Review

Cannabinoids/Endocannabinoids as Possible Antineoplastic Therapy in Comparisson to Cancer Pharmacological Treatments Used Today: Narrative Review

 Fabio Mayorga Niño,[1] Nelson Camilo Gutierrez Alvarado[2]

[1]Department of Pharmacology, Faculty of Medicine, Health Sciences Universidad Pedagógica y Tecnológica de Colombia, Tunja, Colombia
[2]Department of Pharmacology, Universidad Pedagógica y Tecnológica de Colombia, Tunja, Colombia

Abstract

Cancer is a complex pathophysiological condition that produces an important number of death around the world. At present, there are different ways to treat cancer: chemotherapy, radiotherapy and surgery. Cancer chemotherapy used today in many cases is effective, but it is very toxic too. The endocannabinoid system is implicated in a variety of physiological and pathological processes, including cancer. Many studies have shown, since 1975, that both phytocannabinoids Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) offer an antioneoplastic activity. Latter, other researchers have displayed that endocannabinoids as anandamide (ANA) and 2-arachidonoylglycerol (2-AG) also present the same potential activity. Phytocannabinoids and endocannabinoids act through CB1 and CB2 receptors to produce that effect. However, THC -the main phytocannabinoid presenting anticancer action- as well as anandamide employed in pharmacological doses, produce important phycotropic effects, but these cannabinoid compounds do not produce major adverse reactions like conventional antineoplastic drugs. On this basis, scientists have to develop analogs or derivatives of cannabinoids/endocannabinoids that cannot induce psychotropic effects. It is important to study more deeply chronopharmacological aspects of cannabinoids/endocannabinoids in cancer therapy, although some is known today.

Keywords: Antineoplastic drugs, anandamide, apoptosis, angiogenesis, breast cancer, cannabinoids/endocannabinoids, CB1, CB2, 2-arachidonoyl glycerol, glioblastome, metastasis, prostate cancer, side effects

Cite This Article: Niño FM, Gutierrez Alvarado NC. Cannabinoids/Endocannabinoids as Possible Antineoplastic Therapy in Comparisson to Cancer Pharmacological Treatments Used Today: Narrative Review. EJMO 2019;3(2):77–91.

Cancer therapy is a complex process. It can be physical (radiotherapy) or chemical (chemotherapy), as well as psychological. Chemotherapy has only been partially successful due to its highly toxic nature, although .many lives have been able to be saved using these drugs, but not without severe side effects. For several years scientists have been performing a considerable amount of studies in order to try to understand the roles of the endocannabinoid system (ECS) and its concern in physiological and pathophysiological processes.[1] On the other hand, there are many research groups in the world working on the new pharmacological tools for cancer treatment. Cannabinoids and endocannabinoids constitute one of the newest subject of interest on this topic, since Δ9-THC was shown to present an interesting antineoplastic action [2] and the following finding of the same activity of endocannabinoids.[3] One

of the most attractive issues of cannabinoids and endocannabinoids in cancer treatment is their selective action on neoplastic cells. But they cannot be accepted because of their psychotropic effects. Later in the chapter, we will speak about some chronobiological aspects of endocannabinoid system.[4] These concerns perhaps help us to understand possible chronopharmacological considerations to future new treatments based on these compounds. There have been great efforts in the world to get new molecules acting cleanly and selectively on neoplastic cells. Endocannabinoids compounds have been shown their high selectivity on these pathological cells. So, there are important advances in the design, synthesis and pharmacological evaluation of some derivate or analogs of cannabinoids and endocannabinoids looking for obtain new compounds with the same antineoplastic activity of those natural substances, but without their psychological effects.[5]

The history of endocannabinoid system

Cannabis sativa has at least 400 chemical compounds; more or less 60 of them are classified as cannabinoids. Δ^9-THC is the most important of them, because of its psychotropic and medicinal properties. This substance was extracted and characterized at the past century, and later cloned its cellular target, the first cannabinoid receptor found: CB1 receptor.[6] In 1993, Munro et al. informed about the existence of other cannabinoid receptor, named CB2 receptor [7] These are G-protein coupled receptors, whose natural ligands are called endocanabinoids. So, Devane et al. informed about a new derivate of arachidonic acid, which was named anandamide. At the beginning, it was found in brain of pigs.[8] Today we know that anandamide is present in every tissue.

In 1995, scientists from Hebrew University of Jerusalem announced the discovery of the 2-arachidonoylglycerol (2-AG) another important endocannabinoid.[9] Besides the anandamide and 2-AG, other endocannabinoids were found later in animal tissues.

Physiology and biochemistry of endocannabinoid system

The biosynthesis of anandamide (ANA) is similar to that of other N-acylethanolamines (NAEs). It can take three different ways [10]:

1. N-acylphosphatidylethanolamines (NAPEs): produced from phospholipids by the action of N-acyltransferase, NAT- are intermediates in the biosynthesis of N-acylethanolamines. NAEs are released from NAPEs by the action of a specific NAPE-phospholipase D (NAPE-PLD). Because the anandamide is a NAE (N-arachidonoylethanolamine), its biosynthesis passes through a selective NAPE-PLD.

2. Another pathway to the biosynthesis of NAEs involves the phospholipase C-mediated cleavage of NAPE. This new route produces pNAE (phospho N-acylethanolamine), which is cleaved by a phosphatase to release NAE and inorganic phosphate.

3. An alternative route to produce NAEs consists of a sequential hydrolysis of the O-acyl groups into glycerophospho-NAEs (GP-NAEs). Next, phosphodiesterase cleaves GP-NAE to free NAE. These reactions are catalyzed by serine hydrolase and α/β-hydrolase 4. Finally, COX-2 catalyses the anandamide conversion to PGF2α.[11]

In the Figure 1 it is resume the befores ways of biosynthesis.

Biosynthesis of 2-arachionoylglycerol (2-AG)

Biosynthesis of 2-arachionoylglycerol occurs from 2-arachidonoyl-containing diacylglycerols (DAGs) using either sn-1-specific diacylglycerol lipase (DAGL) β or α. DAGL-α has a critical role in the biosynthesis of 2-AG in brain, whereas DAGL-β acts mostly at peripheral level. The DAG precusors come from hydrolysis of membrane phospholipids. Next, COX-2 catalyses the anadamide transformation to PGE2.[11]

The actions of cannabinoids and endocannabinoids result from the interactions between the cannabinoid receptors (CB1 and CB2), the natural ligands and the set of enzymes releasing and degrading those compounds. The previous is known as Endocannabinoid System. This system covers a broad range of physiological functions in the reproductive, central nervous, cardiovascular systems and energy metabolism; in a similar way, the ECS is involved in a growing number of pathophysiological conditions [1, 12] as immunomodulation, food intake, inflammation, multiple sclerosis, analgesia, epilepsy, addictive, cancer, behavior and others.[13, 1]
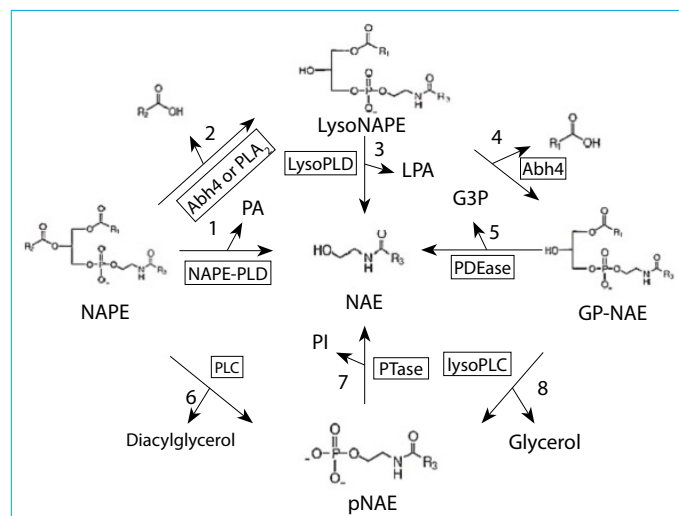

Figure 1. Different routes of biosynthesis of anandamide.[10]

Cannabinoid receptors

Cannabinoid receptors are united to $G_{i/o}$ proteins. So, they regulate the activity of adenylate cyclase, protein kinases and voltage-activated Ca^{++} channels, for the CB1 receptors. Both cannabinoids receptors have a selectivity of distribution in the body. CB1 receptors are mostly located in the CNS. A detailed distribution of this receptor has been proposed in the human brain and in the animal brain, too. The cerebral cortex and hippocampus are especially rich in CB1 cannabinoid binding sites. This explains, for example, why cannabinoids express their effects on cognition and memory; these regions may also mediate the effects of cannabinoids in the perception of time, sound, color and taste. The presence of CB1 receptors in the basal ganglia and cerebellum can explain the effects of cannabis on motor activity and postural control. On the other hand, some sites that are sparsely populated with cannabinoid binding sites include those in which cannabinoids can act to produce hypothermia (hypothalamus) or antinociception (spinal cord). However, a few areas of periphery contain CB1 receptors: prostate, ovaries, heart, spleen, uterus, and presynaptic nervous ending. The principal intracellular mechanisms in which the CB1 receptors are implicated include the inhibition of adenilate cyclase, the regulation of ionic channels and the activation of MAP kinases.[14] The activation of cannabinoid receptors produce the increasing of potassium conductance and inhibition of calcium channels. The effects on both types of channels maybe the base of the inhibition of neurotransmitters release.

CB2 receptors are located mostly in the periphery: amygdala, immune system and the spleen are rich in those cannabinoid binding sites. The inmunesupressors effects of marijuana are explained by the presence of these receptors in the immune system.[15, 16] Also, vanilloid receptors (TRPV1) show partly overlapping medicinal cannabinoid actions.

Cancer is a fatal disease that could be conveniently controlled by cannabinoids and endocannabinoids or their derivatives or analogues through these receptors.

Ligands of endocannabinoid system

In 1992 Devane reported the isolation and characterization of a new substance found in the brain of pigs; this substance was named anandamide.[8] This chemical compound was found in almost every tissue of the animals' bodies, human body, and some plants. Another important endocannabinoid is 2-arachidonoylglycerol (2-AG), which presents a higher affinity to CB1 receptors. Also there are other endogenous cannabinoids less studied until today. These are N-arachidonoyltaurine, noladin, N-arachidonoyldopamine and virodhamine.[17] But there are other "atypi-

cal" endocannabinoids as palmitoyloethanolamide (PAE) and oleoylethanolamide (OEA), that exihibit lower affinity with cannabinoids receptors, and elicit their cannabinoid-like activities by either inhibition of endocannabinoid catabolism, or reducing cellular uptake of anandamide.

The endocannabinoids are derivatives of chain polyunsaturated acids and exhibit different selectivity for the receptors as well as other binding sites. At present, there are endocannabinoid analogues, such as (R)-Met-anandamide and Met-fluor-anandamide. Thus, other synthetic agonists of cannabinoid receptors exist to help to understand the ECS.

In the Figure 2 it is drew the chemical structure of the mains endocannabinoids.

Enzymes involved in the metabolism of endocannabinoids

As we can suppose, there are a complex set of enzymes acting in the anabolic and catabolic processes of endocannabinods. So, let's review in a short manner those enzymes acting in the synthesis and degradation of endocannabinoids. We have to remember that endocannabinoids are produced "on demand"; therefore, the organism must be able to release enzymes if necessary. They can be pharmacologically targeted to modify the concentration of those endogenous compounds, according to needs in a pathological situation. We can classified this set of enzymes in two general groups:

Anabolic enzymes

They intervene in the biosynthesis of N-acylethanolamines like anandamide.

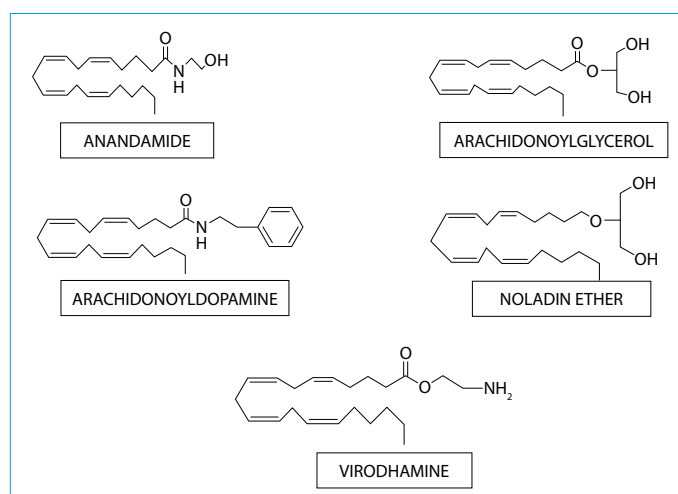- NAPE-Phospholipase D: It catalyses the anandamide release from N-acylphosphatidylethanolamine.

Figure 2. Structures of endocannabinoids.

- Phospholipase C: It helps to cleavage NAPE to release NAE's, as anandamide.

- N-acyltransferase (N-AT): It helps to transfer an acyl group to form NAE's It is situated on intracellular membranes, as well as the NAPE-PLD.

- Diacylglycerol lipase (DAGL): It helps to release 2-arachidonoylglycerol (2-AG).

Catabolic enzymes

They intervene in degradation of NAE's and acylglycerols:

- Fatty acid amide hydrolase (FAAH): It catalyses the anandamide hydrolysis and inactivation of cannabinoid receptors. It is also placed in intracellular membranes, although it is mostly on neurons postsynaptic to CB1 receptors.[18]

- The sn-1-selective diacylglycerol lipase: It has two isozymes, DAGL-α and DAGL-β, which catalyze the hydrolysis of diacylglycerols to 2-acylglycerols. It has been shown that these enzymes possess the amino acid residues Ser443 and Asp495, which are necessary to catalytic activity of DAGLs.[19]

- Monoacylglycerol lipasa (MAGL): It catalyzes the hydrolysis of 2-AG to glycerol and arachidonic acid.[20] This enzyme is located on presynaptic neurons.

There are a few newer enzymes of the ECS system: α, β-hydrolase domain containing 4 (ABHD-4), which is a lysophospholipase selective for NAPE's and hydrolyses substrates with saturated, monounsaturated and polyunsaturated acyl chains; α,β-Hydrolase domain containing 6 (ABHD-6) and α,β-hydrolase domain containing 12 (ABHD -12), which hydrolyse the 2-AG.[18]

Pharmacology of endocannabinoid system

ECS is composed of three types of entities: endocannabinoids or endogenous cannabinoids, cannabinoid receptors and the synthetic and hydrolytic enzymes endocannabinoids'. Thus, a broad range of indications could benefit from this system, because of can be targeted by new drugs designed as derivatives or analogs of the ethanolamides of fatty acids or other endogenous compounds of that system. They act as antagonists or agonists of cannabinoid receptors and in the inhibition the degrading enzymes of the endocannabinoids and transporters of these endogenous ligands.

We can think about several diseases to be treated in a future targeting the ECS.[21-23] These pathologies include cancer, cardiovascular disease, inflammation, sexual diseases, psychiatric disorders, pain, eating disorders, to name just a few.

We will discuss briefly the effects that involvement of ECS in some pathological conditions:

Cardiovascular effects

Endocannabinoids, cannabinoinoids and synthetic analogs perform effects on cardiovascular system. They act on the myocardium and vasculature [24] because their receptors are in the vascular and myocardium tissues. They can also modulating autonomic outflow through central and peripheral nervous system [24]; CB2 are implicated on ischemic events of the heart, in addition CB1 are involved in activation mediates negative inotropism of the heart.[25] It is believed that this effect of CB1 receptors can explain the hypotensive action of the anandamide. The activation of CB1 receptors inhibits norepinephrine release present in sympathetic nerve terminals, which also contributes to bradycardic effects. Otherwise, in animal models have showed that endocannabinoids are implicated in the control of atherosclerosis, for this reason is being studied for treating to this pathology.[25]

Inflammation and pain

Cannabinoids are effective against acute pain.[21] Anandamide has been postulated to present an antihyperalgesic activity.[26] Williams et al. said that endocannabinoids can stimulate the production of endogenous opioids, and a interplay between both systems for giving higher analgesic effect.[27, 21] ECS is implicated in the analgesic activity of acetaminophen [21] or ibuprofen.[28]

Diseases of central nervous system

There are many of CB1 receptors in the CNS; for this reason, ECS is involved in many CNS disorders. The main areas in where we found these receptors are in the cortex, hippocampus, basal ganglia and cerebellum, whereby are implicated in many diseases, which affecting mood, movement, anxiety disorders, learning, and memory. So, ECS acts an important role in several disorders of the CNS, such as in neurotoxicity in where ECS offers neuroprotective action in acute neural injury and in chronic neurodegenerative disorders .Also many studies establish that endocannabinoids protect neurons against glucose deprivation and hypoxia. [29] It is showed that cannabinoids and endocannabinoids can be neuroprotective in cerebral ischemia. Multiple sclerosis in the past since ancient Rome, India and China used cannabis for relieving muscle cramps.[30] THC and the non-psychotropic cannabinoid, dexanabinol, reduce CNS inflammation and improve neurological outcomes.[31] In multiple studies, the administration of cannabinoids or endocannabinoids reduce tremor.[32] In addition, the control

of movement disorders is known because there are high expression of CB1 receptors in areas involved in movement control.[33] At the same places, endocannabinoids can be in great concentration, if necessary. At different areas of the basal ganglia, the endocannabinoids interact with several neutransmitters.[34] For this reason, these authors postulate that endocannabinoids interact with many conditions of movement such as Parkinson's disease, Alzheimer' disease, epilepsy, amiothrophic lateral sclerosis, etc.

Chronobiology of endocannabinoids

The body has circadian regulators, like suprachiasmatic nucleus which regulate the interactions between the physiological processes and the external environment. These last named synchronizers, are the noise, the sunlight, corporal temperature and other. The nadirs of epinephrine or cortisol, for example, occur around 10 pm to 4 am (circadian rhythms). Breathing is a permanent process occurring in periods of less than 22 hours (ultradian rhythms); and the menstrual cycle occurs about every 28 days (infradian rhythms). These are only a few examples of rhythmic patterns in the organisms. Also, the pathological events usually appear at specific times of the day. The episodes of asthma attacks appear with predominance in the night, because of elevated histamine and others mediator levels occur between midnight and early morning. Equally, heart attacks are present principally in the morning because clotting factors and other platelet agreeability are higher at this time.

Some physicians have treated cancer according to biological rhythms of disease cells and healthy cells, and found a better response in light of this condition than when chemotherapy is applied in another time, including fewer side effects. Endocanabinoids presents evidence to work based on biological rhythms. Both endogenous and exogenous cannabinoids affect many physiological processes that show biological rhythms. Hillard et al.[4] proposed that the ECS acts as a bridge between circadian regulators and physiological processes that they affect. Other authors have reported the evidence that exist variations in endocannabinoid tissue content, CB receptors [35] and their enzymes.[36, 4] Experiments made in Sprague-Dawley rats showed significant diurnal variations in anandamide and 2-AG contents in CSF, striatum, hippocampus, hypotalamus, prefrontal cortex, pons and nucleus accumbens. [36, 37, 4] It has been found that anandamide concentration is higher during the asset phase of the rats (darkness), in the nucleus prefrontal cortex, accumbens, hippocampus and striatum. But in the inactive phase the anandamide was found in higher concentrations in CSF and hypotalamus during the inactive phase than in the active phase. Valenti et al. found that FAAH activity could underlie the changes

in anandamide content in hippocampus and striatum. The 2-AG content was higher when anandamide concentrations were lower. So, the activities of both DGL and MAGL are higher during the inactive phase than active phase.[36] There is evidence that the population of CB1 receptor varies in a circadian manner. In both pons [38] and hippocampus [35] the population of CB1 receptor is higher in the inactive than in the active phase. Hillard et al. demonstrated that circulating anandamide concentration rise during the sleep, determining its contents in plasma at 22:00 hours at day 1 and at 7:30 and 17:30 hours at day 2 in a pilot study in which subjects remained in bed with light out from 22:30 at day 1 to 7:00 hours at day 2. They found, besides, that the concentrations of anandamide at 22:00 and at 17:30 hours were similar, but the concentrations at 22:00 and 7:30 revealed significant differences. The 2-AG, however, showed no important differences in the experiment.[4] These results about the chronobiology of anandamide permits to conclude that this endocannabinoid has a clear circadian rhythm and, of course, that its physiological action probably is higher during the rest time, although it is produced mostly "on demand". On the other hand, Other studies have explored the action of ECS in the control of the sleep/wake cycle, maintaining it and/or promoting it.[39]

Treatment of cancer today

At present, cancer is one of the most important public issues in the world. It is the second leading cause of death in America and Europe and one of the major cause of death worldwide. In this article, we don't want to make a review about cancer in general; however, we tried to show in summary the main treatments that at present have been used in the world for several cancer types.

Targets therapy

For the management of cancer is necessary that different therapeutic disciplines to work together to do the best option of treatment. The most effective treatment will depend of the disease, the stage of the disease and the patient. The oldest management includes radiation, surgery and chemotherapy.

Pharmacotherapy

Cytotoxic agents still form the basis for the management of cancer; thus, the cancer therapy lies on the principle that the cancer cells are more likely to be replicating than normal cells. For this reason, the pharmacotherapy`s target is to stop the cell division process of sick cells. The most representative groups of pharmacos used in cancer therapy are:

Alkylating drugs

Six main types of drugs are currently used in neoplastic diseases: nitrogen mustards, ethyleneimines, alkylsulfonates, platinum complexes, nitrosoureas and triazenes; their mechanism of action is subtantiado on the alkylation of DNA through the formation of carbon ion intermediates, which form covalent bonds with several nucleophilic molecules of the purine and pyrimidine bases of DNA, causing damage to the DNA of the cell that leads to cell death. The main problem that entails this mechanism of action is the lack of selectivity for the malignance cells. For this reason, the adverse effects like toxicity of mucous membranes, toxicity of bone marrow, neurotoxicity and toxicity of other organs appear because these drugs have predilection for damage of cells of high proliferation.[40]

Natural products

This group has a lot of pharmacos with very different chemical structures. Some examples of this are:

Analogs of camptotecin: they are potent antineoplastic agents whose site of action is topoisomerase I which is responsible for decreasing the torsional force in the superhelical DNA; this causes accumulation of DNA breaks and its subsequent cell death in the S phase of the cell cycle. Drugs as topotecan and irinotecan are in this group. The most common adverse effects in this group are neutropenia, thrombocytopenia, nausea, diarrhea and mucositis.

Agents that damage microtubles: In this group we found vinca alkaloids which are specific drugs of the cell cycle, explained by the ability to specifically bind beta tubulin and block its ability to bind to alpha tobulin in the microtubules, stopping cell division in metaphase. The most representatives pharmacos of this group are vincristine and vinblastine. The lack of selectivity for malignance cells is the same problem that produce myelosupression, neurotoxicity and intestinal disorders.[41] Other groups with this same mechanism of action are taxanos, stramustine and epotilones.[42]

Podophyllotoxins: like anthracyclines, they form a ternary complex with topoisomerase II and DNA and they cause the DNA rupture. In this group, the main representatives are etoposide and teniposide.[43] The main side effects are bone marrow suppression, fever, easy bruising or bleeding and unusual fatigue.

Antibiotics: Here there are some pharmacos like dactinomycin whose mechanism of action is justified on the ability to disrupt the DNA chain, altering its funtionality. Also in this group are anthracyclines [44] and anthracenediones [45]; these compounds are intercalated with DNA and directly alter the transcription and replication. The principal representatives are doxorubicin, epirubicin and valrubicin. The most common toxic manifestations in this group are anorexia, nausea and vomiting.

Enzymes: The L-asparaginase bases its effect on the principle that every tissues in the body have adequate amounts of asparagine synthase for getting the necessary amino acids from plasma. But in the case of lymphocytic leukemias do not exist quantities adequates of this enzyme. The L-asparaginase catalyzes the hydrolysis of circulating asparagine to transform it into ammonia and aspartic acid, deprives cancer cells of asparagine and so they die.[46] The most common adverse effects in this group are hypersensitivity reactions including urticaria and anaphylaxis.

Glucocorticoids: They acts by binding to specific receptors that translocate to the nucleus and cause a state antiproliferative and they produce apoptotic response in certain cells. By their effects to suppress lymphocyte mitosis, glucocorticoids are used in the treatment of malignant lymphoma and acute leukemia.[47] Side effects include glucose intolerance, immunosuppression, osteoporosis, and psychosis.[42]

Progestins: They are used as second-line hormone therapy for endometrial carcinoma previously treated with radiation therapy and surgery and they can be used in hormone-dependent mammary cancers. They are also used to stimulate appetite and restore feelings of well-being in patients with advanced stages of cancer and acquired immunodeficiency síndrome.[48] The most commonly used drug is medroxyprogesterone. Main side effects include abdominal pain, absent, missed, or irregular menstrual periods, chills, hives or welts, itching, redness, swelling, puffiness skin rash, swelling of the eyelids or around the eyes, tongue, lips, or face.

Estrogens and androgens: Such drugs are useful in prostate and breast cancer.[49] Paradoxically, antiestrogens have also been effective in breast cancer positive for hormone receptors. In this step, the selective modulators of estrogen receptor as tamoxifen act like competitive inhibitor of estradiol binding to estrogen receptors. Thus, in prostate cancer antiandrogens like cyproterone, flutamide and bicalutamide inhibit ligand binding and, as a consequence, cause translocation of the androgen receptor from the cytoplasm and nucleus. Because of the above, the pharmacological and surgical castration (subalbuginous orchiectomy) are used in patients with prostate cancer to continue avoiding the androgenic function with the chemical suppression of pituitary gonadotropin-releasing hormone agonists. Main side effects are reduction or absence of sexual desire, erectile dysfunction (impotence), reduction of the size of the testicles and penis, hot flashes, breast pain and breast tissue growth.[40]

Aromatase Inhibitors: They antagonize the function of the enzyme aromatase types I and II, which convert androgens to estrogens used for hormone receptor positive breast cancer. The most representative drugs are formestano and anastrozole. Side effects include osteoporosis, osteoarthritis and hypercholesterolemia.

Other pharmacos: In this group there are some drugs working through different mechanisms of action like mitomycin. It inhibits DNA synthesis and binding crossed in such nucleic acid at the N-6 position of the adenine and at O-6 and N-7 positions of guanine. Another pharmaco is hydroxyurea whose mechanism of action is through the inhibition of the enzyme diphosphate of ribonucleoside reductase, which catalyzes the reductive conversion from ribonucleotides to deoxyribonucleotides, step limiting the rate in the DNA biosynthesis. Different agents belong this group and act avoiding cancerous transformation blockingdifferentiation. It is not known if this blockade is complete or partial.[50]

Antimetabolites:

Folic acid analogs: Folic acid is a very important factor for methylation reactions in the synthesis of purine and pyrimidine bases, which later will form nucleic acids. Purine ribonucleotides and thymidine monophosphate are active metabolites in nucleic acids synthesis. For this reason, if folic acid is absent, DNA replication is inhibited. Antineoplastic drugs as methotrexate function inhibiting dihydrofolate reductase and thus prevent the reduction of dihydrofolic acid to tetrahydrofolic acid. The most representative drugs of this group are methotrexate, pralatrexate and pemetrexed.[51] The main adverse effects in this group are hemorrhage, myelosuppression, infection, cirrhosis, alopecia, teratogeny, abortion and nephrotoxicity.

Purine analogs: Perhaps, the function of this group is based on the inh ibition of the reaction of glutamine and phosphoribosyl pyrophosphate to form ribosyl-5-phosphate and the conversion of inosine-5'-monophosphate to adenine and guanine. The most representative drugs of this group are 6-mercaptopurine, 6-thioguanine. On the other hand, another pyrimidine analog is pentostatin wich inhibits the enzyme adenosine deaminase, unlike the cladribine that is purine analog resistant to adenosine deaminase. Nelarabine is a single nucleoside guanine which is used in human beings. Its basic mechanism of action closely resembles that of other purine nucleosides, because of it is incorporated to the DNA chain and its synthesis ends. It shows selective toxicity by T lymphocytes and the cancers of these cells.

Pyrimidine analogs: They encompass diverse drugs that inhibit the function of RNA and DNA. Fluoropyrimidines and some purine analogues inhibit the synthesis of essential DNA precursors. Others, such as the nucleoside analogues of cytidine and adenosine, are incorporated into DNA and block their greater elongation and function. The most representative pharmacos are 5-fluorouracil, floxuridine, cytosine arabinoside and 5-azacitidine.[52] The most common side effects are metallic taste in mouth during infusion, nausea and possible occasional vomiting, diarrhea, poor appetite, mouth sores, sensitivity to light (photophobia), watery eyes, taste changes, discoloration along vein through which the medication is consumed.

Receptor inhibitors of epidermal growth factor

This receptor is essential for the growth and differentiation of epithelial cells through intracellular domain tyrosine protein kinase. In epithelial cancers, there is excessive expression of this receptor, for this reason the drugs erlotinib and gefitinib are important drugs in these types of cancer because they inhibit the growth receptor dependent of tyrosine kinase and antagonize its enzymatic function.[53] The side effects related to this group include acneiform rash, nail changes, headache and diarrhea.

Inhibitors of tyrosine kinase protein

Protein kinases are critical in signal transduction pathways that regulate cellular growth and adaptation, which are classified into three categories: kinases that phosphorylate serine and threonine residues, kinases that specifically phosphorylate tyrosine residues and kinases with activity in the three residues. The drugs here we found are imatinib, dasatinib and nilotinib.[54] The most common toxic manifestations in this group are diarrhea, nausea, pleural effusion and hepatotoxicity.

Inhibitors of angiogenesis

Neoplastic cells secrete angiogenic factors that induce the formation of new blood vessels for ensuring blood flow. Among these factors we can find growth factor, vascular endothelial growth factor (VEGF), platelet derivative and transforming factor of growth β. Today, three small molecules (pazopanib, sorafenib and sunitinib) are in use. They inhibit the function of vascular endothelial growth factor receptor (VEGFR2) kinase, a member of the VEGFR family, or bevacizumab, which is an antibody directed to VEGF-A.[55] The main adverse effects in this group are the possibility of vascular injury, hemorrhage, hypertension, proteinuria and arterial thromboembolic events.[42]

Modifiers of the answer biological

Monoclonal Antibodies: The murine antibodies are monoclonal antibodies that react against unique or highly ex-

pressed antigens on pharmacological targets and a few of these monoclonal antibodies possess antitumor activity and induce an immune response against the murine antibodies, and are usually replaced by important portions of human IgG molecules. Available drugs include trastuzumab, bevacizumab, rituximab, Cetuximab, alemtuzumab and panitumumab, which can destroy the cell employing many ways as complement dependent cytotoxicity, antibody-dependent cellular cytotoxicity and direct induction of apoptosis by antigen binding.[56] The most common toxic manifestations in this group are limited to fever, chills, pain pharyngeal, urticaria and mild hypotension.

Interleukin-2: It is a 133 aminoacids glycoprotein encoded by a gene on chromosome 4q26-27. It is produced by natural killer cells and by activated T lymphocytes. It acts in favor of proliferation of activated T lymphocytes and increases the destruction by the natural cytolytic lymphocytes.[57] The predominant toxic effects is the leakage of intravascular fluid toward the extravascular space, tissues and lungs causing hypotension, edema, difficulty breathing, confusion, tachycardia, oliguric renal disease, electrolyte disorders, thrombocytopenia and neutropenia.[40]

Radioimmunoassay

They supply directed radionuclides to tumor cells. ^{131}I is used by its easy availability, low cost and because it easily conjugates with monoclonal antibodies. Gamma rays emitted by ^{131}I can be used for studies and some treatments, but protein conjugates with iodine have the problem of releasing ^{131}I and ^{131}I-tyrosine into the blood, and thus so it represents a health risk for people who are in contact with the patient.

Gene therapy

It is about the transfer of genetic material into a cell to change the cellular phenotype permanently or transiently. Gene transfer may be performed *in vivo* or *in vitro*. This is still in study.[58]

Vaccines for cancer

Active immunotherapy appears as an adjunct to conventional cancer treatments. Vaccines are an efficacious system for overcoming related immunosuppression; they should be combined with complementary immunotherapies to induce robust and sustained antitumor responses. However, these are under study.

Radiation therapy

It involves the administration of ionizing radiation to patients with cancer, for the purpose of palliation, complement to the surgical treatment and cure. This therapy is used in tumors of colorectum, bladder, head and neck. Also, radiation therapy can be supplied after surgery to control it or to eradicate residual disease.

Surgery

It performancies an important role in the prevention, erradicative treatment, progressive and palliative treatment of patients. It is important the role of surgery since the beginning of the lesions with high risk of malignancy. In the second instance, they erradicate the affected organ and metastasis of the same and in advanced stages it focuses on performing paliative interventions that alleviate the symthomatology of patients as in colon cancer in which colostomies are performed to prevent intestinal obstructions that affect the patient's wellbeing.
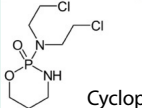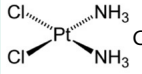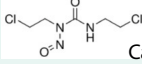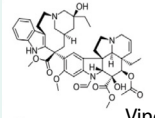
In the Table 1 it is mentioned the mains pharmacological groups used in cancer and theirs structures

Pharmacotherapy

Cannabinoids and endocannabinoids pharmacology in cancer

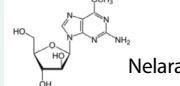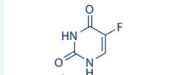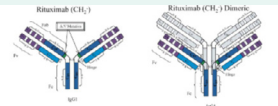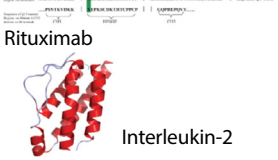As we said previously, since 1975 it is known that cannabis presents an interesting profile of antineoplastic activities in many types of cancer cells. These properties are due mostly to Δ^9-THC and cannabidiol. The synergistic action of both mentioned compounds has been studied principally in glioblastoma.[59, 60] On the other hand, it has been demonstrated that endocannabinoid signalling is enhanced in some human cells malignancies compared with corresponding healthy tissues [61, 62], and in neoplastic cells with high invasiveness.[63] ECS has an emerging modulating activity on nuclear factors and proteins that regulate cell differentiation, survival and proliferation.[64] Therefore, it is possible to suppose that ECS can be involved in the control of fundamental homeostatic processes and in neoplastic transformation. Natural cannabinoids and endocannabinoids as well as synthetic CB1 agonists and other molecules presenting indirect agonist cannabinoid activity, such as endocannabinoid-degradation inhibitors and endocannabinoid-transport, have been shown to constrain tumor growth and the progression of several kinds of cancer. These include, among others, lymphoid tumors, leukemia; thyroid, breast, prostate and skin cancer; glioma and glioblastoma multiform.[65] Next we will discuss some aspects of the action of endocannabinoids in cancer: mechanisms of action, side effects, possible criteria of chronophamacology and the risk of developing cancer by cannabinoids.
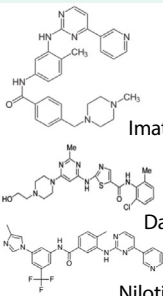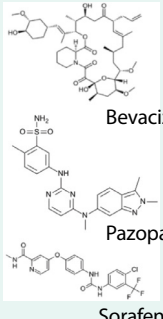
Table 1. Pharmacological groups, uses and structures (42)		
Group	**Main uses**	**Examples**
Alkylating drugs		
Nitrogen mustards, Ethyleneimines, Alkylsulfonates, Platinum Complexes, Nitrosoureas and Triazenes	Hodgkin's disease Multiple myeloma Malignant melanoma Acute and Chronic Lymphocytic Leukemia	Cyclophosphamide Cisplatin Carmustine
Natural products		
Analogs of camptotecin, Agents that damage microtubles, Epipodophotoxins, Antibiotics, Enzymes, Glucocorticoids, Progestins, Estrogens and androgens, Aromatase Inhibitors,	Lung and breast cancers Acute lymphoblastic leukemia in children Ovarian Cancers Colon cancer Acute lymphocytic leukemia Gastric, anal and pulmonary cancers	Vincristine Irinotecan Valrubicin
Antimetabolites		
Follic acid analogs: Purines analogs and Pyrimidine analogs	Mesothelioma Pancreatic, ovarian, lung cancers Myelodysplasia T-cell leukemia, lymphoma	Methotrexate Nelarabine 5-fluorouracil
Modifiers of the answer biological		
Monoclonal Antibodies Interleukin-2 Radioimmunoassay	Hepatocellular cancer, renal cancer Breast cancer Multiple myeloma Myelodysplasia Acute promyelocytic leukemia	Rituximab Interleukin-2

Mechanisms of action

Cannabinoids may induce growth arrest and cell death, as well as stop migration by linking to CB receptors of tumor cells. Some researchers have postulated that cannabinoids and endocannabinoids act interfering with immune system or inhibiting the angiogenesis process. It is believed that the inhibition of proliferation may occur through adenylyl cyclase and cAMP/protein kinase A [66], cell cycle arrest that induces the kinase inhibitor p27^{kip}, the decreasing of epidermal growth factor receptor (EGF-R) expression or lower activity of EGF-R tyrosine kinase; low levels of nerve growth factor (NGF) and prolactin and vascular endothelial growth factor tyrosine kinase receptors (VEGF-R

Table 1. Cont.

Group	Main uses	Examples
Inhibitors of tyrosine kinase protein		
Imatinib, Dasatinib and Nilotinib	Chronic myelogenous leukemia; Stromal tumors Gastrointestinal syndrome Hypereosinophilia	Imatinib Dasatinib Nilotinib
Inhibitors of angiogénesis		
Bevacizumab Pazopanib, Sorafenib and Sunitinib	Acute lymphocytic leukemia; Glioblastoma, tumor of Wilms, rhabdomyosarcomas; Hodgkin's disease; Non-Hodgkin's lymphom	Bevacizumab Pazopanib Sorafenib

tyrosine kinase) Cell cycle arrest that induces the kinase inhibitor p27[kip], the decreasing of epidermal growth factor receptor (EGF-R) expression or lower activity of EGF-R tyrosine kinase; low levels of nerve growth factor (NGF) and prolactin and vascular endothelial growth factor tyrosine kinase receptors (VEGF-R tyrosine kinase).[67] Anandamide stops the proliferative effects of human thyroid carcinoma, cholangiocarcinoma, breast cancer, non-melanoma skin cancer and hepatocellular carcinoma. This endocannabinoid suspends breast cancer cell proliferation through the inhibition of *brca 1* gen, because of this action helps to the down regulation of prolactin receptor.[23] It is known that very low concentration of anandamide (micromolar levels) may arrest prostate cancer cells proliferation by blocking G1 step [68] It has shown that the anandamide analog R(+)-methanandamide acts through CB2 receptor and so can be able to induce apoptosis in prostate cancer and to decrease the endothelial growth factor receptor (EGFR) expression. The same occurs to androgen-stimulated LNCaP cells. It has been observed that these inhibitions also happen by down-regulated EGF-R levels, mediated by CB1 receptors.[68] Nithipatikom et al. showed that some types of cancer cells produced 2-Arachidonoyl glycerol (2-AG) at high concentrations, and the inhibition of diacylglycerol

lipase decreased the production of 2-AG in these cells. On the other hand, when this diacylglycerol lipase inhibitor was applied, the invasion of PC3, DU145 and LNCaP cells increased. Other studies have showed that cannabinoid agonists can produce decrease in LNCaP cells proliferation, as well as androgen receptor expression, VEGF-R and levels of PSA, a marker prostate cancer. As scientists have demonstrated, cannabinoids and endocannabinoids can attack several stages of the cell cycle, interfering with the regulation of that cycle. Cannabinoids and endocannabinoids produce an up-regulation of p21 waf, a loss of Cdk2 activity and a reduced active complex cyclin E/Cdk2 kinase, which allows them act in the S phase of the cell cycle. The activation of Chk1 and Cdc25A proteolysis, as well as inhibition of Cdk2 phosphorylation on Thr 14/Tyr15, lead to S phase arrest. Because of cannabinoids/endocannabinoids block the G2/M by producing down-regulation of Cdc2, they can inhibit the breast cancer cell proliferation. The activation of ERK1/2, the inhibition of cyclin D and the induction of P27/KIP1 can block the G0/G1 phase of the cell cycle. In short, cannabinoids/endocannabinoids are effective in the control of cancer progression by their action on the expression of any proteins as cyclin D1, cyclin D2 and cyclin E, and of some genes as cdk2, cdk4 and

cdk6; in the same way, by the activation of Chk1, and Cdc25A proteolysis.[68] In short, cannabinoids/endocannabinoids are effective in the control of cancer progression by their action on the expression of any proteins as cyclin D1, cyclin D2 and cyclin E, and of some genes as cdk2, cdk4 and cdk6; in the same way, by the activation of Chk1, and Cdc25A proteolysis (85). On the other hand, cannabinoids/endocannabinoids exert their pro-apoptotic effect through several ways: stimulated synthesis of ceramide, prolonged activation of Raf1, inhibition of akt and of RAS-MAPK/ERK and PI3K/AKT. The down regulation of Raf1/MAPK, as well as translocation of BAD to mitochondria, also can produce the pro-apoptotic effect. So, in colorectal cancer cells, apoptosis was induced by CB1 receptors activation through inhibition of RAS-MAPK and phosphatidyl inositol 3-kinase-protein kinase B pathways. These and other are targets to control the advance of cancer. But their activation/deactivation is mediated mostly by CB1 receptors; sometimes that effect is mediated by CB2 o TRPV1 receptors, FAAH, COX-2, EGF-R. MMP's (metaloproteinases of matrix) are a family of enzymes that acts in tumor invasion. The inhibition pof angiogenesis induced by cannabinoids/endocannabinoids is related to VEGF. Another important aspect of the cannabinoid and endocannabinoid antitumor action is their selectivity. It has been demonstrated that both the plant compounds, such as Δ^9-THC and cannabidiol, and endocannabinoids, such as anandamide and 2-AG, should selectively affect tumor cells, while they might inclusive protect the equivalent healthy cells.[69] The apoptosis of glioma cells is mediated by ceramide generation. This protective action of cannabinoids is mediated by CB1 receptor and PI3K-AKT survival pathway.[70] Cannabinoids attenuate, nevertheless, ceramide-induced apoptosis of normal astrocytes, which can be interpreted as the ability of cannabinoids to distinguish between normal and sick cells. In summary, although we have discussed briefly only few mechanisms through which cannabionoids and endocannabinoids can produce their antineoplastic effects, we can confirm that there are a plethora of mechanisms of action to control the progression of cancer.[70]

Side effects

The more known adverse reaction of cannabinoids is the psychoactive effects. These are apparent as depressing and stimulatory effects, and they can be expressed as euphoria, drowsiness, dizziness and motor discoordination, temporal and spatial disorientation and confusion and difficulties in concentration. These adverse effects maybe pronounced in recreational consumers, but are unlikely in a controlled clinical setting. When tetrahydrocannabinol (THC-dronabinol) and the synthetic cannabinoid nabilone

are administrated as antiemetic drugs, they are usually innocuous. The tolerance developed by cannabinoids used therapeutically has not been substantiated. The addictive profile of cannabinoids is very poor. Irritability, insomnia, restless and sudden sensation of heat -which together form the withdrawal syndrome- have been observed occasionally in chronic users. Similarly, when cannabinoids have been used in a chronic way in animal models, no signs of withdrawal appear, even at high doses.[70] Individuals who receive dronabinol in long-term surveys have shown no signs of dependence.[69] The explanation of the low-addictive power of Δ^9-THC could be that cannabinoids are stored in adipose tissue and excreted at a low rate, which maintains levels of the drug during a long period of time. The side effects of cannabinoids are not only on CNS. Because of ubiquitous distribution of cannabinoid receptors in the body can be able to affect almost all functions. So, cannabinoids may develop tachycardia, bronchodilation, muscle relaxation and decreased motility. The Spanish Ministry of Health approved six years ago a phase I/II clinical trial aimed at investigating the effect of local administration of Δ^9-THC as a single agent, on the growth of recurrent glioblastoma multiforme. This study was developed without any traditional antineoplastic drug. The safety profile of Δ^9-THC, together with the great anticancer potential of this compound, will permit to improve future trials to employ cannabinoids in the treatment of different types of cancer.[71] From these considerations, we can establish some conclusions: first, that because endocannabinoids have demonstrated the same effects of plant cannabinoids, and they display a fair safety profile, the ECS is an important target to treat cancer in a near future; second, cannabinoids and endocannabinoids present a safer action than traditional antineoplastic drugs used today; third, although the most important problem of cannabinoids is its psychoactive potential, it is really low and does not lead to dependence.

Chronopharmacology

As we discussed previously, endocannabinoids are produced according to biological rhythms, anandamide being produced mostly in the inactive phase and 2-AG in the active phase. Because cannabinoids and endocannabinoids present a selective action against tumor cells, they could be administered at any hour of the day. Currently, however, studies are needed to establish the best hour of the day to practice the antineoplastic treatment. It would be important, for example, to study whether a specific type of cancer alters the formation of cannabinoid receptors, because of the pathological condition can modify the behavior of the organism.[4]

Cannabinoids and endocannabinoids as potential inducing cancer

We have considered the antiproliferative effects of cannabinoids and endocannabinoids through different mechanisms. However, However, some authors have reported that cannabinoids can present pro-proliferative and anti-apoptotic effects in different cancer cell lines al submicromolar doses.[71] The antiproliferative and pro-apoptotic action of these compounds is reached at micromolar range. The immunossupressive action of cannabinoid agonists through the activation of CB2 receptor in the immune system has an increasing risk of tumor growth due to a repression of the natural antitumor immune response. Thus, those tumors whose cells express low levels of CB2 receptors are more prone to immunosuppression and enhanced tumor growth.[18]

In the Table 2 it is resumed the mains side effects of cancer' drugs.

Conclusions

Cancer is a great cause of death and its conventional treatment is often effective, but generally it is also very toxic. Researchers in the world have found that cannabinoids or endocannabinoids derivatives or analogs posses an important potential to cancer treatment in the future, since they exhibit high specificity of action on cancer cells, and best fair profile of side effects in comparison to traditional antineoplastic drugs used today. However, the principal problem with cannabinoids and endocannabinoids is their psychoactive potential and their ability to trigger some form of cancer; this last consideration is known that can occur at submicromolar doses. It is important to study more deeply the synchronization between chronobiology of endocan-

Table 2. Some side effects from Cancer`s drugs (40)	
Treatments	**Main side effects**
Alkylating Drugs	Mucous membranes, toxicity of bone marrow, neurotoxicity and toxicity of other organs appear because these drugs have predilection for damage of cells of high proliferation.
Analogs Of Camptotecin	Neutropenia, thrombocytopenia, nausea, diarrhea and mucositis.
Agents That Damage Microtubles	Myelosupression, neurotoxicity and intestinal disorders.
Podophyllotoxins	Bone marrow suppression, fever, easy bruising or bleeding and unusual fatigue.
Antibiotics	Anorexia, nausea and vomiting.
Enzymes	Hypersensitivity reactions including urticaria and anaphylaxis.
Glucocorticoids	Glucose intolerance, immunosuppression, osteoporosis, and psychosis.
Progestins	Abdominal pain, absent, missed, or irregular menstrual periods, chills, hives or welts, itching, redness, swelling, puffiness, or skin rash, or swelling of the eyelids or around the eyes, or lips, face and tongue.
Estrogens and androgens	Reduction or absence of sexual desire, erectile dysfunction (impotence), reduction of the size of the testicles and penis, hot flashes, breast pain and breast tissue growth.
Aromatase Inhibitors	Osteoporosis, osteoarthritis and hypercholesterolemia.
Folic acid analogs	Hemorrhage, myelosuppression, infection, cirrhosis, alopecia, teratogeny, abortion and nephrotoxicity.
Purine analogs	Selective toxicity by T lymphocytes and the cancers of these cells.
Pyrimidine analogs	Nausea, diarrhea, , mouth sores, poor appetite, sensitivity to light (photophobia), watery eyes, taste changes, metallic taste in mouth during cosume, vomiting discoloration along vein through which the medication is given
Receptor inhibitors of epidermal growth factor	Acneiform rash, nail changes, headache and diarrhea.
Inhibitors of tyrosine kinase protein	Diarrhea, nausea, pleural effusion and hepatotoxicity
Inhibitors of angiogenesis	Vascular injury, hemorrhage, hypertension, proteinuria and arterial thromboembolic events.
Monoclonal Antibodies	Fever, chills, pain pharyngeal, urticaria and mild hypotension
Interleukin-2	Hypotension, edema, difficulty breathing, confusion, tachycardia, oliguric renal disease, electrolyte disorders, thrombocytopenia and neutropenia.
Cannabinoids	Psychoactive effects, tachycardia, bronchodilation, muscle relaxation, decreased motility and neoplastic effects

nabinoids and the biological rhythms of the pathology, to get a best outline for the treatment.

Disclosures

Ethics Committee Approval: Authors Nelson Gutierrez and Fabio Mayorga declare that this paper does not contain any studies with animals performed or human participants by any of the authors.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors Nelson Gutierrez and Fabio Mayorga declare that they haven't conflict of interest.

Authorship Contributions: Concept – Concept – F.M.N.; Design – F.M.N.; Supervision – F.M.N.; Materials – N.C.G.A.; Data collection &/or processing – N.C.G.A.; Analysis and/or interpretation – F.M.N.; Literature search – N.C.G.A.; Writing – N.C.G.A.; Critical review – F.M.N., N.C.G.A.

References

1. Hermanson DJ, Marnett LJ. Cannabinoids, endocannabinoids, and cancer. Cancer Metastasis Rev 2011;30:599–612. [CrossRef]

2. Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA. Antineoplastic activity of cannabinoids. J Natl Cancer Inst 1975;55:597–602. [CrossRef]

3. Burstein S, Salmonsen R. Acylamido analogs of endocannabinoids selectively inhibit cancer cell proliferation. Bioorg Med Chem 2008;16:9644–51. [CrossRef]

4. Vaughn LK, Denning G, Stuhr KL, de Wit H, Hill MN, Hillard CJ. Endocannabinoid signalling: has it got rhythm? Br J Pharmacol 2010;160:530–43. [CrossRef]

5. Bifulco M, Di Marzo V. Targeting the endocannabinoid system in cancer therapy: a call for further research. Nat Med 2002;8:547–50. [CrossRef]

6. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–4. [CrossRef]

7. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61–5. [CrossRef]

8. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946–9.

9. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR,et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995;50:83–90. [CrossRef]

10. Farrell EK, Merkler DJ. Biosynthesis, degradation and pharmacological importance of the fatty acid amides. Drug Discov Today 2008;13:558–68. [CrossRef]

11. Iannotti FA, Di Marzo V, Petrosino S. Endocannabinoids and endocannabinoid-related mediators: Targets, me-tabolism and role in neurological disorders. Prog Lipid Res 2016;62:107–28.

12. Wang J, Ueda N. Biology of endocannabinoid synthesis system. Prostaglandins Other Lipid Mediat 2009;89:112–9.

13. Guindon J, Hohmann AG. The endocannabinoid sys-tem and cancer: therapeutic implication. Br J Pharmacol 2011;163:1447–63. [CrossRef]

14. Svízenská I, Dubový P, Sulcová A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures--a short review. Pharmacol Biochem Behav 2008;90:501–11. [CrossRef]

15. Flygare J, Sander B. The endocannabinoid system in cancer-potential therapeutic target? Semin Cancer Biol 2008;18:176–89. [CrossRef]

16. Mayorga NF, CÁRDENAS RHS. Endocannabinoids: A thera-peutic option to cancer treatment. [Article in Spanish] Vitae 2009;16:259–67.

17. Taylor AH, Amoako AA, Bambang K, Karasu T, Gebeh A, Lam PM, et al. Endocannabinoids and pregnancy. Clin Chim Acta 2010;411:921–30. [CrossRef]

18. Di Marzo V. The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation. Pharmacol Res 2009;60:77–84. [CrossRef]

19. Bisogno T, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, et al. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J Cell Biol 2003;163:463–8. [CrossRef]

20. Baggelaar MP, van Esbroeck AC, van Rooden EJ, Florea BI, Overkleeft HS, Marsicano G, et al. Chemical Proteomics Maps Brain Region Specific Activity of Endocannabinoid Hydrolases. ACS Chem Biol 2017;12:852–61. [CrossRef]

21. Guindon J. A novel inhibitor of endocannabinoid catabolic enzymes sheds light on behind the scene interplay between chronic pain, analgesic tolerance, and heroin dependence. Neuropharmacology 2017;114:168–71. [CrossRef]

22. Moreno E, Chiarlone A, Medrano M, Puigdellívol M, Bibic L, Howell LA, et al. Singular Location and Signaling Profile of Adenosine A2A-Cannabinoid CB1 Receptor Heteromers in the Dorsal Striatum. Neuropsychopharmacology 2018;43:964–77.

23. Malfitano AM, Ciaglia E, Gangemi G, Gazzerro P, Laezza C, Bifulco M. Update on the endocannabinoid system as an anti-cancer target. Expert Opin Ther Targets 2011;15:297–308.

24. Wheal AJ, Bennett T, Randall MD, Gardiner SM. Cardiovascular effects of cannabinoids in conscious spontaneously hypertensive rats. Br J Pharmacol 2007;152:717–24. [CrossRef]

25. Von Der Haar J, Talebi S, Ghobadi F, Singh S, Chirurgi R, Rajeswari P, et al. Synthetic Cannabinoids and Their Effects on the Cardiovascular System. J Emerg Med 2016;50:258–62.

26. Li MH, Suchland KL, Ingram SL. Compensatory Activation of Cannabinoid CB2 Receptor Inhibition of GABA Release in the Rostral Ventromedial Medulla in Inflammatory Pain. J Neurosci 2017;37:626–36.

27. Williams IJ, Edwards S, Rubo A, Haller VL, Stevens DL, Welch SP. Time course of the enhancement and restoration of the analgesic efficacy of codeine and morphine by delta9-tetrahydrocannabinol. Eur J Pharmacol 2006;539:57–63.

28. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur J Pharmacol 2006;531:280–1.

29. Katz PS, Sulzer JK, Impastato RA, Teng SX, Rogers EK, Molina PE. Endocannabinoid degradation inhibition improves neurobehavioral function, blood-brain barrier integrity, and neuroinflammation following mild traumatic brain injury. J Neurotrauma 2015;32:297–306.

30. Baron EP. Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been ….Headache 2015;55:885–916.

31. Achiron A, Miron S, Lavie V, Margalit R, Biegon A. Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis. J Neuroimmunol 2000;102:26–31. [CrossRef]

32. Notcutt WG. Clinical Use of Cannabinoids for Symptom Control in Multiple Sclerosis. Neurotherapeutics 2015;12:769–77.

33. Fagan SG, Campbell VA. The influence of cannabinoids on generic traits of neurodegeneration. Br J Pharmacol 2014;171:1347–60. [CrossRef]

34. Kluger B, Triolo P, Jones W, Jankovic J. The therapeutic potential of cannabinoids for movement disorders. Mov Disord 2015;30:313–27. [CrossRef]

35. Rueda-Orozco PE, Soria-Gomez E, Montes-Rodriguez CJ, Martínez-Vargas M, Galicia O, Navarro L, et al. A potential function of endocannabinoids in the selection of a navigationstrategy by rats. Psychopharmacology (Berl) 2008;198:565–76.

36. Koch M, Ferreirós N, Geisslinger G, Dehghani F, Korf HW. Rhythmic control of endocannabinoids in the rat pineal gland. Chronobiol Int 2015;32:869–74. [CrossRef]

37. Atkinson HC, Leggett JD, Wood SA, Castrique ES, Kershaw YM, Lightman SL. Regulation of the hypothalamic-pituitary-adrenal axis circadian rhythm by endocannabinoids is sexually diergic. Endocrinology 2010;151:3720–7. [CrossRef]

38. Murillo-Rodríguez E, Machado S, Rocha NB, Budde H, Yuan TF, Arias-Carrión O. Revealing the role of the endocannabinoid system modulators, SR141716A, URB597 and VDM-11, in sleep homeostasis. Neuroscience 2016;339:433–49. [CrossRef]

39. Murillo-Rodríguez E, Millán-Aldaco D, Di Marzo V, Drucker-Colín R. The anandamide membrane transporter inhibitor, VDM-11, modulates sleep and c-Fos expression in the rat brain. Neuroscience 2008;157:1–11. [CrossRef]

40. Brunton LL, Dandan RH. Goodman and Gilman's Manual of Pharmacology and Therapeutics. 2nd ed. McGraw-Hill Education; 2013.

41. Chandrasekaran G, Tátrai P, Gergely F. Hitting the brakes: targeting microtubule motors in cancer. Br J Cancer 2015;113:693–8. [CrossRef]

42. Hilal-Dandan R, Brunton L. Goodman and Gilman manual of pharmacology and therapeutics: McGraw Hill Professional; 2013.

43. Kushner BH, Modak S, Kramer K, Basu EM, Roberts SS, Cheung NK. Ifosfamide, carboplatin, and etoposide for neuroblastoma: a high-dose salvage regimen and review of the literature. Cancer 2013;119:665–71. [CrossRef]

44. Koziolova E, Janouskova O, Chytil P, Studenovsky M, Kostka L, Etrych T. Nanotherapeutics with anthracyclines: methods of determination and quantification of anthracyclines in biological samples. Physiol Res 2015;64 Suppl 1:S1–10.

45. Fouillaud M, Venkatachalam M, Girard-Valenciennes E, Caro Y, Dufossé L. Anthraquinones and Derivatives from Marine-Derived Fungi: StructuralDiversity and Selected Biological Activities. Mar Drugs 2016;14. [CrossRef]

46. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma 2015;56:2273–80. [CrossRef]

47. Chen R, Sanchez J, Rosen ST. Clinical Management Updates in Mantle Cell Lymphoma. Oncology (Williston Park) 2016;30:353–60.

48. Park JY, Nam JH. Progestins in the fertility-sparing treatment and retreatment of patients with primary and recurrent endometrial cancer. Oncologist 2015;20:270–8. [CrossRef]

49. Yasuda MT, Sakakibara H, Shimoi K. Estrogen- and stress-induced DNA damage in breast cancer and chemoprevention with dietary flavonoid. Genes Environ 2017;39:10. [CrossRef]

50. Singh A, Xu YJ. The Cell Killing Mechanisms of Hydroxyurea. Genes (Basel) 2016;7. pii: E99. [CrossRef]

51. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist 2016;21:1471–82. [CrossRef]

52. Elgemeie GH, Salah AM, Abbas NS, Hussein HA, Mohamed RA. Pyrimidine non-nucleoside analogs: A direct synthesis of a novel class of N-substituted amino and Nsulfonamide derivatives of pyrimidines. Nucleosides Nucleotides Nucleic Acids 2017;36:213–23. [CrossRef]

53. Zhang K, Yuan Q. Current mechanism of acquired resistance to epidermal growth factorreceptor-tyrosine kinase inhibitors and updated therapy strategies in human nonsmall cell lung cancer. J Cancer Res Ther 2016;12:131–37. [CrossRef]

54. Wehrli M, Oppliger Leibundgut E, Gattiker HH, Manz MG, Müller AM, et al. Response to Tyrosine Kinase Inhibitors in Myeloproliferative Neoplasia with 8p11 Translocation and CEP110-FGFR1 Rearrangement. Oncologist 2017;22:480–83. [CrossRef]

55. Aggarwal R, Thomas S, Pawlowska N, Bartelink I, Grabowsky J, Jahan T, et al. Inhibiting Histone Deacetylase as a Means to Reverse Resistance to Angiogenesis Inhibitors: Phase I Study of Abexinostat Plus Pazopanib in Advanced Solid Tumor Malignancies. J Clin Oncol 2017;35:1231–9. [CrossRef]

56. de Oliveira Taveira M, Nabavi S, Wang Y, Tonellato P, Esteva FJ, Cantley LC, et al. Genomic characteristics of trastuzumab-resistant Her2-positive metastatic breast cancer. J Cancer Res Clin Oncol 2017;143:1255–62.

57. Siurala M, Havunen R, Saha D, Lumen D, Airaksinen AJ, Tähtinen S, et al. Corrigendum to "Adenoviral Delivery of Tumor Necrosis Factor-α and Interleukin-2 Enables Successful Adoptive Cell Therapy of Immunosuppressive Melanoma. Mol Ther 2016;24:2033 [CrossRef]

58. Li B, Gao N, Zhang Z, Chen QM, Li LJ, Li Y. Historical and Clinical Experiences of Gene Therapy for Solid Cancers in China. Genes (Basel) 2017;8. pii: E85. [CrossRef]

59. Rocha FC, Dos Santos Júnior JG, Stefano SC, da Silveira DX. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. J Neurooncol 2014;116:11–24. [CrossRef]

60. Marcu JP, Christian RT, Lau D, Zielinski AJ, Horowitz MP, Lee J, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinolon human glioblastoma cell proliferation and survival. Mol Cancer Ther 2010;9:180–9. [CrossRef]

61. Khan MI, Sobocińska AA, Czarnecka AM, Król M, Botta B, Szczy-lik C. The Therapeutic Aspects of the Endocannabinoid System (ECS) for Cancerand their Development: From Nature to Labo-ratory. Curr Pharm Des 2016;22:1756–66. [CrossRef]

62. Javid FA, Phillips RM, Afshinjavid S, Verde R, Ligresti A. Cannabinoid pharmacology in cancer research: A new hope for cancer patients? Eur J Pharmacol 2016;775:1–14. [CrossRef]

63. Birdsall SM, Birdsall TC, Tims LA. The Use of Medical Marijuana in Cancer. Curr Oncol Rep 2016;18:40. [CrossRef]

64. Pisanti S, Bifulco M. Endocannabinoid system modulation in cancer biology and therapy. Pharmacol Res 2009;60:107–16.

65. Caffarel MM, Andradas C, Pérez-Gómez E, Guzmán M, Sánchez C. Cannabinoids: a new hope for breast cancer therapy? Cancer Treat Rev 2012;38:911–8. [CrossRef]

66. Portella G, Laezza C, Laccetti P, De Petrocellis L, Di Marzo V, Bifulco M. Inhibitory effects of cannabinoid CB1 receptor stimulation on tumor growthand metastatic spreading: actions on signals involved in angiogenesis and metastasis. FASEB J 2003;17:1771–3. [CrossRef]

67. Mimeault M, Pommery N, Wattez N, Bailly C, Hénichart JP. Antiproliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. Prostate 2003;56:1–12. [CrossRef]

68. Nithipatikom K, Endsley MP, Isbell MA, Wheelock CE, Hammock BD, Campbell WB. A new class of inhibitors of 2-arachidonoylglycerol hydrolysis and invasionof prostate cancer cells. Biochem Biophys Res Commun 2005;332:1028–33.

69. Guzmán M, Duarte MJ, Blázquez C, Ravina J, Rosa MC, Galve-Roperh I, et al. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer 2006;95:197–203. [CrossRef]

70. Rodrigues LC, Gobira PH, de Oliveira AC, Pelição R, Teixeira AL, Moreira FA, et al. Neuroinflammation as a possible link between cannabinoids and addiction. Acta Neuropsychiatr 2014;26:334–46. [CrossRef]

71. Tegeder I. Endocannabinoids as Guardians of Metastasis. Int J Mol Sci 2016;17:230. [CrossRef]