diesel exhaust, and genetic predispositions [2,3].

The treatment of NSCLC depends on its stage, histological type, genetic and molecular characteristics, and the patient's individual situation. For early stages, the treatment involves radical resection or radical radiotherapy, with adjuvant chemo- or radiotherapy. In advanced stages of NSCLC the treatment options are chemotherapy (CTH), radiotherapy (RTH), immunotherapy (ITH) and molecularly targeted therapy. In patients with the presence of genetic abnormalities the treatment of choice is molecularly targeted therapy with epidermal growth factor receptor (EGFR), ALK or ROS1 tyrosine kinase inhibitors. The other option in stage IV cancer, both NSCLC and SCLC, is ITH with immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA4).

SCLC can be very rarely treated with surgical excision. The therapeutic options in early-stage SCLC are CTH, usually with cisplatin and etoposide, alone or combined with RTH; for advanced SCLC - CTH or ITH [3]. Although there are a lot of therapeutic options, the prognosis in lung cancer remains poor. There are also some patients who cannot respond to iplemented treatment, due to resistance to medicine or not having any mentioned genetic mutations. Therefore, there is a need to develop new therapeutic options [4].

Shortly, the endocannabinoid system contains the main receptors - G-protein coupled CB1 and CB2 receptors, and other receptors, such as transient receptor potential (TRP) channels and peroxisome proliferator activated receptors (PPARs), among others. Its endogenous ligands are anandamide and 2-arachidonoylglycerol (2-AG) whereas their degradative enzymes are fatty acid amide hydrolase (FAAH), diacylglycerol lipase (DAGL) and monoacylglycerol lipase (MAGL) [5].

CB1 receptor is expressed in multiple tissues. Its activation in the central nervous system is responsible for psychiatric effects of Δ9 -tetrahydrocannabinol (THC). CB2 receptor is mainly expressed in immune cells, microglia, endothelial and vascular smooth muscle cells. Both types of receptors are expressed in multiple cancers, e.g. human skin carcinomas, melanoma, colorectal and breast cancer, finally in lung cancer [6]. NSCLC cells tend to present high CB1 receptor mRNA expression, and low CB2 receptor [7].

The multiple natural and synthetic cannabinoid ligands act as agonist and antagonist/inverse agonist of these receptors in their individual diverse affinity. *Cannabis sativa* contains about 120 phytocannabinoids of 11 chemical classes, with Δ9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most recognized compounds. THC is CB1- and CB2-partial agonist presenting mixed agonist-antagonist effects. CBD acts as antagonist/inverse agonist of CB1 and a partial agonist of CB2 and at sub-micromolar concentrations as negative allosteric modulator of CB1 receptors [8]. Both THC and CBD reveal antiproliferative properties in lung cancer cells, with additive effect when administered in combination [9]. The synthetic derivatives used in studies on lung cancer cells and discussed below are ACEA (CB1-agonist), JWH-133 (CB2-agonist), AM-251 (CB1-antagonist), AM-630 (CB2-antagonist), JWH-015 (CB2-agonist), WIN 55,212-2 (CB1- and CB2-agonist), olvanil and arvanil (CB1-agonists) [10-12].

In recent years, the CBD oils have gained massive popularity. Some remarkable case reports continue to emerge, implying that regular intake of CBD oil alone can significantly decrease the size of NSCLC tumour. Citing one of them, 80 y.o. male patient with adenocarcinoma (T1c N3 M0), after self-administration of the CBD oil twice daily for over a month, achieved the tumour size reduction from 2.7 x 2.8 cm to 1.3 x 0.6 cm [13]. Stories like this one are spectacular, however the clinical evidence on cannabinoids' influence on lung cancer in humans remains poor, with no clinical trials ongoing. The knowledge we already have comes from the *in vitro* and preclinical studies *in vivo* (murine models). Nevertheless, these studies imply that cannabinoids may have promising potential as a supportive therapy in treatment of lung cancer.

In this review, we analyse the available data on the application of cannabinoids in the treatment of lung cancer and assess the possible mechanisms of their anti-cancer action.

Current literature was reviewed by searching for publications using terms “cannabinoids”, “CBD”, “cannabidiol”, “THC”, “tetrahydrocannabinol”, “Cannabis”, “olvanil”, “arvanil”, “ACEA”, “lung cancer” in compilations on PubMed and Scopus databases. Relevant literature on the anticancer properties of cannabinoids in lung cancer was included in results, with emphasis on the latest studies from the last 8 years.

## 2. State of knowledge:

Cannabinoids have been investigated in various types of cancer. In preclinical studies they exert anticancer activity in lung cancer, glioma, neuroblastoma, leukaemia, melanoma, breast cancer, pancreatic cancer, colorectal cancer, prostate cancer, renal cancer, and ovarian cancer [14]. Interestingly, there are some studies saying that cannabis smokers may have an increased risk of developing lung cancer, however this subject is contestable [15, 16].

### *Anticancer properties of cannabinoids:*

Several studies describe multiple mechanisms in which cannabinoids reduce the cancer cells’ viability and alter the tumour microenvironment. These include induction of apoptosis, oxidative stress and mitochondrial damage, alteration of intracellular metabolic pathways in cancer cells, and influence on fibroblasts and leukocytes in order to stop angiogenesis, invasion and forming metastasis.

Various cannabinoids reduce cell viability by promoting apoptosis in studies *in vitro* and *in vivo*. In human NSCLC cell line A549 *Cannabis sativa* extracts lead to cell death by initiation of early apoptosis and cell cycle arrest at sub G1 phase. These effects are achieved by the elevation of intracellular reactive oxygen species (ROS) levels and caspase-3 activation [17]. Caspase-dependent apoptosis is also the leading mechanism of decreased cell viability in A549 treated with CB1- and CB2-agonist, WIN 55,212-2 [11]. Similarly, CBD acts in a dose-dependent manner on NSCLC cell lines (A549 and H1299) and on SCLC cell line (H69) by caspase-dependent apoptosis. In the same study the mechanism of intrinsic mitochondrial apoptosis in lung cancer stem cells was also suggested. The lower efficacy of apoptosis was observed in the presence of serum, because of CBD binding to albumin. Inconsistently, in SCLC cell line (H69) CBD induces apoptosis only in the presence of serum and does not induce apoptosis in non-serum conditions at all. The anticancer action of cannabinoids in SCLC cells in non-serum conditions is unclear with the possible autophagy-dependent cell death or other pathways [18].

CBD was also found to promote apoptosis independently from CB1, CB2 and TRPV1 receptors. In CBD-treated lung cancer *in vitro* and *in vivo* the apoptosis was induced by the upregulation of cyclooxygenase-2 (COX-2) and peroxisome proliferator-activated receptor (PPAR-gamma) [19]. CBD has been proven to be effective against treatment-resistant lung cancer stem cells, inhibiting their self-renewal (A549, H1299, H69 cell lines). Along with apoptosis CBD reduces formation of spheres with cancer stem cells, increases oxidative stress and mitochondrial damage [18]. Arachidonoylcyclopropylamide (ACPA), synthetic CB1-agonist, decreases proliferation and promotes apoptosis via inhibition of AKT/PI3K pathway and alteration in multiple metabolites of glycolysis, TCA cycle, amino acid biosynthesis and urea cycle in NSCLC cells (A549, H1299, H358, and H838 cell lines) [7]. Decreased cell viability, without determined mechanism, was observed in both *in vitro*

(murine LL2 and human A-549 lung cancer cell lines) and *in vivo* (murine model with LL2 cells) after treating with THC-loaded nanoparticles (PLGA) [20].

Via binding to CB1, CB2 and TRPV1, cannabinoids may affect not only cancer cells, but also the elements of the tumour microenvironment. Cancer-associated fibroblasts (CAFs) are one of the main components of the tumour microenvironment, along with endothelial, mesenchymal and inflammatory cells. CAFs control the proliferation, invasion and metastasis in lung cancer. CBD and THC decrease cell density and expression of type I collagen in CAFs isolated from tumours, without any effect on normal fibroblasts obtained from the same patients [21]. The other components of the tumour microenvironment are macrophages, which usually infiltrate tumours, promoting its growth and enhancing epithelial to mesenchymal progression. Activation of CB1 and CB2 receptors on lung-cancer associated macrophages by multiple cannabinoids' derivatives (ACEA, JWH-133, AM-251, AM-630, JWH-015) inhibits release of angiogenic factors [10, 22].

In *in vitro* study on NSCLC (A549, H460 and H1792 cell lines), CBD and THC, separately or in combination with additive effect, was proven to inhibit expression of EGFR and reduce proliferation. Additionally, they decrease cell motility and suppress epithelial-to-mesenchymal transition (EMT) responsible for forming metastases and local invasion to surrounding tissue [9]. In A549 and H460 cell lines CBD by binding to CB1, CB2 and TRPV1 receptors was found to decrease the expression and secretion of plasminogen activator inhibitor-1 (PAI-1), which was found to be crucial in the invasiveness of cancer cells [23]. CBD, THC, R(+)-methanandamide and JWH-133 via binding to CB1, CB2 and TRPV1 receptors on A549 lung cancer cells induce the expression of tissue inhibitor of matrix metalloproteinases-1 (TIMP-1). Upregulation of TIMP-1 results in changes to the tumour microenvironment - suppressing the migration of cancer cells and angiogenic potential of the endothelial cells [24]. The same mechanism was described in studies on suppressors of the enzymes catalysing the degradation of endocannabinoids. Inhibitors of FAAH and MAGL have been proven to act against metastasis and invasion, indirectly via substrates of these enzymes. In A549 cell line FAAH inhibitors (AA-5HT and URB597) increase levels of AEA, 2-AG, OEA, PEA; and MAGL inhibitor JZL184, increases 2-AG levels [25, 26]. In human lung cancer *in vivo* (murine model) treated with MAGL inhibitor, the elevated levels of 2-AG decrease invasiveness and metastasis acting by CB1 receptor. The anti-invasive effect of FAAH and MAGL inhibitors in these studies is associated with TIMP-1 upregulation [26]. In mice treated with JZL184 or mice with MAGL-deficient lung tumour the reduction in tumour growth was observed. During tumour progression, MAGL derived from the tumour microenvironment is suspected to inhibit the immune cell infiltration, differentiation and activity of CD8+ T cells. The deficiency of MAGL was accompanied by the CD8+ T cells and eosinophils level increase. Both CD8+ T cells and eosinophils have anticancer activity in NSCLC, which suggests that MAGL is responsible for the pro-cancer environment in NSCLC [27].

Cannabinoids promote the expression of cannabinoid-induced intercellular adhesion molecule 1 (ICAM-1), and as a result enhance the adhesion to lymphokine-activated killer (LAK) and LAK cell-mediated cytotoxicity, thus exerting anti-invasive and anti-metastatic action on lung cancer cells. This new mechanism was proposed in *in vitro* study on metastatic cells obtained from a patient with lung cancer, and on A549 and H469 human lung carcinoma cell lines, which were treated with AM-251, AM-630 and capsazepine (synthetic antagonist of capsaicin) [28].

The capsaicin-like CB1-agonists, arvanil and olvanil, have anti-invasive activity in small cell lung cancer cells (SCLC), which is independent of CB1 and TRPV pathway activation. They probably reveal their action by AMPK (5'AMP-activated protein kinase)

activation. AMPK is a pathway that regulates cellular energy homeostasis and is activated in cellular stress conditions, such as hypoxia, ischemia, and glucose deprivation. Activation of AMPK by arvanil/olvanil inhibits the invasion to surrounding tissue, blood vessels, distant locations and forming metastases [12].

*The role of cannabinoids in clinical oncology:*

The place of cannabinoids in clinical oncology is mainly considered as a part of symptomatic treatment in palliative care due to their possible analgesic, antiemetic and appetite improving properties. Nevertheless, the meta-analysis on the efficacy of cannabinoids vs. placebo in palliative care in oncology highlights a very low quality of clinical evidence [29]. Similarly, the anticancer potential of cannabinoids in treatment of lung cancer and the role of endocannabinoid system components alterations as a prognostic factor in clinical practice has not yet been determined. Unfavaurably, due to immunomodulatory properties of cannabinoids, it has been already retrospectively observed that regular cannabis intake during immunotherapy in NSCLC decreases response rate to nivolumab. It does not alter overall survival and progression-free survival [30].

Plenty of cannabinoids are effective to treat chemotherapy-induced nausea and vomiting, alone or in combination with conventional antiemetics. Patients seem to prefer cannabinoids than conventional antiemetics, despite more frequently occured adverse effects [31]. Overall, nausea and vomiting are suppressed by CB1 agonists, and promoted by CB1 inverse agonists. The mechanism of action of CBD is explained by indirect activation of somatodendritic 5-HT1A receptors in the dorsal raphe nucleus, which reduces the release of 5-HT in terminal forebrain regions. Cannabinoids may have superiority in treatment of nausea produced by chemotherapy, which unlike the vomiting is less vulnerable to conventional antiemetics [32].

As nutritional statuses of patients influence the quality of life, therapeutic outcomes and toxicity profile of chemotherapeutic drugs, it is crucial to treat or prevent anorexia. Nabilone, a synthetic THC form, increases the intake of calories, improves functioning and reduces chronic pain, plus, is considered safe in the treatment of lung cancer. Nabilone's main side effect, the somnolence was reported to have a positive impact on frequently reported insomnia [33].

Cannabinoids antinociceptive properties are well established in preclinical studies. THC exerts analgesic effects via CB1 and CB2 receptors on neurons of the spinothalamic pain pathway. CBD as an antagonist/inverse agonist of CB1 and a weak CB2-agonist has analgesic properties and reduces the adverse psychotropic effects of THC. In clinical studies conducted on patients with cancer pain, cannabinoids alleviate the pain, decrease opioid use and have a positive impact on quality of life reported by patients [34]. In the spectrum of lung cancer, inhibitors of MAGL cause antinociceptive effects in murine model, even in chronic chemotherapy-induced peripheral neuropathic pain (paclitaxel-induced). Interestingly, it seems to not alter the antitumor effects of paclitaxel in A549 lung cancer cells. In the future, MAGL may be promising agents in patients with advanced stages of lung cancer during systemic therapy, as neuropathy is paclitaxel's common side effect, however it requires further studies [35].

Upregulation of CB2 has potential to be used as a prognostic factor in patients with NSCLC, however, as a positive or negative prognostic factor, depending on the authors. In a study on a cohort of patients with NSCLC it is claimed that CB1 and CB2 overexpression is associated with prolonged survival, and is indicated as a potential positive prognostic factor [9]. The other authors decided to verify if agonists of CB2 induce proliferation of lung cancer

cells, as it was identified in colon cancer cells. They revealed that CB2 receptors were upregulated in the human NSCLC cell lines A549 and H1299, like in studies on colon cancer. The expression level of CB2 mRNA was compatible with poor prognosis of patients with lung cancer in advanced stages. The CB2 knockdown resulted in increased apoptosis and decreased proliferation, migration, invasion ability and viability of A549 and H1299 cells. The role of the upregulation of CB2 as a prognostic factor should be investigated in the future [36].

Cannabinoids potentialize the effects of conventional anticancer methods. They can be radiosensitizers, as they tend to work synergically with radiotherapy in cancer treatment and enhance damage to lung cancer cells. In *in vitro* study on A549 human lung cancer line, CBD-induced apoptosis acts synergically with DNA damage caused by radiotherapy, which may reduce the dose of RT, thus its toxicity. Interestingly, in *in vitro* study, 5 μg dose of CBD was found to have greater antitumor effect than 4 Gy of radiotherapy. In murine models the best outcomes were achieved when CBD was delivered in prolonged exposure *in situ* with the use of smart radiotherapy biomaterials, followed by RT [37]. The promising new route of administration of cannabinoids in lung cancer is the inhalation of nanoparticle drones before radiotherapy. This route helps to limit the administered dose of radiotherapy, as well as substance due to 3.5–14.6 times higher nanoparticle concentrations in the tumour compared to the intravenous route [38].

Summary:

The majority of preclinical studies demonstrate that cannabinoids inhibit lung cancer cell viability both *in vitro* and *in vivo*. The induction of apoptosis plays a major role in the reduction of tumour growth. Apoptosis can be led by CB1, CB2 and TRPV1 receptors activation, or independently via COX-2 and PPAR-gamma upregulation, mitochondrial damage, oxidative stress, intracellular multiple metabolites alterations and other less defined pathways. The invasive potential and metastasis forming are regulated by various cells of the tumour microenvironment. Cannabinoids can alter this microenvironment by exerting influence on fibroblasts, macrophages and LAK-cells, and modifying the other leukocytes infiltration into anticancer proportion. Moreover, they inhibit expression of EGFR and PAI-1, increase the expression of TIMP-1 and activate the AMPK pathway. These actions result in induction of LAK-cell-mediated cytotoxicity and decreased proliferation, cell migration, invasiveness, angiogenesis and metastasis forming in lung cancer. The patient with advanced lung cancer may benefit from analgesic, antiemetic and appetite improving properties of cannabinoids, although the clinical evidence on cannabinoids' efficacy in palliative care in cancer remains poor.

Cannabinoids seem to be promising agents in therapy of lung cancer, however the full potential of cannabinoids has to be determined, as well as the exact mechanisms of action, specific doses in anticancer treatment in patients with lung cancer, routes of administration and interaction with other anticancer drugs.

Contribution of authors:

M. Drozd - study concept and design; acquisition of data; analysis and interpretation of data; writing the manuscript

P. Marzęda - conception or design of the work; critical revision of the manuscript for important intellectual content; study supervision

J. Czarnota - acquisition of data; analysis and interpretation of data; technical support

M. Dobrzyński - acquisition of data; analysis and interpretation of data; technical support

T. Skubel - acquisition of data; analysis and interpretation of data; technical support

I. Dudek – acquisition of data; analysis and interpretation of data; technical support

N. Rybak - acquisition of data; analysis and interpretation of data; technical support

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