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Review

PHYTOCANNABINOIDS

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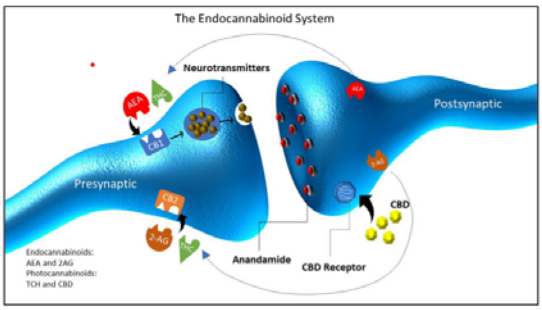
The interest in evidence-based knowledge regarding the therapeutical potential of cannabinoids has considerably grown in the last decade not only for public health specialists, but for any medical specialty, as the use of medicinal cannabis was progressively legally adopted in most states of the world. The article represents a review regarding the most studied phytocannabinoids as chemical messengers of the endocannabinoid system in the human body. It brings basic, up to date information, in terms of these compounds' biosynthesis in the plant, their classification, their chemical structure and properties, the health effects and benefits in several human pathologies.



1. *CANNABIS* PLANT AND HUMAN HEALTH, THROUGH CANNABINOIDS AND OTHER SECONDARY PLANT METABOLITES

Cannabis, a plant from the *Cannabaceae* family, has been cultivated for thousands of years and used with various purposes.[1] For example, Assyrians (2nd Millenium BC up to 4th Century BC) used cannabis both for its psychoactive and medical effects. In Europe, the plant was brought by Napoleon's soldiers, when returning from Egypt and by British doctors, at their return from India.

Cannabinoids were isolated and their structure was clarified after the 1960s, by the team led by Raphael Mechoulam, „the dean of the transnational cannabinoid research community". It was his team who discovered the endocannabinoid system in vertebrates, too, during the early 1990s, when looking for the phytocannabinoids mechanism of action in the human body.[2]

The cannabinoids, revealed as chemical messengers of the endocannabinoid system in the human body, may be of exogenous or endogenous origin. The exogenous ones are natural or synthetic. The first, so called "phytocannabinoids", are present in the highest amounts in the cannabis plant, but they were isolated from echinacea, broccoli, ginseng, carrots, black pepper, clove, too. In the *cannabis* plants, they are secondary metabolites, next to terpenes, flavonoids, phenols and so on, up to 1600 compounds from this species being isolated to date, of which 180 phytocannabinoids.[3]

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The most studied phytocannabinoids are Δ^9-tetrahydrocannabinol, (Δ^9-THC or THC), – the main psychoactive cannabinoid, cannabidiol (CBD) – the cannabinoid most used for its medicinal potency, known as major cannabinoids. There is a great variation within the 3 subspecies of *Cannabis sativa L.* (sativa, indica and ruderalis) and within the hybrid species, regarding their content of cannabinoids and the CBD/THC ratio, characteristics that depend not only on the genetic profile of the plants, but also on the conditions and growth climate.

The minor cannabinoids include cannabinol (CBN), cannabichromene (CBC), cannabigerol (CBG), cannabidioloic acid (CBDA), cannabigerolic acid (CBGA), tetrahydrocannabinolic acid (THCA), cannabinolic acid (CBNA), cannabidivarin (CBDV), tetrahydrocannabivarin (THCV), cannabigerovarin (CBGV), cannabichromevarin (CBCV), and others[3]. Future research is needed for health benefits and pharmaceutical potential of minor cannabinoids, as long as plants rich in this profile are or are soon going to be on markets.[4]

There are ongoing scientific evidences that the cannabinoids effects in the human body result from their individual actions, as well from summing up (synergism) or from potentiation (entourage effect) of their actions with those of other secondary metabolites in the cannabis plants, especially with terpenes.[5-7]

In the human body, the phytocannabinoids act through the endocannabinoid system, targeting its many cellular receptors, among which CB1 and CB2 are the first and most studied ones.

It has been shown that not only the phytocannabinoids from *cannnabis*, but also other molecules (beta-caryophyllene, N-alkylamide, falcarinol, rutamarin, etc) of some other vegetal species (echinaceae, brasicaceae, apicaceae, etc) have certain degrees of affinity for CB1 or CB2 receptors, as well as for some other components of the endocannabinoid system.[8] The endogenous cannabinoids are produced by the human body, as part of the endocannabinoid system (see section 4).

2. CHEMICAL STRUCTURES, CLASSIFICATION, PHARMACOLOGICAL ACTION OF THE PHYTOCANNABINOIDS

11 structural families or classes are defined up to now. Each class contains carboxylated, decarboxylated or methylated forms, derived from the „C3 or /and C5 lateral chain" types. The actual number of compounds of each class is also presented in Table 1**,** next to the compound from each class, showed to have pharmacological action.[9-13]

While in the raw cannabis plant the carboxylated form of the phytocannabinoids is dominant, as it will be showed in section (3), regarding their biosynthesis, when expose the plant to heat, or to light or air, to get ageing, chemical transformations occur, such as decarboxylation. Such processing conversions have been showed to modify the therapeutical properties spectrum of the plants.[14-22] As to the psychoactive best known phytocannabinoids, their acid forms are not psychoactive.

Last decades, scientific research also showed the modulation of the phytocannabinoids therapeutical effects either by synergistic, or by entourage effect of other natural components in *Cannabis* plant, the terpenoides, that give the scent of the plant. Hence, the superior efficacy of natural full or broad spectrum cannabis products in therapy, than the synthetic or highly extracted ones.[23-27]

The most abundant cannabinoids in the plant are Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabinol (CBN), cannabidiol (CBD), cannabigerol (CBG), and cannabichromene (CBC), Δ^9-tetrahydrocannabivarin (THCV), cannabivarin (CBV), cannabidivarin (CBDV). Other phytocannabinoids such as cannabinodiol (CBND), cannabielsion (CBE), cannabicyclol (CBL) and cannabitriol (CBT) showed much smaller amounts in the plant, yet have also been the subjects of study in the last decades.[28]

Further on we update some notorious therapeutical actions of the most studied phytocannabinoids listed in Table 1, mainly the non-psychoactive ones.

Cannabigerolic Acid (CBG-A). Formula: $C_{22}H_{32}O_4$. Molecular mass: 360.48708 g/mol. Cannabigerolic acid CBGA is the head of series THCA, CBDA, CBCA, produced in the plant (see section 3). It has medicinal properties (**analgesic** and **anti-inflammatory** effects) and is not psychoactive. Its analgesic effect is sinergized by the terpenoides Bomeol, Myrcene, while its anti-inflammatory effect by alpha-Pinene, beta-Caryophyllene, Cineol.[23-27] Neuroprotection, anticonvulsant, antiseizure are other important effects, highlighted in recent animal studies.[29,30] In full spectrum cannabis products, it has effects through its decarboxylated form too, that is also found in the plant, but in much smaller amounts.

Table 1

Phytocannabinoids. Structural families and representatives with known actions. The main action is underlined. Adapted from[9-13]

Class Name	Compound with pharmacological known action	Pharmacological action
1.**"Cannabigerol**" type class (16 compounds)	Cannabigerolic Acid, CBGA	Antibiotic
	Cannabigerol, CBG	Antibiotic, antifungal, anti-inflammatory, analgesic
2.**"Cannabichromene**" type class (9 compounds)	Cannabichromene, CBC	Anti-inflammatory, Antibiotic, antifungal, analgesic, neuroprotection
3.**"Cannabidiol**" type class (7 compounds)	Cannabidiolic Acid, CBDA	Antibiotic,
	Cannabidiol, CBD	Anxiolytic, antipsychotic, anti-inflammatory, analgesic, antioxidant, antispasmodic
4.**"Delta-9- Tetrahydro- cannnabinol**" type class (23 compounds)	Tetrahydrocannabinol, THC	Euphoriant Analgesic, Anti-inflammatory, Antioxidant, antiemetics
	Delta-9- tetrahydrocannabivariv THCV	Analgesic, euphoriant
5.**"Delta-8- Tetrahydro- cannnabinol**" type class (5 compounds)	Delta-8- Tetrahydro-cannnabinol	Similar to THC, with weaker action
6.**"Cannabinol"** type class (11 compounds)	Cannabinol, CBN	Sedative, antibiotic, anti-inflammatory, anticonvulsant
7.**"Cannabinodiol**" type class (2 compounds)	Cannabinodiol, CBND	Exists in low concentrates in Cannabis plant. This is why very little is known of it. Possible psychoactive.
8.**"Cannabicyclol**" type class (3 compounds)	CBL	Anti-inflammatory, antitumor, non-psychoactive
9.**"Cannabielsoin**" type class (5 compounds)	CBE	The least researched of the cannabinoids; non-psychoactive. It is believed that function as CBD.
10.**"Cannabitriol**" type class (9 compounds)	CBT	Anti breast cancer, through inhibitory activity on estrogen receptors-alpha,
11.**"Miscellaneous cannabinoids**" type class (30 compounds)		

Cannabigerol (CBG). Formula: C21H32O2. Molecular mass: 316.485 g/mol. Cannabigerol is not psychoactive, either. It was shown to stimulate the growth of new brain cells, including in the elderly, while real **neurogenic** compounds are extremely rare.[31] CBG also stimulates **bone growth**, shows **antibacterial** properties (synergistic terpenoids: alpha-Pinene, beta-Caryophyllene, Cineol, Humulene, Limonene, Linalool, Terpinolene),[23-27,32,33] **antifungal** properties (synergistic terpenoids: alpha-Pinene, beta-Caryophyllene, Caryophyllene oxide, Limonene, Nerolidol, Terpinolene)[23-27,35,36] and **antitumoral**[67-77] properties (synergistic terpenoids: beta-Caryophyllene, Citronellol, Humulene, Limonene, Myrcene).[23-27] It **fights insomnia**, too.

Last decade animal studies (on mice or rats) highlighted the following effects of CGB: reduced **bladder contractions** more effectively than four other cannabinoids, suggesting its potential use in bladder dysfunction disorders[34]; decrease inflammation on inflammatory bowel disease (IBD);[35] reduced neuroinflammation in mice with multiple sclerosis (MS);[36] as well reduced neuroinflammation associated with many neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS);[37] protected the neurons of mice with Huntington's disease;[38] can reduce keratinocyte proliferation, the process largely responsible for psoriasis;[39] had appetite-stimulating effects, offering a non-intoxicating alternative to THC, for counteracting weight loss in people with HIV, cancer, and other serious conditions.[40] CBG inhibited colorectal cancer and other human carcinoma cell growth.[41,42]

Most recently, CBG – quinone derivatives showed neuroprotection in Parkinson's disease, using 6-hydroxydopamine-lesioned mice. In vitro

studies confirmed the relevance of PPARG receptors for such effects.[43] Such findings encourage the usefulness of chemotype IV cannabis plants.

CBG, in plant extracts associating CBD and THCV, showed anti-inflammatory effect in Coronavirus disease 2019 (COVID-19)[44] too.

Tetrahydrocannabinolic acid (THC-A). Formula: C22H30O4. Molecular mass: 358.4733 g/mol. Tetrahydrocannabinolic acid, like other acid phytocannabinoids, is not psychoactive. THC-A is strongly **anti-inflammatory** (synergistic terpenoids: alpha-Pinene, beta-Caryophyllene, Cineol, Citronellol, Humulene, Myrcene),[23-27] anti seizure[45] and neuroprotective;[29] it encourages **appetite**, has **antitumoral**[67-77] (synergistic terpenoids: beta-aryophyllene, Citronellol, Humulene, Limonene, Myrcene) and **antispasmodic** properties (synergistic terpenoids: Citronellol, Myrcene),[23-27] it **fights insomnia**. The highest content of THCA is found in female plants without seeds (sinsemilla), whose flowers were not pollinated: quite often, over 30% of dry substance.

Tetrahydrocannabinol Delta 9 (Δ-9-THC). Formula: C21H30O2. Molecular mass: 314.2246 g/mol. Δ-9-tetrahydrocannabinol (commonly named "Δ9-THC", "D9-THC", "d9-THC" or simply "THC") is a neutral cannabinoid, known for its strongly psychoactive properties. Of all the scientific discoveries on THC, probably the most important was the way in which THC allowed scientists to discover the presence of the endocannabinoid system in vertebrates (including humans): a critical part of physiology that, until then, was unknown.

THC has been included in the formula of products that have proven to be efficient in the treatment of various conditions and disorders, including **pain**[17-20,50,74,76] (synergistic terpenoids Bomeol, Myrcene), **tumors**[66-75] (synergistic terpenoids beta-Caryophyllene, Citronellol, Humulene, Limonene, Myrcene), nausea or ADHD (attention-deficit/hyperactivity disorder), as **antispasmodic** (synergistic terpenoids Citronellol, Myrcene, bronchodilator- alpha-Pinene, Bomeol, Cineol), as **antibacterial** (synergistic terpenoids alpha-Pinene, beta-Caryophyllene, Cineol, Humulene, Limonene, Linalool, Terpinolene),[23-27,32,33] **anti-inflammatory**[46,49,62,76] (synergistic terpenoids alpha-Pinene, beta-Caryophyllene, Cineol, Citronellol, Humulene, Myrcene).[23-27] Such benefits are put in value only in products that associate THC with other non-psychoactive cannabinoids, mainly CBD, the last in much larger amounts, counteracting the psychotropic effect of THC. Otherwise, its toxic effects could be notable, both in adults and children: **neurological, ophthalmological**, **cardiovascular** and **gastrointestinal.**[46]

Δ-8-Tetrahydrocannabinol (Δ-8-THC). Formula: C21H30O2. Molecular mass: 314.4617 g/mol. Delta-8-Tetrahydrocannabinol is an isomer of tetrahydrocannabinol (THC), having lower psychotropic potency than Delta-9-Tetrahydrocannabinol (Delta-9–THC), with **anti-vomiting**, **anxiolytic** (synergistic with Linalool, Limonene), **appetite** stimulating, **analgesic and neuroprotective** properties CB1 mediated.[47,62,76] It results from Δ9-THC, during the maturation process of the dried inflorescences.

Cannabinolic acid (CBN-A). Formula: C22H31O4. Mollecular mass: 359.48 g/mol. The quantity of CBN-A in the plant is high. CBN-A is an **anti-inflammatory** and probably an antibiotic.

Cannabinol (CBN). Formula: C21H26O2. Molecular mass: 310.1933 g/mol. Cannabinol is not produced in the raw plant, but it is an oxidation product of the raw THC, after prolonged exposure to hot, dry air of the plant fragments, after harvesting. As such, high concentrations of CBN in a cannabis product suggest the treatment of the plant through aging and significant exposure to heat. CBN is lightly psychoactive, might be a stronger **sedative** than other known cannabinoids;[48] plant fragments with CBN close to 1% may be used in treating insomnia (synergistic with Bomeol, Citronellol, Linalool, Myrcene, Nerolidol, Phytol, Terpinolene). It is somehow efficient as **anti-vomiting and anticonvulsant, anti inflammatory**,[49,62,76] **anti pain effect.**[50]

Cannabidiolic acid (CBD-A). Formula: C22H30O4. Mollecular mass: 358.2144 g/mol. Until recently, cannabidiolic acid was much more frequently found in high concentrations in Cannabis Ruderalis than in the other 2 subspecies. Lately, there were produced hybrids (including "Cannatonic-C6" and "ACDC") where there is synthesized more CBDA than THCA. It was proven that CBDA has both **anti-inflammatory** (synergistic terpenoids: alpha-Pinene, beta-Caryophyllene, Cineol, Citronellol, Humulene, Myrcene) and **antitumoral**,[51,67-77] (synergistic

terpenoids: beta-Caryophyllene, Citronellol, Humulene, Limonene, Myrcene)[23-27] effect.

Cannabidiol (CBD). Formula: C21H30O2. Molecular mass: 314.2246 g/mol. Cannabidiol is a "non-psychoactive" (it does not cause euphoria, time dilatation or anxiety, like THC). CBD proved extremely useful and benefits of regulatory approval for the treatment of seizures associated with **Dravet syndrome**, **Lennox-Gastaut syndrome** and **tuberous sclerosis complex** (the cannabidiol oral solution Epidyolex) (synergistic terpene-Linalool).[52] Its lack of psychoactivity makes it ideal in treating children, the elderly and patients who prefer to stay clear-headed and focused. The mechanisms responsible for protection against seizures are not fully understood, but they are likely to be multifactorial and to include, among others, antagonism of G protein-coupled receptor, desensitization of transient receptor potential vanilloid type 1 channels, potentiation of adenosine-mediated signaling, and enhancement of GABAergic transmission.[53]

CBD is often as efficient as THC in managing chronic **pain**[46,49,50,62,76,78] (synergistic: Bomeol, Myrcene) and **tumors**[16-19,67-77] (synergistic: beta-Caryophyllene, Citronellol, Humulene, Limonene, Myrcene). Also, CBD lowers blood sugar and was used in **diabetes treatment**.[54,55]

CBD has a **calming effect** and is useful in the treatment of stress **and sleep loss disorders** (synergistic: Bomeol, Citronellol, Linalool, Myrcene, Nerolidol, Phytol, Terpinolene).[23-27] CBD clinical trials, observational studies and case reports support the effect of CBD (300–800 mg) of reducing anxiety in healthy volunteers, patients with social anxiety disorder, those at clinical high risk of psychosis, in patients with Parkinson's disease, in individuals with heroin use disorder, in patients with anxiety and sleep disorders, Crohn's disease, depression.[56,57]

Preliminary data show that CBD may be beneficial in cannabis and tobacco addiction in humans. However, more research is needed to evaluate CBD as a potential **treatment for drug addiction.**[58]

Recent studies concluded CBD maintains keratinocyte proteostasis and therefore could be suggested as a protective measure in the **prevention of UV-induced metabolic changes in epidermal keratinocytes.**[59] Both CBD and CBG and their acid forms showed neuroprotective effects on toxic and neurodegenerative processes; in the mechanisms of action of CBG, the role of 5-HT1A receptors is a certitude.[60]

Cannabichromic acid (CBC-A). Formula: C22H30O4. Molecular mass: 358.2144 g/mol. Cannabichromic acid is one of the three compounds synthesized by the plant, from CBG-A. CBC-A is **anti-inflammatory**, poorly antifungal and strongly **antibacterial.**[32,33]

Cannabichromene (CBC). Formula: C21H30O2. Molecular mass: 314.2246 g/mol. Cannabichromene is also non-psychoactive and it was proven to be approximately 10 times more efficient than CBD in treating **anxiety and stress.**[61] Also, it shows efficiency in treating **inflammation, pain relief**[46,49,76] (synergistic: Bomeol, Myrcene) and is both **antiviral**[32,33] **and antitumoral**[67-77] (synergistic: beta-Caryophyllene, Citronellol, Humulene, Limonene, Myrcene).[23-27]

In several studies Cannabichromene (10-75 $mg \cdot kg^{-1}$), Δ^9-tetrahydrocannabinolic acid (20 $mg \cdot kg^{-1}$), and tetrahydrocannabivarin (range 0.025-2.5 $mg \cdot kg^{-1}$) showed promise in models of seizure and hypomobility, Huntington's and Parkinson's disease[29]. CBG and CBC showed significantly higher rates of cancer cell death, compared to other cannabinoids and suggest the need for further investigation into synergistic efficacy.[62]

Cannabicyclol acid (CBL-A). Formula: C22H3004. Molecular mass: 358.2144 g/mol. Few things are known about CBL-A, as the plant produces very little of it. It is the most stable acid form of cannabinoids, heating not causing decarboxylation. It has both an **anti-inflammatory** (synergistic terpenoids: alpha-Pinene, beta-Caryophyllene, Cineol, Citronellol, Humulene, Myrcene) and **antitumoral** effect,[63,64] (synergistic: beta-Caryophyllene, Citronellol, Humulene, Limonene, Myrcene).

Cannabicyclol (CBL). Formula: $C_{21}H_{30}O_2$. Molecular mass: 314.2246 g/mol. Cannabicyclol is a degraded product; by light exposure, the cannabichromene turns into CBL. Its medical properties are not known, as they appear in quite low concentrations in comparison to other cannabinoids. Cannabicyclol is non-psychoactive.

Cannabitriol (CBT). Formula: $C_{21}H_{30}O_4$. Molecular mass: 346.5 g/mol.

A recent study concluded Cannabitriol could have relatively better inhibitory activity (on

estrogen receptors-alpha), than tamoxifen – the in use chemotherapeutic; Therefore, CBT could be a better therapeutic candidate in the treatment of breast cancer. Further research such as in vivo and/or in vitro assays could be conducted to attest its ability.[65]

Since the first study in 1975, potential antitumor activity of plant-derived or phyto-cannabinoids, *e.g.*, (−)-trans-Δ9-tetrahydro-cannabinol (THC), cannabinol (CBN), Δ8-THC, cannabidiol (CBD) and cannabicyclol (CBL), as well as of synthetic cannabinoids, is the focus of current research.[66]

The intimate mechanisms for **anticancer effects** mentioned above, for some of the phytocannabinoids, might be detailed as follows:[67]

- induce autophagy in glioma, melanoma, liver, prostate, and pancreatic cancer cell lines, [68-71]
- inhibit angiogenesis by blocking the vascular endothelial growth factor (VEGF) signaling pathway. CBR agonists decrease the expression of VEGF and its receptors 1 and 2 (VEGFR1, VEGFR2) in glioma and skin and thyroid cancers. Moreover, can inhibit endothelial cell proliferation, which is also induced by cancers, thus additionally contributing to cancerous angiogenesis inhibition;
- inhibit spontaneous and induced metastasis in animal models and restrict cancer cell invasion in vitro (in lung, breast, and cervical cancers, and gliomas)[72-74]

Some data show that low expression of CBR1 in colorectal cancer positively affects the metastatic process, inhibiting apoptosis and deregulating the main signaling pathways. These observations contribute to the idea that drugs directed at regulating the endocannabinoid system through the induction of CB1 receptor can be helpful in order to develop new anti-cancer therapies or improve existing ones.[75]

As to the "C3 lateral chain" type of pytocannabinoids, **CBGV-A, THCV-A, CBDV-A, CBCV-A,** of the raw extract of Cannabis, **anti-inflammatory** properties have been evidenced, as to such effects synergistic terpenoids being alpha-Pinene, beta-Caryophyllene, Cineol, Citronellol, Humulene, Myrcene, or some neuroprotective effects, necessiting more studies.[10-23, 29,44,76]

Since the beginning of the 21st century over 42 countries all over the world have authorized and regulated medical cannabis for its therapeutic effects. Cannabinoids available on the world market or under research and clinical trials include Marinol®, Cesamet™, Sativex®, Epidiolex®, Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Bedrolite® Namisol® and Syndros® (Dronabinol® oral solution), and Arvisol®. Medical cannabis can be used in a number of different ways, for example, as pills, tablets, capsules, soft gel, dissolved in an oil solution (olive, sesame, coconut, or hempseed oil), tea, or by inhaling it after vaporization.[77-79]

The scientific investigation of cannabis has been restricted due its classification as a schedule 1 controlled substance. In late 2020 the Court of Justice of the European Union ruled that CBD is not a narcotic and the UN's Commission for Narcotic Drugs voted to reclassify cannabis from Schedule IV, where it was placed alongside drugs such as heroin, into a less harmful category.

There is currently a strong need to invest in research and innovation at European level to build an evidence base for the effectiveness of treatments derived from the cannabis plant, and also to invest in educating people to understand the fundamental difference between medical and recreational cannabis use.

3. BIOSYNTHESIS OF THE PHYTOCANNABINOIDS

In the *cannabis* plant, 2 "synthesis series" have been described: series I, "of cannabigerovarin" and series II, "of cannabigerol", after the name of the series' heads.

1. Geraniol, $C_{10}H_{18}O$ is a monoterpenoid, 3.7-dymethylocta-2.6-dien-1-ol (**Figure 1**).

It is a plant metabolite terpenoid, volatile oil, with odorant and allergenic actions. Geraniol, like most terpenes of cannabis, has strong antibacterial, antifungal, anti-inflammatory actions, too, making it quite useful in various therapies.[80-84]

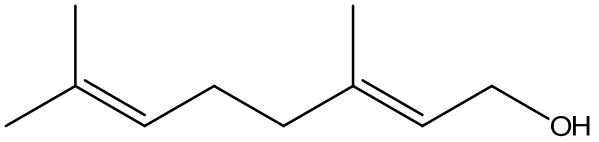


Fig. 1 – Geraniol molecule, 2D.

2. Polyketides are secondary metabolites in the plant, with various structure and functions. They are synthesized by polyketide-synthases (PKSs), using precursors of Acyl-CoA, for the condensation reaction.[85, 86]

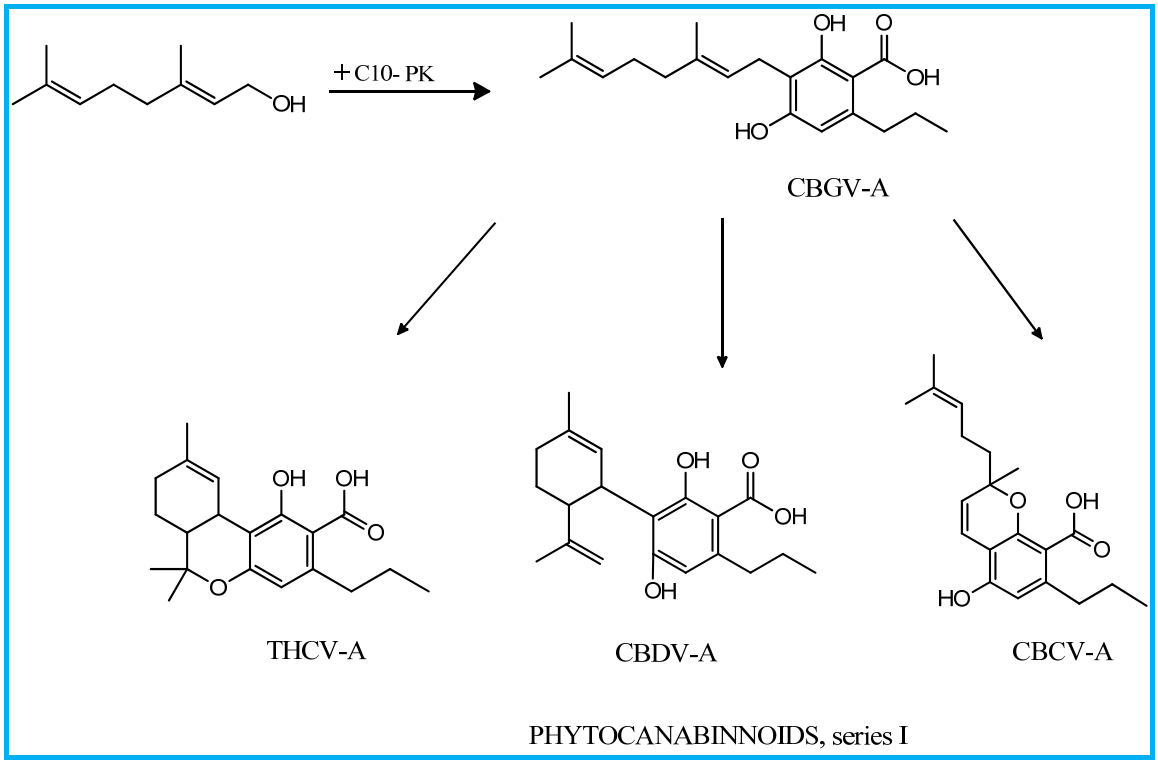


Fig. 2 – The principle of "C3 lateral chain" phytocannabinoids synthesis.

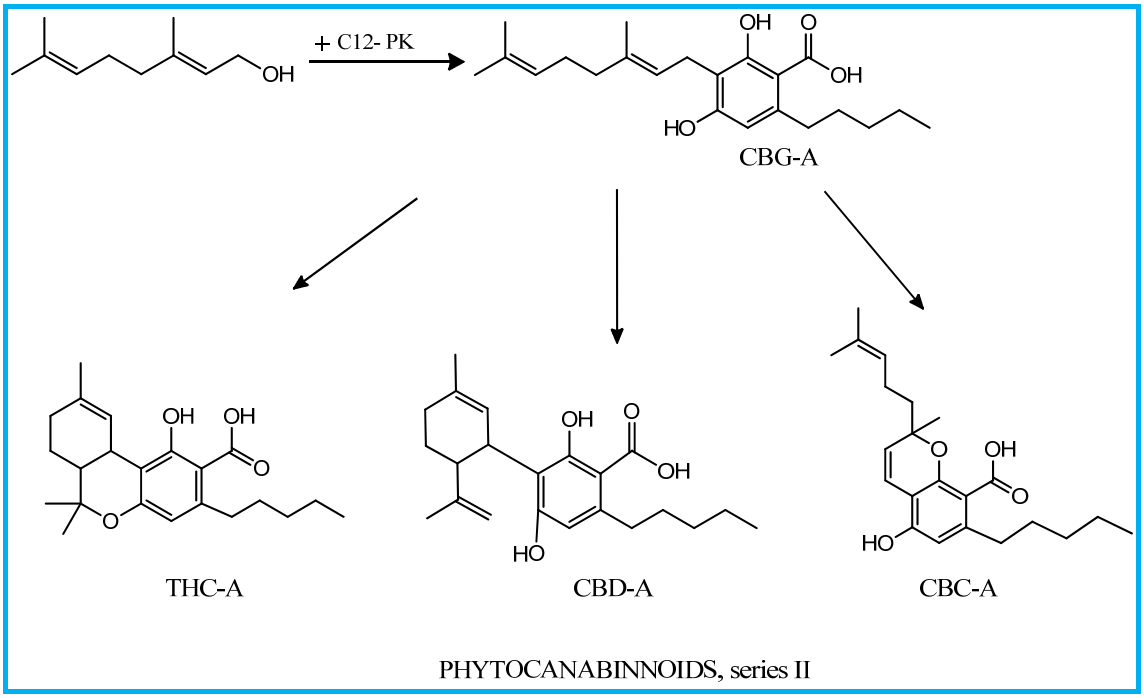
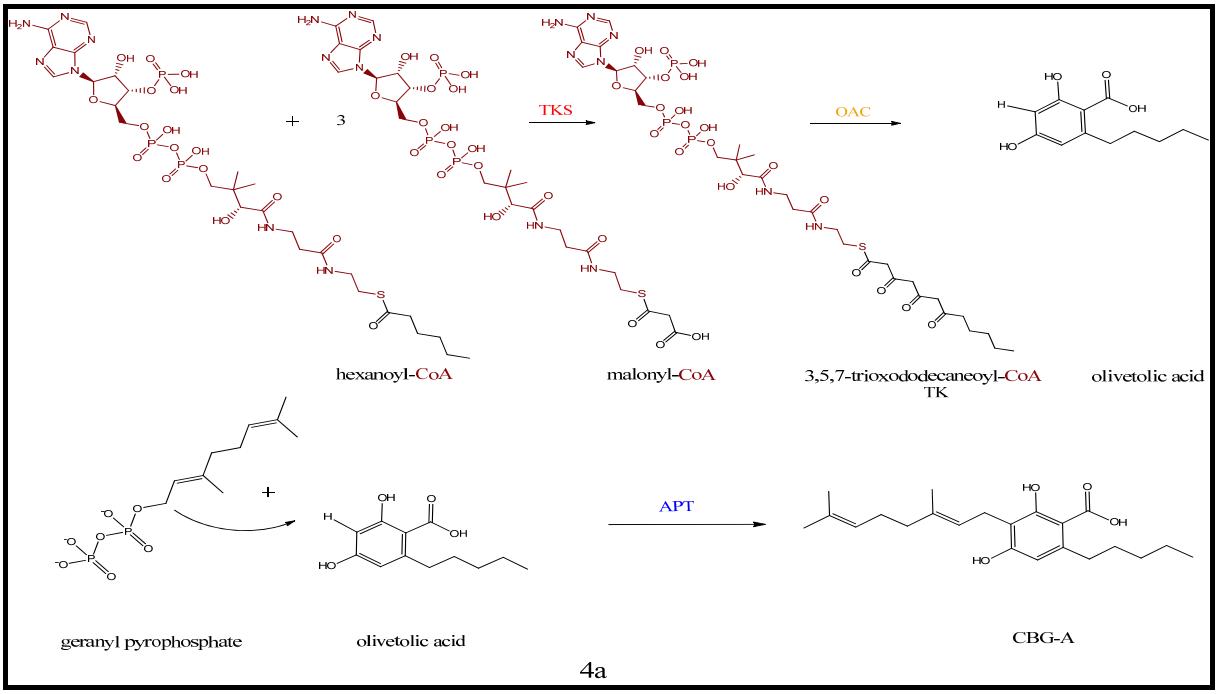


Fig. 3 – The principle of "C5 lateral chain" phytocannabinoids synthesis.

CBGV-A (cannabigerovarin acid) results out of Geraniol and C10 Polyketide condensation. It is a plant's core intermediate, of which derive the carboxylated forms of THCV (tetrahydrocannabivarin), CBDV (cannabidivarin), CBCV (cannabichromevarin), all with C3 lateral chain, as common molecular structure characteristic (**Figure 2**). They belong to the so called series I of biosynthesis. The carboxylated forms turn into decarboxylated, the two type of forms coexisting in the plant, the first type being dominant.



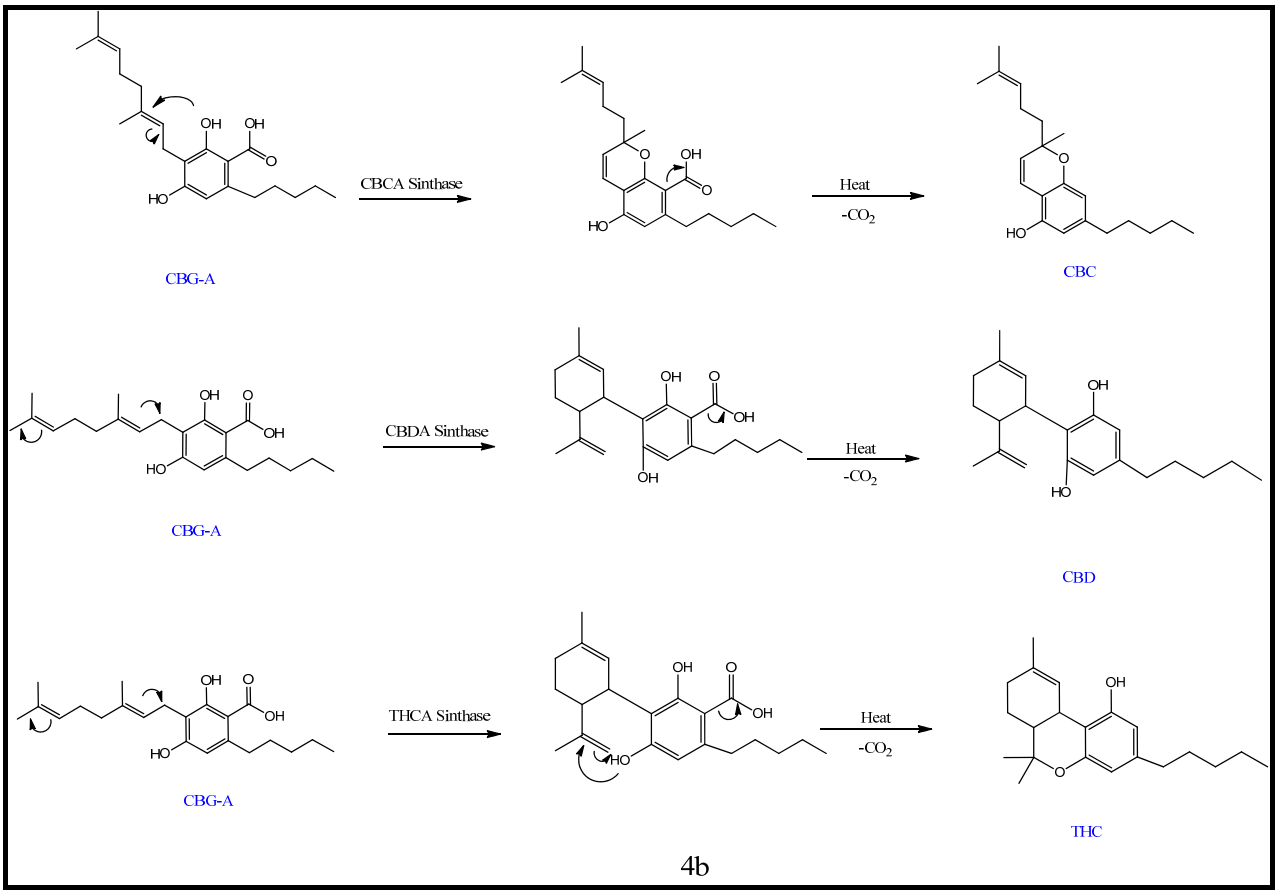


Fig. 4a and 4b – Biosynthesis pathways in the C5 lateral chain cannabinoids series.
TKS = tetraketide synthase, OAC = olivetolic acid cyclase, APT = aromatic prenyltransferase.

CBG-A (**cannabigerolic acid)** results in the plant, out of Geraniol + C12 Polyketide condensation, as the other core intermediate, of which derive the members of series 2: the carboxylated forms of THC (tetrahydrocannabinol), CBD (cannabidiol), CBC (cannabichromen), all with C5 lateral chain,

as common molecular structure characteristic[85,86] **(Figure 3).** The same mixture of carboxylated and decarboxylated forms ocures in series 2.

The cannabinoids are biosynthesized in the glandular trichomes, that cover, at the highest density, the female inflorescences.

An **initial pathway** is uptodate clarified, namely (**Figure 4**):

a. Sequential condensations of acyl-CoA, cathalized by TKS, produce a C10 or C12 poliketide;[87,88]
b. The poliketide is enzymatically (OAC) cyclized to olivetolic acid;[89]
c. The prenyl group of *geranyl*_pyrophosphate is enzymatically (APT) additioned to the olivetolic acid molecule,[90] resulting cannabigerolic or cannabigerovarinic acid, that are the heads of the 2 series of phytocannabinoids (CBGA/CBGVA). What leads these syntheses towards one series or another, and their resulting ratio, are among the things that still need to be clarified.
d. Finally, the cannabigerolic / cannabigerovarinic acid is enzymatically turned into THC (V)A, CBD(V)A and CBC(V)A. The sinthases THCAS and CBDAS are flavinated enzymes, with His114 and Cys176 being most likely the FAD-binding sites. CBDAS abstracts a proton from the terminal methyl group of CBGA, instead of from the hydroxyl group targeted by THCAS, this change in regioselectivity determines the cyclization.[91,92]
e. A non-enzymatic decarboxylation of these acid forms then occur, both in the plant, but more during the plant processing.[93]

4. THE ENDOCANNABINOID SYSTEM (ECS)

Many physiological processes in all vertebrates are regulated by ECS: appetite and digestion, metabolism, pain, inflammation and other immunological reactions, sleep, psychological mood, learning and memorizing, motor function control, functioning of the cardiovascular system, muscle formation, bone growth and remodeling, liver function, reproductive function, skin and peripheral nerves function, cellular proliferation.[94,95] **ECS** consists of: endocannabinoids, receptors and regulatory enzymes.[96,97]

4.1. The endocannabinoids: the first and most commonly studied are **AEA** (anandamide, N-arachidonoylethanolamide) and **2-AG** (2-arachidonoylglycerol), derivates of the arachidonic acid, with intracellular synthesis. They have been shown to act as retrograde, transitory neurotransmitters, synthesized on request, in the GABAergic synapses (**Figure 5**).[98]

4.2. The main receptors in the endocannabinoid system and the first discovered are CB1 and CB2 receptors.

CB1 are localized mainly in the central nervous system and spine, being the main psychoactive receptors, as well as in the adipose tissue, liver, pancreas, skeletal muscles and immune system cells. **CB2** receptors are localized mainly in the periheral nervous system and the immune system cells.[99]

To date, up to100 fatty-acid-derived mediators, together with their receptors (**Table 2),** as well as other ways of synthesis and degradation (with over 50 enzymes involved) of such mediators were identified within the ECS, which became the "expanded ECS system" or „endocannabinoidome", as it was recently revised by Di Marzo and Silvestri.[100,101] These findings changed the perception on the therapeutical potential of *cannabis*-based medicines, on their medicinal interactions, as well as on the possible adverse effects of this therapy.

The tissue in which the receptors are located and the ligand type explain the effects of cannabinoids. For example, CB1 receptors in the hypothalamus are involved in regulating the appetite, the ones in the amigdala cause emotional reactions, the ones in the peripheral nerves are involved in reducing the pain sensation. The CB1 receptor is the main target of the endocannabinoid AEA, with a partially agonistic action, as well as the phytocannabinoid THC, a psychothropic component from cannabis. Endocannabinoid 2-AG acts as an agonist for both types of receptors. CBD is a phytocannabinoid whose main action mechanism is through the TRPV1, TRPM8 and GPR55 receptors, as well as by inhibiting the enzyme hydrolyzing anandamide. The CB2 receptors mainly have an immunomodulating and anti-inflammatory function.[102]

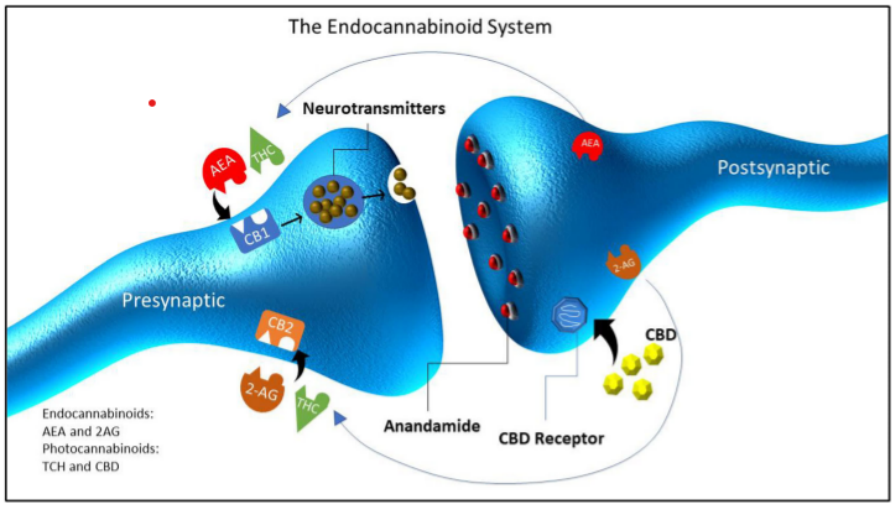


Fig. 5 – The endocannabinoid system. Reproduced from.[102]

Table 2

Mediators, receptors and specific interactions, in the **expended ECS** (see abbreviations; ++, + stimulation, - inhibition).

Adapted from[104, 105]

		Mediators													
		NAEs					PA	2AcGs			LipoAAs			Ac Neuro	
		AEA	OEA	PEA	LEA	DHEA	OA	**2-AG**	2-OG	2-LG	taurines	glycines	serines	serotonins	dopamines
Receptors	**CB1**	++				+	+	++							++
	CB2	++				+		++							
	GPR18											++			
	GPR55			++											
	GPR110					++									
	GPR119		++		++				++	++					
	TRPV1	++	++		++	+		+	+	+	++			-	++
	TRPV4										++				
	Cav3	-										-		-	-
	PPARA		++	++			++					++			
	PPARG	-				-									

4.3. Regulatory enzymes of the ECS: the first discovered are responsible for the synthesis or catabolysis of the main 2 endocannabinoids:

- Anandamide is released from N-arachidonoyl phosphatidyl ethanol (NAPE), under the catalytic action of NAPE phospholipase D type (**NAPE PLD**)[103] and is decomposed by arachidonic acid hydroxylase (**FAAH**) and cyclooxygenase 2 (**COX-2**)[104]
- 2-arachidonoylglyerol (2-AG) is synthesized under the action of diacylglycerol lipase (**DAGL**), and hydrolazed by monoglycerol (**MAGL**)[105]

Phytocannabinoids from the *cannabis* plant were shown to act as agonists, reverse agonists, antagonists or allosteric modulators on the human endocannabinoid receptors, thus justifying the potential of medicinal cannabis products in modelling the physiological and pathological processes in humans.

CONCLUSIONS

Natural products have always been valuable sources of novel compounds developed into pharmaceuticals. The last 3 decades in the field of medical research have brought the discovery of the phytocannabinoids, followed by details about their structure, physicochemical properties, and have revealed the intimate mechanisms of producing

their effects on human health, via the endocannabinoid system. There is an ever growing number of proof showing the benefits of cannabinoids for a large number of conditions, such as: pain, inflammation, neurodegeneration, emesis, anorexia, epilepsy, symptoms of multiple sclerosis and other disorders. Although we are at the beginning of understanding the impact of cannabinoids on human health state, the process of including cannabinoids in well-standardized prescription drugs has a rapid progress and compel the healthcare staff to acknowledge any updated information in this field, and to work together with regulatory officials to ensure that phytocannabinoid products meet the necessary therapeutic and safety standards.

ABBREVIATIONS

Mediators

2-AcGs 2-acylglycerols
2-AG 2-arachidonoylglycerol
2-LG 2-linoleoyl glycerol
2-OG 2-oleoylglycerol
AcNeuro acyl neurotransmitters
AEA N-arachidonoylethanolamine
DHEA N-docosahexanoylethanolamine
LEA N-linoleoylethanolamine
Lipo-AAs lipoamino acids
NAEs N-acylethanolamines
OA oleoylamide
OEA N-oleoylethanolamine
PA fatty acid primary amides
PEA N-palmitoylethanolamine

Receptors

Cav3 T-type Ca2+ channel
CB1 cannabinoid receptor 1
CB2 cannabinoid receptor 2
GPR110 G protein-coupled receptor 110
GPR119 G protein-coupled receptor 119
GPR18 G protein-coupled receptor 18
GPR55 G protein-coupled receptor 55
PPARA peroxisome proliferator-activated receptor alpha
PPARG peroxisome proliferator-activated receptor gamma
TRP, transient receptor potential
TRPV1 transient receptor potential cation channel sub-family V member 1
TRPV4 transient receptor potential cation channel subfamily V member 4

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