ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2021, *66*(5), 435–444
DOI: 10.33224/rrch.2021.66.5.06

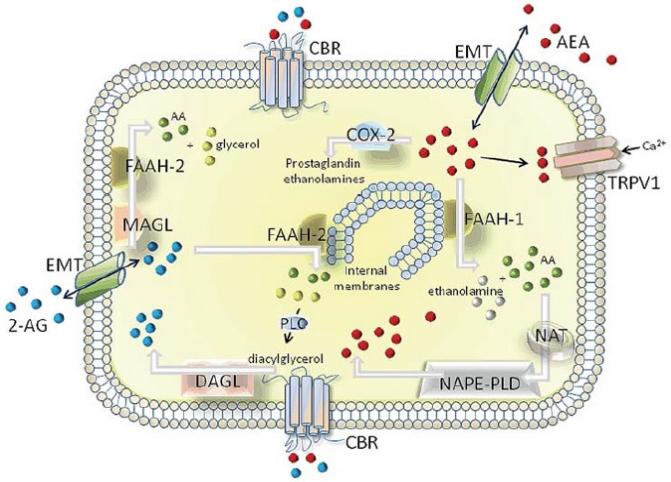
CONSIDERATIONS ON THE THERAPEUTICAL POTENTIAL OF MEDICINAL CANNABIS, FROM A BIOCHEMICAL VIEW

Dana Maria POPESCU-SPINENI,[a,b] Răzvan CHIVU,[a,*] Alexandru Constantin MOLDOVEANU,[a,d] Constantin IONESCU-TÎRGOVIŞTE[b] and Anca Magdalena MUNTEANU[a,c]

[a] "Carol Davila" University of Medicine and Pharmacy Bucharest, Bulevardul Eroii Sanitari 8, Bucureşti 050474, Roumania
[b] Roumanian Academy Bucharest, Calea Victoriei 125, Bucureşti 010071, Roumania
[c] National Institut of Public Health, Bucharest, Doctor Leonte Anastasievici 1-3, Bucureşti 050463, Roumania
[d] University Emergency Hospital Bucharest, Splaiul Independenței nr. 169, Bucharest, Roumania

Received December 17, 2020

Since the early 90s, when the endocannabinoid system was first described together with its role in human physiology and pathologies, medicine research has been focused in manipulating it, in order to treat diseases. Related to this, there is of top actuality that the medical chemistry is challenged as to the participation to the development of cannabis medicines. The latest description of an "expanded endocannabinoid system", allowed recent explanations of the potential therapeutic uses of non-psychotropic phytocannabinoids in pain, nausea, cancer, neurodegenerative diseases, obesity, metabolic syndrome, etc.The tens of FAAH inhibitors discovered until present creates expectations to generate medicines with selectivity to treat severe neuropathies. The discovery of an epigenetic modulation of the human endocannabinoid system, brought new perspectives to health interventions and disease treatment, as well. The present paper brings to discussion these topics, from a biochemical view, a perspective without which, modern understanding of human health, disease and its treatment, might be poor.



INTRODUCTION

Cannabis was also used as a medical remedy for thousands of years, but the interest upon this subject increased considerably in the last 30 years, after the Mechoulam's discovery in the 90's of the endocannabinoid system (ECS) in the human body, a main system of homeostatic regulation of the body.[1-3] Although the research in the field progress quite rapidly (a synthesis of over 24 000 scientific papers regarding the therapeutical use of cannabinoids, selected from the quality point of view, published by The National Academy of Sciences, Engineering and Medicine in 2017 being already overdue from some points of view), it is stated that barely the first steps are made in this area, which only highlighted the complexity of the phenomena and the huge potential that "cannabis medicine" has in treating a multitude of conditions, but also in improving the quality of life. The present paper brings into discussion the therapeutical potential of cannabis from a biochemical point of view, a perspective without which the process of understanding the phenomena is not possible.

* Corresponding author: razvan.chivu@umfcd.ro

Brief overview of the human ECS biochemistry, in relation to the therapeutic potential of medicinal cannabis

The endocannabinoid system was discovered because its receptors are the targets of the psychotropic compound of *Cannabis sativa* L., the Δ-9-tetrahydrocannabinol (THC). At first, it was described as being constituted of two endocannabinoids, derived from fatty acids that stimulate the cannabinoid receptors, a few of the metabolic enzymes and their transporters.[4] The first, and most studied, cannabinoids discovered are anandamide (AEA, N- arachidonoylethanolamine)[5,6] and 2-arachidonoylglycerol (2-AG),[7,8] with the respective biosynthetic precursors, *e.g.* the N-arachidonoyl-phosphatidylethanolamines (NArPEs) and the 1-acyl-sn-2- arachidonoyl-glycerols (AcArGs). The first receptors described were the two G protein-coupled receptors, the cannabinoid receptor type-1 (CB1) and type 2 (CB2). The main synthesis path of AEA is the transfer of Ca-dependent of arachnoid acid from a phosphatidylcholine to phosphatidylethanolamine (PE), thus forming N-arachidonoilphosphatidyletanolamine- phospholipase D (NAPE), which is hydrolyzed by N-acyl-phosphatidylethanolamine-specific phospholipase D-like (NAPE-PLD) in anandamide (AEA) and phosphatidic acid (PA). 2-arahidonoilglycerol (2-AG) is formed by conversion of diacylglycerol (DAG) under the action of diacyglycerol lipase (DAGL).[9,10] Biodegradation of anadamide and 2-AG was discovered that it has an intra cellular place by the action of fatty acids hydrolasis: AEA is degraded by cytoplasmatic FAAH[11] or by the hydrolysis of an acid upon lysosomal amidase N-acyletanolamine-hydrolysis (NAAA),[12] while 2-AG is degraded by the action of monoaciglycerol lipase (MAGL) (Figure 1).

There were described alternative ways of degradation, by the oxidation of the two endocannabinoids by cyclo-oxygenase 2 (COX-2), thus resulting the prostaglandine compounds, or their hydroxylase by 12-lipoxygenase (12-LOX).[13-15]

An optimally functioning ECS creates endocannabinoids based on the demands and needs of the body.[16] The endocannabinoids created engage ECS-receptor-sites in a lock and key fashion. Consecutively, neurotransmitters are released sending messages to cell tissues and organs. The body may maintain a constant ECS balance by enzymatically degrading endocannabinoids when necessary in order to ensure its homeostasis.

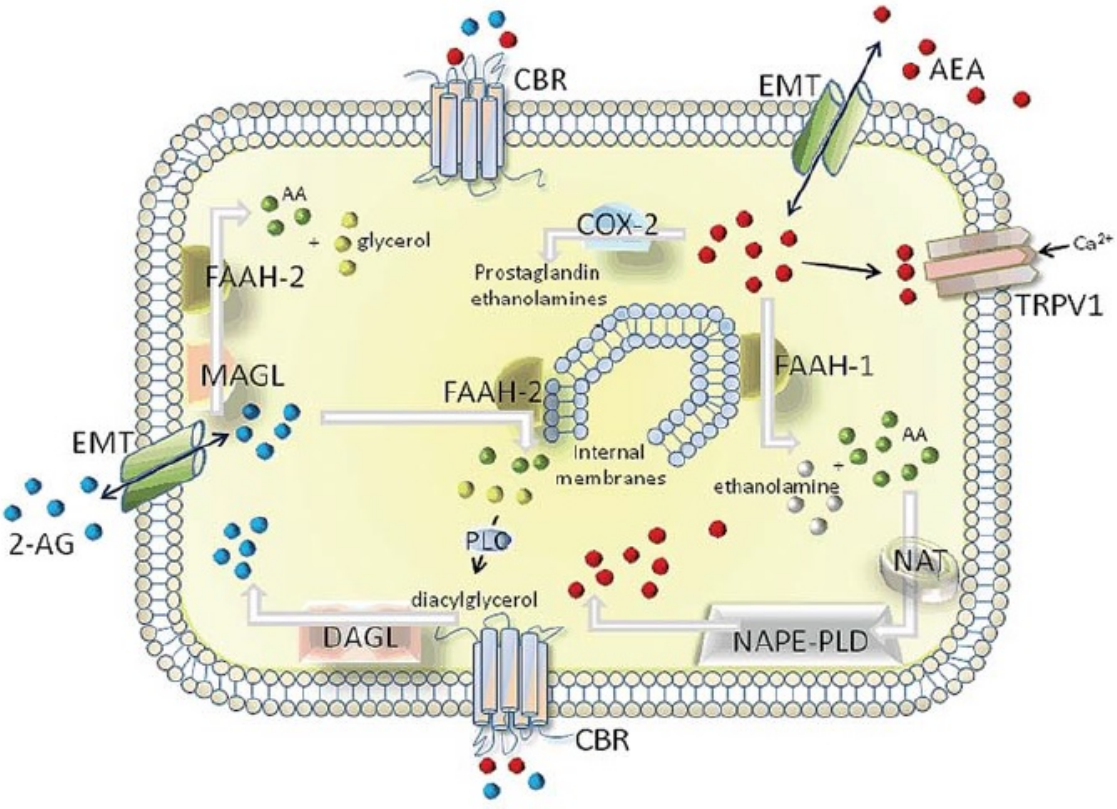


Fig. 1 – The endocannabinoid system – synthesis and degradation of AEA and 2-AG.[8]

AEA presents a high affinity for the CB1 receptor and it is partially agonist for the CB2 receptor. 2-AG presents a low affinity for the CB1 receptor, but it is less potent than the first one, being a full agonist for both cannabinoid receptors.[17,18] It is believed that in vitro 2-AG does not bind to the CB2 receptor, as they are localized in different cellular areas. There should be studied its interaction *in vivo*.[19]

In the body, the CB1 receptor is found both in the central nervous system and in other tissues and organs, such as the ovary, the endometrium, the testicle, the liver, the heart, the small intestine, the urinary bladder, and also in cells like the lymphocytes.[20,21] Activating the CB1 receptor stimulates the mitogen-activated protein-kinase (MAPK)[22] and inhibits adhenylil-cyclase, thus leading to a decrease of the cyclic adenosine-monophosphate level (AMPc),[23,24] to the closure of Ca voltage-dependant channel, to the opening of the K ones and to the activation of nitric acid oxidase. The CB2 receptor is also found in the central nervous system, but also in other cells, tissues and organs, such as the immune cells, the embryonic stem cells, the placenta, the myometrium, the ovary, the gastrointestinal tissues, the liver, the heart.[25] Activating the CB2 receptor stimulates MAPK and cytosolic A2 phospholipase inhibits the nitric oxide synthesis, but it does not influence the ionic currents[26]. Alterations in endocannabinoid signaling were found to be associated with diverse pathological conditions.

In the last years, other ways of synthesis and degradation (with over 50 enzymes involved) were identified within ECS (Table 2, 3), as well as other types of mediators (over 100 fatty-acid-derived mediators) together with their receptors (Table 1), the system being presented as it was recently revised by Di Marzo and Sivestri.[27,28] These findings led to the definition of the "expanded ECS system" or endocannabinoidome[28], which 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.

As to Di Marzo and Sivestri,[27,28] the most studied non-psychotropic phytocannabinoids act their effects in human body through the components of this "expanded endocannabinoid system", as it follows:

►CBD has its potential therapeutic uses in chronic and inflammatory pain, epilepsy, inflammatory bowel diseases (IBD_s), schizophrenia, cancer and neuroinflammatory diseases, based on its actions on:

- CB1 receptors (as negative allosteric modulator),
- TRP channels: TRPV1, TRPV2, TRPV3, TRPA1 (+) and TRPM8 (-)
- PPARs and orphan GPCRs: PPARγ (+) and GPR55, GPR3, GPR6, GPR12 (-)
- enzymes and transporters: FAAH, ENT, eCB transport across the membrane (-)
- neurotransmitter receptors and voltage-dependent ion channels: $5\text{-}HT_{1A,}$ Glycine receptors, R (+) and Ca_v3s, Ca_v1s, $Na_v1.6$, VDAC1 (-);

Table 1

Mediators, receptors (see abbreviations) and specific interactions, in the expended ECS.
Dark/light yellow- more/less stimulation, blue-inhibition. Adapted from Di Marzo and Sivestri[27,28]

		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														

Table 2

Mediators and anabolic enzymes in expended ECS. Dark/light yellow- more/less stimulation. Adapted from Di Marzo and Sivestri[27,28]

		Mediators														
		NAEs					PA	2AcGs			LipoAAs			Ac Neuro		
		AEA	OEA	PEA	LEA	DHEA	OA	2-AG	2-OG	2-LG	taurines	glycines	serines	serotonins	dopamines
Anabolic enzymes	PLC														
	PTN22														
	sPLA2														
	Lyso-PLD														
	ABHD4														
	GDE1														
	NAPEPLD														
	LPA-Phos														
	PLA1A														
	Lyso-PLC														
	PA-phos. hyd.														
	PLCB														
	DAGLA/B														
	AANATL2														
	GLYATL3														
	PAM														

Table 3

Mediators and catabolic enzymes in expended ECS. Dark/light yellow- more/less stimulation., blue- inhibitory interactions; "a" indicates that enzymes only function with arachidonyl homologs. Adapted from Di Marzo and Sivestri[27,28]

		Mediators														
		NAEs					PA	2AcGs			LipoAAs			Ac Neuro		
		AEA	OEA	PEA	LEA	DHEA	OA	2-AG	2-OG	2-LG	taurines	glycines	serines	serotonins	dopamines
Catabolic enzymes	FAAH														
	NAAA														
	MAGL														
	ABHD6														
	ABHD12														
	COX2											a			
	LOX12/15											a			a
	CYP450s													a	
	COMT														
	MAGK														
	PAM														

►CBDV has its potential therapeutic uses in Epilepsy, based on its actions on:
- TRP channels: TRPV1, TRPA1(+) and TRPM8 (-)
- enzymes and transporters: DGLα, eCB transport across the membrane (-);

► CBDA has its potential therapeutic uses in nausea and cancer, based on its actions on:
- PPARs and orphan GPCRs: PPARγ (+)
- enzymes and transporters: DGLα and NAAA (-)
- neurotransmitter receptors and voltage-dependent ion channels: positive allosteric modulator for 5-$HT_{1A;}$

► THCV has its potential therapeutic uses in obesity, metabolic syndrome, insulin resistance, steatosis, schizophrenia, cancer and inflammatory pain, based on its actions on:
- CB1 (-), CB2(+)
- TRP channels: TRPV1,TRPV2,TRPV3, TRPA1(+) and TRPM8 (-)
- neurotransmitter receptors and voltage-dependent ion channels: 5-HT_{1A} (+);

► CBG has its potential therapeutic uses in cancer, neurodegenerative diseases and IBD, based on its actions on:
- weak CB2 agonist
- TRP channels: TRPV1,TRPV2, TRPA1(+) and TRPM8 (-)
- PPARs and orphan GPCRs: PPARγ (+)
- enzymes and transporters: eCB transport across the membrane (-)
- neurotransmitter receptors and voltage-dependent ion channels: ADRA2 (+), 5-HT_{1A} (-);

► CBC has its potential therapeutic uses in pain and gliosis, based on its actions on:
- TRP channels: TRPA1(+)
- enzymes and transporters: ENT and eCB transport across the membrane (-)

► THCA has its potential therapeutic uses in neurodegenerative diseases, based on its actions on:
- PPARs and orphan GPCRs: PPARγ (+)
- enzymes and transporters: DGLα and MAGL (-).

Moreover, the human ECS tonus proved to be under an epigenetic modulation, the studies being performed on subjects with pathologies, such as: Alzheimer's disease, glioblastoma, colorectal cancer.[29]

CB1 gene and FAAH gene expressions are modulated through such epigenetic mechanisms, consisting in chemical modifications of DNA and histones tail that lead to changes in chromatin architecture, modifying the transcription. Several types of noncoding ARNs have also been described accompanying, as biomarkers, gene expression modulations. Hence, methylation of the DNA in the gene promoter region results in inactive transcription.

This methylation is transferred to descendents.[30-33] Histone tails showed acetylation or mono-, di-, tri-methylation at lysine level, with activating or repressive actions, phosphorylation, ubiquitination, being the most well studied epigenetic modifications.[34] Some examples of DNA or histone chemical modifications proven by studies: alcohol and exercise create opposite DNA methylation patterns;[35] binge-eating is associated with downregulation of FAAH gene expression;[36] THC and tobacco smoking was correlated with decreased CB1 expression in peripheral blood cells, by methylation at CB1 gene promoter;[37] extra virgin olive oil diet increased CB1 expression and reduced colon cancer cell proliferation, in rats and humans, by DNA methylation at CB1 gene promoter,[38] while maternal high fat diet over expressed CB1 in rat hypothalamus, resulting in overweight, by histone acetylation rate.[39] In this context, it is all the more obvious the necessity of individualizing the therapy with medicinal cannabis, which should definitely be performed only by doctors specialized in the field.

Brief overview of phytocannabinoids biochemistry in relation to the therapeutic potential of medicinal cannabis

The female plant of cannabis produces phytocannabinoids, compounds that are endowed with many pharmacological properties, due to their ability to hit and modulate (as agonists, antagonists or even positive or negative allosteric modulators) different cellular targets.[41-44] The complexity of these properties, as well as the endocannabinoid system, changed the perspective on the medicines based on cannabis plant. For example, in the CNS, the pain is diminished by activating the CB1 receptors by the AEA endocannabinoid. Hence, the interest of research within applied chemistry in medicine, for an analgesic medication, for manipulating ECS.

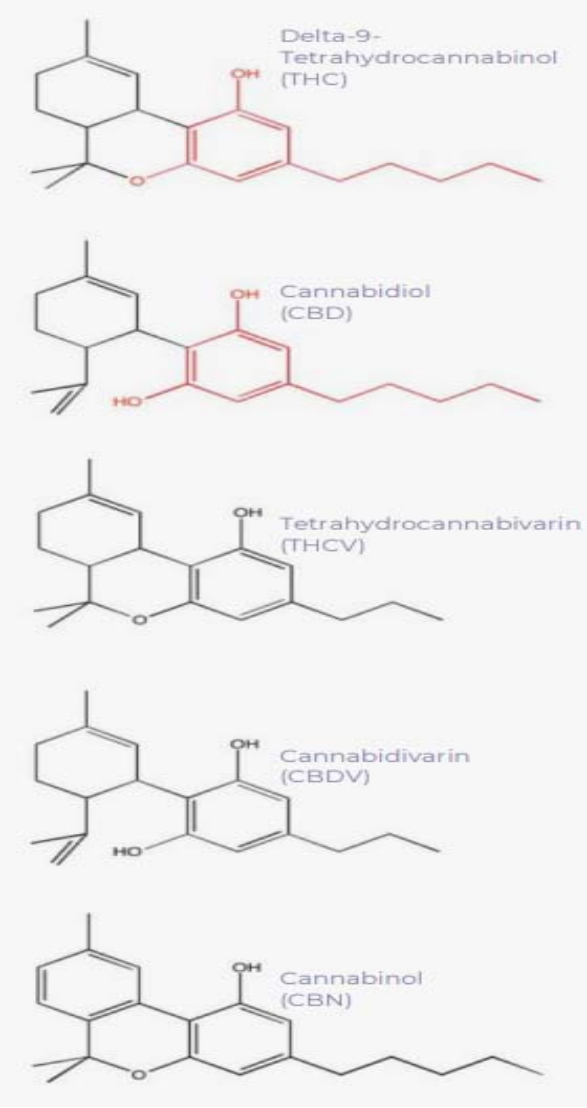


Fig. 2 – Five common phytocannabinoids[54].

The solution for using the agonists of CB1 proved to have the major inconvenience of generating multiple adverse reactions, due to a large spread of this type of receptors in the body. Thus, the agonist CB1 drugs may affect the cognitive functions[45] or the antagonist or reverse agonist CB1 ones may lead to depression and anxiety.[46] An encouraging solution was the reduction of AEA degradation, by inhibiting the FAAH hydrolase, thus increasing the persistence of the endocannabinoid in the synaptic space and, thus, the pain inhibiting action through an action upon the CB1 receptor. In the FAAH inhibitors, there were also proven anti-inflammatory and neuroprotective effects, via the reduction of the arachidonic acid production. The synthesis of potent and more selective inhibitors of FAAH, with an action on the enzyme from certain target tissues, required, without all targets completely attained, the knowledge of the enzyme composition and stericity and, of course, of the catalysis mechanism of the anandamide hydrolysis (AEA).

The amidic chain (R-NH-C=O) of the anandamide (AEA) is cleaved, thus releasing the amine and remaking the carboxylic (arahidonic) acid, by the interaction of the carbonyl group of AEA, with the hydroxyl group (OH) of serine Ser 241 from the FAAH structure, previously activated by serine Ser 217 and lysine Lys 142 from the same enzyme structure.[47,48]

Up to now, there were discovered blockers of the catalytic sites of FAAH, initially of the "single target inhibitors" type, the research going towards the most recent ones, the "dual target inhibitors". The principle of the action of the latter ones is the inhibitory action exerted by a single compound upon 2 enzymes, FAAH and another enzyme, the effect being, of course, superior to inhibiting only the FAAH.[49] The classes of FAAH inhibitors, single/dual target, discovered until now, belong to the classes of chemical compounds presented in Table 4 (their potency is quantified through IC50=half maximal inhibitory concentration).

From these compounds come expectations to generate medicines with CNS selectivity to treat: neuropathic pain, neuroinflammation, neuro-degenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, spinal cord injury, levodopa-induced dyskinesia, dystonia, Gilles de la Tourette syndrome, epilepsy, amyotrophic lateral sclerosis, schizophrenia, depression, anxiety, neurotoxicity, neurotrauma, stroke, etc). FAAH modulation in other peripheral tissues is the fundament of other alternative therapies in: appetite regulation, AIDS wasting syndrome, anorexia, cachexia, obesity, nausea, emesis, drug additions, alcohol disorders, atherosclerosis, hypertension, myocardial reperfusion injury, retinopathy, glaucoma, osteoporosis, asthma, peripheral pain and inflammation, etc.

Cannabis sativa L. is known to have numerous active compounds representing different chemical classes. Generally, the metabolic profile of this plant is extremely rich, more than 480 compounds being discovered, of which 180 belong to the cannabinoids family.[50] Five of the most known phytocannabinoids have the chemical formula presented in Figure 2. The therapeutical potential of medicinal cannabis cannot be objectified unless we can understand the ways of metabolizing

phytocannabinoids in the human body. There are described two phases of its metabolization. The first includes reactions of oxidation, reduction, hydrolysis, which increase the molecular hydrophilicity. The second phase involves conjugation reactions with endogenous hydrophilic molecules (glucuronidation, sulfation, amino acid conjugation, acetylation, methylation, glutathione conjugation), which lead either to the increase of water solubility, or they inhibit the pharmacological activity.[51-53] A very important class of metabolizing enzymes is that of cytochrome P450 (CYP). CYP is expressed especially in the liver, the lungs and the intestinal tract. Inhibiting a CYP enzyme by phytocannabinoids may lead to an increase of the blood concentration of another drug, and the other way round. The ”pentylresorcinol” or ”olivitol” moiety, red marked in Figure 2, contribute to the inhibition of most CYPs.

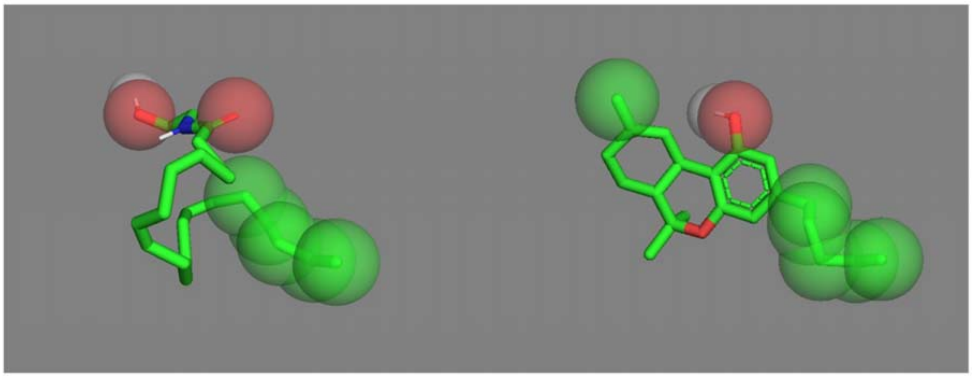
The scientific community could not have wondered about how compounds with such a different chemical structure, like Δ9 -THC (a terpeno-phenol) and AEA (an N-arachidonoylethanolamine) can share common cellular targets. Van der Stelt and colleagues[15] discovered that these molecules happened to share 3D structures that present spatial arrangements of atoms that are essential to interact with specific receptor target, at the same position. Figure 3 presents these tridimensional structures.

Table 4

FAAH inhibitors, discovered 2015–2019, adapted from Rati Kailash Prasad Tripathi[40]

FAAH inhibitors, by chemical structure	**Chemical substrate of the inhibitory action**	**Number of representatives**	**Potency, IC50* range**
1. Carbamates	Covalent	1–127	nM
2. Urea derivates	irreversible binding	128–165	nM
3. Propan-2- derivates	Covalent reversible binding	167–262	μM
4. 3Carboxamido-5-arylisoxazoles	noncovalent binding	263–273	nM
5. Oleoylethanolamide derivatives		274	
6. Aryloxyacetamides		275–294	μM
7. Amide derivates		295–298	μM
8. Steroids**			
9. Pyrimidine derivates		299–300	nM
10. 1,3, 4 Oxadiazol-2(3H)- ones		301–307	In vivo, 10–30 mg/kg, p.o.
11. Isatin based analogs		308	μM
12. Pyridine heterocycles		309–d	nM

* = half maximal inhibitory concentration; ** = they are regulators of FAAH affinity for membranes



AEA **Δ^9 -THC**

Fig. 3 – 3D structures of Δ9 -THC and AEA - Stereo view of anandamide (AEA, PubChem 5281969, on the left) and Δ9 -tetrahydrocannabinol (Δ9 -THC, PubChem 16078, on the right), obtained with the Pymol program (Schrodinger, www.pymol.org) to depict van der Waals surfaces of the pharmacophores and highlight corresponding positions. Carbon atoms are shown in green, oxygen atoms in red, nitrogen atoms in blue and polar hydrogen in white[54].

Also, research highlighted that the endocannabinoid system, which is not present only in humans, appeared in nature long before the phytocannabinoids and it took several million years for the plants to be able to mime the structure and activity of the endocannabinoids. Recent research revealed the entourage effects regarding the cannabis plant, namely a superior medicinal activity of the crude extract versus a single compound.[55,56] There are millions of possible biochemical interactions in the cannabis plant. In scientific literature, it is reminded the intra-entourage and inter-entourage effect.[57] Intra-entourage effect refers to the potentiation of biological activity by synergistic interactions between different phytocannabinoids[58,59] or between different terpenes,[60] compounds that may act independently from phytocannabinoids. The inter-entourage effect is defined as the increase of the therapeutical action by the interaction between the phytocannabinoids and terpenes or other type of molecules from the cannabis plant.[61] Moreover, there was observed that the interaction is stronger between the compounds that are found in a chain, namely in a specific chemovar.[42] It is suggested that the mixture of compounds that are found in cannabis chemovars today derive from selective cultivation during ancient times, favoring specific beneficial activity.[62,63] The therapeutic consequences of this ecophenotypic plasticity, led to the idea of redefining the current cannabis chemotaxonomy according to chemical content and medicinal activity and not according to the concentration in THC and CBD, as performed by Small and Becksteed in 1973.[57, 64]

CONCLUSIONS

The present level of knowledge up to now on the complexity of the endocannabinoid system and on the biological action of phytomolecules from cannabis on the human body, do not suggest anything else than the huge therapeutical potential of this plant. It is of top actuality that the medical chemistry is challenged as to the participation to the development of cannabis medicines. Within the present international context, and under the circumstances in which the cannabidiol oil is already present on the Romanian market, the specialists in public healthcare should also be involved more in educating the population for a clear differentiation between the therapeutical and recreational administration, and the acknowledgement of the fact that the treatment should be performed only by medical personnel specialized in the field.

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
TRPA1, transient receptor potential cation channel subfamily A member 1
TRPM8, transient receptor potential cation channel subfamily M member 8
5-HT_{1A}, 5-hydroxytryptamine receptor 1A
ADRA2, -adrenergic receptor
Ca+ls, L-type Ca^{2+} channels
R, receptor
Na+1.6, voltage-gated sodium channel type 1.6 (also known as SCN8A)
VDAC1, voltage-dependent anion-selective channel protein 1

Anabolic enzymes

AANATL2 arylalkylamine N-acyltransferase-like 2, isoform A
ABHD4 alpha/beta-hydrolase domain containing 4
DAGLA/B diacylglycerol lipase alpha/beta
GDE1 glycerophosphodiester phosphodiesterase 1
GLYATL3 glycine N-acyltransferase-like protein 3
LPA-Phos lysophosphatidic acid phosphatase
Lyso-PLC lysophospholipase C Lyso-PLC, lysophospholipase D
NAT (N-aciltransacilaza),
NAPEPLD N-acyl phosphatidylethanolamine-hydrolyzing phospholipase D
PA-phos. hyd. phosphatidic acid phosphohydrolase
PLA1A phospholipase A1 member A
PLC phospholipase C
PLCB phospholipase C beta
PTPN22 tyrosine protein phosphatase non-receptor type 22
sPLA2 soluble phospholipase A2.

Catabolic enzymes

ABHD12 alpha/beta-hydrolase domain containing 12
ABHD6 alpha/beta hydrolase domain containing 6
COMT catechol-O-methyltransferase
COX2 cyclooxygenase 2
CYP450 cytochrome P450
FAAH fatty acid amide hydrolase
LOX12/15 arachidonate lipoxygenase 12/15
MAGK monoacylglycerol kinase
MGLL monoacylglycerol lipase
NAAA N-acylethanolamine-hydrolyzing acid amidase
PAM peptidyl-glycine α-amidating monooxygenase

Others

CBC, cannabichromene
CBD, cannabidiol
CBDA, cannabidiolic acid
CBDV, cannabidivarin
CBG, cannabigerol
THCA, -tetrahydrocannabinolic acid
THCV, -tetrahydrocannabivarin
eCB, endocannabinoid
IBDs, inflammatory bowel disorders
EMT, endocannabinoid membrane transporter

REFERENCES

1. F. Grotenhermen, *Chem. and Biodiversity*, **2007**, *4*, 1744–1769.
2. A. Hazekamp and F. Grotenhermen, *Cannabinoids*, **2010**, *5*, 1–21.
3. P. Sharma, P. Murthy and M. M. S. Bharath, *Iran. J. Psychiatry*, **2012**, *7*, 149–156.
4. R. Mechoulam, L. Hanus, R. G. Pertwee and A. Howlett, *Nature Reviews Neurosci.*, **2014**, *15*, 757–764.
5. V. Di Marzo, *Biochim. Biophys. Acta,* **1998**, *1392*, 153-175.
6. W. Devane, L. Hanus, A. Breuer, R. Pertwee, L. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger and R. Mechoulam, *Science*, **1992**, *258*, 1946-1949.
7. R. Mechoulam, S. Ben-Shabat, L. Hanus, M. Ligumsky, N. E. Kaminski, A. R. Schatz, A. Gopher A, S. Almog, B. R. Martin and D. R. Compton, *Biochem. Pharmacol.*, **1995,** *50*, 83-90; doi: 10.1016/0006-2952(95)00109-d. PMID: 7605349.
8. T. Sugiura, S. Kondo, A. Sukagawa, S. Nakane, A. Shinoda, K. Itoh, A. Yamashita and K. Waku, *Biochem. Biophys. Res. Commun.*, **1995**, *215*, 89-97.
9. Y. Okamoto, J. T. K. Morishita, T. Tonai and N. Ueda, *J. Biol.* Chem., **2004**, *279*, 5298–5305.
10. T. Sugiura, Y. Kobayashi, S. Oka and K. Waku, *Prostaglandins Leukot Essent Fatty Acids,* **2002**, *66*, 173-192.
11. M. McKinney and B. Cravatt, *Annu. Rev. Biochem.,* **2005**, *74*, 411-432.
12. K. Tsuboi, Y. Sun, Y. Okamoto, N. Araki, T. Tonai and N. Ueda, *J. Biol. Chem.*, **2005**, *280*, 11082-11092.
13. C. Rouzer and L. Marnett, *J. Biol. Chem.,* **2008**, *283*, 8065-8069.
14. R. Kevin, R. Kozak, B. C. Crews, J. D. Morrow, L.-H. Wang, Y. H. Ma, R. Weinander, P.-J. Jakobsson and L. J. Marnett, *J. Biol. Chem.*, **2002**, *277*, 44877-44885, https://doi.org/10.1074/jbc.M206788200M.
15. M. van der Stelt, J. A. van Kuik, M. Bari, G. van Zadelhoff, B. R. Leeflang, G. A. Veldink, A. Finazzi-Agrò, J. F. G. Vliegenthart, and M. Maccarrone, *J. Med. Chem.,* **2002**, *45*, 3709-3720.
16. L. De Petrocellis, M. Cascio and V. Di Marzo, *Br. J. Pharmacol.,* **2004**, *141*, 765-774.
17. T. Sugiura, T. Kodaka, S. Nakane, T. Miyashita, S. Kondo, Y. Suhara, H. Takayama, K. Waku, C. Seki, N. Baba and Y. Ishima, *J. Biol. Chem.,* **1999**, *274*, 2794-2801.
18. A. C. Howlett, C. S. Breivogel, S. R. Childers, S. A. Deadwyler, R. E. Hampson and L. J. Porrino, *Neuropharmacology*, **2004**, *47*, 345-58; doi: 10.1016/j.neuropharm.2004.07.030. PMID: 15464149.
19. T. Karasu, T. Marczylo, M. Maccarrone and J. Konje, *Human Reproduction Update,* **2011**, *17*, 347-361.
20. R. Pertwee, *Pharmacol Ther,* **1997**, *74*, 129-180.
21. R. Pertwee and R. Ross, *Prostaglandins Leukot Essent Fatty Acids,* **2002**, *66*, 101-121.
22. A. Riahi, M. Kharrat, M. E. Ghourabi, F. Khomsi, A. Gamoudi, I. Lariani A. E. May, K. Rahal and H. Chaabouni-Bouhamed, *Clin Genet*., **2015,** *87*, 155-60; doi: 10.1111/cge.12337. Epub 2014 Feb 23. PMID: 24372583.
23. B. Paria, S. Das and S. Dey, *Proc. Natl. Acad. Sci. USA,* **1995**, *92*, 9460-9464.
24. J. A. Rachel, A. Helliwell, L. W. Chamley, K. Blake-Palmer, M. D. Mitchell, J. Wu, C. S. Kearn and M. Glass, *J. Clinical Endocrinology & Metabolism*, **2004**, *89*, **2004**, 5168–5174; https://doi.org/10.1210/jc.2004-0388.
25. M. T. Viscomi, S. Oddi, L. Latini, N. Pasquariello, F. Florenzano, G. Bernardi, M. Molinari and M. Maccarrone, *J. Neurosci*., **2009,** *29*, 4564-70; doi:

10.1523/JNEUROSCI.0786-09.2009. PMID: 19357281; PMCID: PMC6665736.
26. D. Demuth and A. Molleman, *Life Sci,* **2006**, *78*, 549-563.
27. V. Di Marzo, *Nat. Rev Drug Discov.,* **2018**, *17*, 623–639.
28. V. Di Marzo and C. Silvestri, *Nutrients*, **2019**, *11*, 1956.
29. R. Meccariello, A. Santoro, S. D'Angelo, R. Morrone, S. Fasano, A. Viggiano and R. Pierantoni, *Int. J. Mol. Sci*., **2020,** *21*, 1113-1118; doi: 10.3390/ijms21031113. PMID: 32046164; PMCID: PMC7037698.
30. J. K. Kim, M. Samaranayake and S. Pradhan, *Cell. Mol. Life Sci.,* **2009**, *66*, 596-612.
31. L. D. Moore, T. Le and G. Fan, *Neuropsychopharmacology,* **2013**, *38*, 23-38.
32. A. C. Ferguson-Smith, *Nat. Rev. Genet.,* **2011**, *12*, 565-575.
33. B. Jin, Y. Li and K. D. Robertson, *Genes Cancer,* **2011**, *2*, 607-617.
34. N. Javaid and S. Choi, *Genes,* **2017**, *8*, 196.
35. J. Chen, K. E. Hutchison, A. D. Bryan, F. M. Filbey, V. D. Calhoun, E. D. Claus, D. Lin, J. Sui, Y. Du and J. Liu, *Front. Psychiatry,* **2018**, *9*, 594.
36. M. Pucci, M. V. Micioni Di Bonaventura, E. Zaplatic, F. Belli, M. Maccarrone, C. Cifani and C. D'Addario, *Int. J. Eat Disord.,* **2019**, *52*, 51-60.
37. A. Rotter, K. Bayerlein, M. Hansbauer, J. Weiland, W. Sperling, J. Kornhuber and T. Biermann, *Eur. Addict. Res.,* **2013**, *19*, 13-20.
38. A. Di Francesco, A. Falconi, C. Di Germanio, M.V. Micioni Di Bonaventura, A. Costa, S. Caramuta, M. Del Carlo, D. Compagnone, E. Dainese, C. Cifani, M. Maccarrone and C. D'Addario, *J. Nutr. Biochem.,* **2015**, *26*, 250-258.
39. M. M. Almeidaa, C. P. Dias-Rochaa, C. F. Reis-Gomesa, H. Wangb, G. C. Atellac, A. Cordeiroa, C. C. Pazos-Mouraa, L. Joss-Mooreb and I. H. Trevenzolia, *Psychoneuroendocrinology,* **2019**, *103*, 306-315.
40. R. K. P.Tripathi, *Eur. J. Med. Chem.*, **2020**, *188*, 11953.
41. P. Morales, D. P. Hurst and P. H. Reggio, *Prog. Chem. Org. Nat. Prod.*, **2017**, *103*, 103-131.
42. S. E. Turner, C. M. Williams, L. Iversen and B. J. Whalley, *Prog. Chem. Org. Nat. Prod.*, **2017**, *103*, 61-101.
43. L. Cristino, T. Bisogno and V. Di Marzo, *Nat. Rev. Neurol.*, **2020**, *16*, 9–29.
44. L. O. Hanuš, S. M. Meyer, E. Muñoz, O. Taglialatela-Scafati, G. Appendino, *Nat. Prod. Rep.*, **2016**, *33*, 1357–1392.
45. E. Puighermanal, A. Busquets-Garcia, R. Maldonado and A. Ozaita, *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **2012**, *367*, 3254–3263.
46. M. K. Sharma, P. R. Murumkar, A. M. Kanhed, R. Giridhar and M. R. Yadav, *Eur. J. Med. Chem.*, **2014**, *79*, 298–339.
47. E. I. Chudyk, E. Dyguda-Kazimierowicz, K. M. Langner, W. A. Sokalski, A. Lodola, M. Mor, J. Sirirak, and A. J. Mulholland, *J. Phys. Chem. B,* **2013**, *117*, 6656-6666.
48. A. Lodola, L. Capoferri, S. Rivara, G. Tarzia, D. Piomelli, A. Mulholland, M. Mor, *J. Med. Chem.,* **2013**, *56*, 2500-2512.
49. D. Fazio, E. Criscuolo, A. Piccoli, B. Barboni, F. Fezza and M. Maccarone, *Expert Opinion on Drug Discovery,* **2020**, *15*, 765-778.
50. J.T. Fischedick , A. Hazekamp, T. Erkelens, Y. H. Choi, R. Verpoorte, *Phytochemistry*, **2010**, *71*, 2058–2073.
51. J. Kirchmair, A. H. Göller, D. Lang, J. Kunze, B. Testa, I. D. Wilson and G. Schneider, *Nature Reviews Drug Discovery*, **2015**, *14*, 387–404.
52. J. Kirchmair, A. Howlett, J. Peironcely, D. Murrell, M. Williamson, S. Adams and R. Glen, *J. Chem. Inf. Model.*, **2013**, *53*, 354–367.
53. J. Tyzack and J. Kirchmair, *Chem. Biol. Drug Des.*, **2019**, *93*, 377–386.
54. M. Maccarone, *Rendiconti Lincei. Scienze Fisiche e Naturali*, **2020**, *31*, 931-938.
55. E. Russo, *Br. J. Pharmacol.*, **2011**, *163*, 1344-1364.
56. S Ben-Shabat, E Fride, T Sheskin, T Tamiri, M H Rhee, Z Vogel, T Bisogno, L De Petrocellis, V Di Marzo, R Mechoulam, *Eur. J. Pharmacol.*, **1998**, *353*, 23–31.
57. H. Koltai and D. Namdar, *Trends in Plant Science*, **2020**, *25*, 976-984.
58. P. Berman, K. Futoran, G.M. Lewitus, D. Mukha, M. Benami, T. Shlomi and D. Meiri, *Sci. Rep.*, **2018**, *8*, 14280.
59. D. Namdar, H. Voet, V. Ajjampura, S. Nadarajan, E. Mayzlish-Gati, M. Mazuz, N. Shalev, and H. Koltai, *Cannabis Cannabinoid Res.*, **2018**, *3*, 120–135.
60. E. Russo, *Front. Plant Sci.*, **2019**, *9*, 1969.
61. D. Namdar, H. Voet, V. Ajjampura, S. Nadarajan, E. Mayzlish-Gati, M. Mazuz, N. Shalev and H. Koltai, *Molecules*, **2019**, *24*, 3031.
62. O. Aizpurua-Olaizola, U. Soydaner, E. Öztürk, D. Schibano, Y. Simsir, P. Navarro, N. Etxebarria and A. Usobiaga, *J. Nat. Prod.*, **2016**, *79*, 324–331.
63. S. Pisanti and M. Bifulco, *J. Cell. Physiol.*, **2019**, *234*, 8342–8351.
64. E. Small and H. Beckstead, *Nature*, **1973**, *245*, 147–148.