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Review

CONSIDERATIONS ON RESEARCH IN THE FIELD OF MEDICINAL CANNABIS

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As more and more countries legalize medicinal cannabis, and more and more people start using this therapy, it is absolutely necessary that there should be identified some research priorities regarding therapeutic cannabis, using the pioneering research results from various countries from all over the world. It is also required an accurate preventive or curative professional information for the medical staff of any specialty. The present paper brings an overall image on the research in this field, which, despite of its novelty, already proves to have a great potential in medical research and practice.

INTRODUCTION

Nowadays, medicinal cannabis is legalized in 42 countries world widely and also in US 35 states. In Europe, up to now, 22 countries legalized the use of medicinal cannabis, others still having this problem present on their agenda. This is also the case of Roumania. In this context, there is an international consensus regarding 2 types of strategic directions in this field: 1. identifying the research priorities on medicinal cannabis, using the results from other pioneering research studies in other countries; 2. providing professional information and formation, curative or preventive, about medicinal cannabis to the medical staff in any specialty. As a result, the present paper proposes to emphasize the results and challenging of this new research field, through its unquestionable complexity and potential.

Evidence-based research results

The most important contribution in reviewing the literature on the use of medicinal cannabis was brought in by the National Academies of Sciences, Engineering and Medicine from the USA. An *ad-hoc* board of experts from three academies published the report entitled *The Health Effects of*

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Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, a comprehensive research of existing evidence regarding the health effects of using cannabis in medicine.[1] This report of 487 pages, published in 2017, represents a synthesis of the review on all the reference studies in the field, published between January 1st 1999 – August 1st 2016 (over 24 000 papers), the work methodology complying with all the quality and accuracy criteria (*e.g.*, Cochrane Quality Assessment, Newcastle-Ontario scale). The committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO.

The above-mentioned report had four parts, with 16 chapters: part I *Introduction and Background*, part II *Therapeutic Effects* (Therapeutic Effects of Cannabis and Cannabinoids), part III *Other Health Effects*, and part IV *Research Barriers and Recommendations*. In part II, the report highlighted the therapeutic effect of medicinal cannabis in the following areas: chronic pain, cancer, nausea/ vomiting induced by chemotherapy, anorexia and weight loss, irritable bowel syndrome, epilepsy, multiple sclerosis spasms, Huntington disease, Parkinson disease, dystonia, dementia, glaucoma, brain injury/ hemorrhage, addiction, anxiety, depression, sleep disorders; cancer (lung cancer, head and neck cancer, testicular cancer, esophageal cancer, other cancers); cardiometabolic risk (acute myocardial infarction, stroke, metabolic disorder, dysmetabolic syndrome, prediabetes, diabetes mellitus); respiratory diseases (chronic obstructive pulmonary disease, respiratory symptoms -including chronic bronchitis, asthma); immune system: immune function, infectious diseases; accidents (all causes of mortal accidents; work accidents, traffic accidents, accidents caused by overdose); prenatal, perinatal and postnatal exposure to cannabis (complications during pregnancy for the mother; impact on the fetal growth and development, neonatal conditions, various fetal complications); psychosocial (cognition-learning, memorizing, attention, intelligence; educational/ academic accomplishments; job and income; socializing and other social roles; mental health (schizophrenia and other psychotic disorders; bipolar disorder, depression; suicidal tendency; post-traumatic stress disorder PTSD; problems caused by recreational cannabis intake.

Quite an important fact was that, for every medical problem, the results of research were grouped into 4 levels of evidence (clear, substantial, moderate, limited), according to the number and quality of the existing studies (including limitations of the statistic methodology, like the analysis of the considered confusion factors or biases). Next, we present the criteria used for every of the four evidence levels:

Clear evidence, both for the *therapeutic effects* and for *other effects on health* means there should exist strong evidence from randomized control studies to support or reject the statistic association, without any opposing conclusions to be taken into consideration;

Substantial evidence, both for *therapeutic effects* and for *other effects on health* ***means*** there should exist strong evidence coming from high quality research studies, with very few or no result to support the opposite of the statistical hypothesis.

M**oderate evidence**, both for *therapeutic effects* and for *other effects on health* means there should exist strong evidence coming from high quality or reliable research studies, with very few or no result supporting the opposite of the statistical hypothesis, so that there could be stated a general conclusion, although the bias errors, chance or confusion factors cannot be excluded based on a high degree of trust.

Limited evidence, both for *therapeutic effects* and for *other effects on health* means there should be a low evidence to support the statistical association taken into consideration, from high quality research studies, or with mixed results from various studies, still in favor of the analyzed conclusion. In this case, there is a high uncertainty level due to chance, bias, confusion factors.

As to the level **"No evidence"** or **"insufficient evidence",** in order to support a conclusion of efficiency or inefficiency of medicinal cannabis with a certain therapeutic effect, there are mixed results, either a single study with no high quality, or the subject was not approached at all. There cannot be drawn any conclusions due to the high level of uncertainty caused by chance, bias or confusion factors.

We present a synthesized list of the most well-documented therapeutic effects of medicinal cannabis according to the previously mentioned report:

There is **clear or substantial evidence** for the medicinal cannabis efficiency in: treatment of chronic pain in adults; nausea/ vomiting caused by chemotherapy; improving multiple sclerosis spasms.

There is **moderate evidence** for the efficiency of medicinal cannabis in: short-term improvement of sleep in individuals with sleep disorders

associated with obstructive apnea, in fibromyalgia and multiple sclerosis.

There is **limited evidence** for the efficiency of medicinal cannabis in: increase of appetite and decrease of weight loss associated with HIV/AIDS; improvement of symptoms in Tourette syndrome; improvement of anxiety symptoms, caused by performing a public speech in individuals with social anxiety disorder; improvement of symptoms in PTSD.

There is **limited evidence** for a statistical association between medicinal cannabis and: low mortality or disability rate after a traumatic brain injury or brain hemorrhage.

There is **limited evidence** for the efficiency of medicinal cannabis in: improvement of symptoms associated with dementia; improvement of intraocular pressure associated with glaucoma; decrease of depressive symptoms in individuals with chronic pain or multiple sclerosis.

Due to the fact that research constantly brings new data in this field, some information from the report published in 2017 needs to be updated so far. An example is the certainty of medicinal cannabis for two childhood-onset refractory epilepsies as Dravet syndrome and Lennox-Gastaut syndrome.[2–4] In June 2018, the US Food and Drug Administration (FDA) approved a pharmaceutical preparation of highly purified, plant-derived cannabidiol (CBD) (Epidiolex®, GW Pharmaceuticals, Cambridge, UK) for the treatment of Dravet syndrome and Lennox-Gastaut syndrome.[5] In September 2019 the European Medicine Agency (EMA) also granted the approval of CBD (under the trade name of Epidyolex) as adjunctive treatment for Dravet syndrome and Lennox-Gastaut syndrome, in combination with clobazam.[6]

By exemplifying the intense rhythm of the discoveries, we remind the reader that, at present, it is well-known that in the human body there is not only an endocannabinoid system (ECS), but an "expanded ECS" with tens of receptors, ligands and regulatory enzymes; also, there continue to be discovered new phytocannabinoids and new interactions with the human body, through this expanded ECS. This kind of discoveries continuously (re)direct research on cannabis-based drugs.[7]

Returning to the report of the *National Academy of Sciences, Engineering and Medicine*, its last chapter provides several **observations and recommendations for the improvement and support of research in the field of medicinal Cannabis,** such as: solving the barriers of legal regulations still present that impede the advancement of research on cannabis and cannabinoids; solving the problems related to the access of researchers to the quantity, quality and type of cannabis products, necessary for their research on the effects of medicinal cannabis on health; starting some efforts for creating a network of financing entities to support research on the beneficial or adverse effects of the use of medicinal cannabis; standardizing to a high quality level of the research methodology, in order to reach conclusive evidence regarding the use of medicinal cannabis and its short and long term effects on health.

As the need for evidence-based research for the therapeutic use of cannabis was more and more acutely brought to discussion, there started to appear articles to provide an overview on the current research gaps and points out the future directions of research in the field. Next, we present a short review of these.

Standardizing and assessing the quality of cannabis therapeutic products

Since the description in the 60 s, of the chemical structure of the 2 major phytocannabinoids, THC and CBD, until now, the analitic laboratory brought a huge and progressive contribution to the knowledge of medical effects of this plant, through its most bioactive groups of compounds: the phytocannabinoids, the terpenes and the phenols.

Up to now, there were identified hundreds of compounds in this plant, among which 125 phytocannabinoids,[8,9,10] 262 terpenes, 49 flavonoid glycosides, 62 ferments, 58 steroids, 58 polyphenols, 26 metals and elements, 27 amino acids and peptides, 17 vitamins, 14 spirans.[7,8,11–15]

Beneficial effects on health or on some pathologies have been studied and published for some of these compounds.[16–30]

Recent research revealed an entourage effects regarding this plant, namely a superior medical activity of the crude extract, versus a single compound.[31,32] In full or broad spectrum plant extracts both an intra-entourage and an inter-entourage effect have been revealed.[33–40] Intra-entourage effect refers to the potentiation of biological activity among different phytocannabinoids[41,42] or among different terpenes.[43] The inter-entourage effect is defined as the increase of the therapeutical action, through the potentiation of phytocannabinoids by terpenes or other type of molecules from the cannabis plant.[44] The interactions are stronger among the compounds belonging to the same chemovar.[45]

Besides the need for a sustained research upon this "universe of the cannabis plant", there have been required highly equipped laboratories, in order to analyze the composition and quality of cannabis-derived products presently found on the market, through standardized methods.

Hence, the challenge for the analytical laboratory in the field of medicinal cannabis to develop wet chemistry methods, to:

1. extract as faithfully as possible the bioactive compounds from anatomical parts of the plant;
2. separate and identify cannabinoids and terpenes from extracts, successively, or simultaneous;
3. measure the concentration of each component separately, with accuracy, reproducibility, low detection limit.

Moreover, we reviewed that encouraging results were obtained when wet chemistry was put to work together with optic chemistry, within the cannabis research ongoing process.

With such gains, the laboratory can ensure a correct dosage of the active compounds in phytotherapeutics and a correct labeling of medicinal Cannabis products.

As to the step of extraction of the bioactive compounds from the plant, a lot of extraction methodes have been published, arguing its own effectiveness. They have been reffered as "conventional"[46–51] extraction methodes, or "advanced" extraction methodes[52–59] (Fig. 1*)*. What is needed in the near future is to compare the effectiveness of such methodes. Moreover, recent works suggested the utilisation of mathematical prediction models, instead of laboratory tests, to achive such comparisons.[60]

Laboratory research was the one that highlighted a lot of factors that influence the final composition in bioactive compounds of such "full or broadspectrum extracts", generated from Cannabis chemovars: analytical conditions (time, solvents, pH, temperature, pressure, and material-to-solvent ratio) as well as plant conditions[61–64](Fig.1).

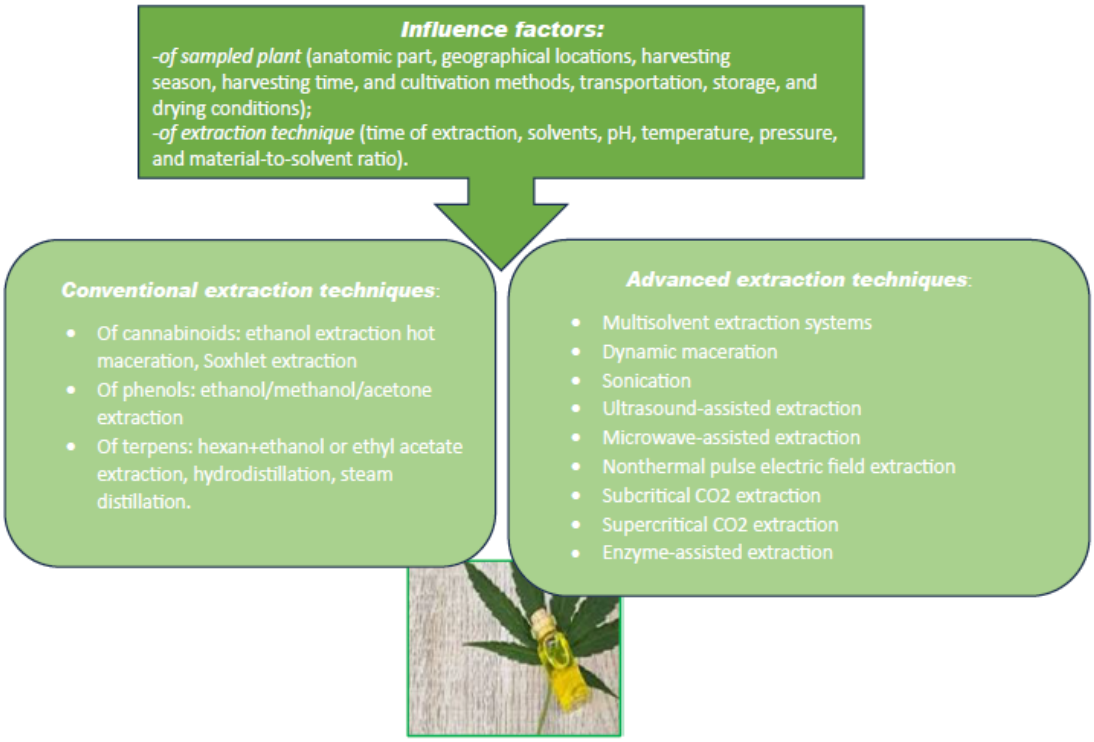

Fig. 1 – Extraction of bioactive compounds from medicinal Cannabis: extraction techniques and influence factors.

As to the quantification of bioactive compounds in Table 1 we present a summary of physical and chemical methodes published until present, that quantify bioactive cannabis compounds.[65–67]

Tabel 1

Methodes of detection and quantification of bioactive medicinal cannabis compounds	Notices
Gas chromatography coupled with mass spectrometry, GC-MS	large number of compounds in the extract, neutral forms of cannabinoids or terpens
Gas chromatography coupled with flame ionization detection, GC-FID	more accurate cannabinoid quantification then GC-MS
Gas chromatography with vacuum ultraviolet spectroscopy, GC-VUV	rapid cannabinoid detection, but high limit of detection
Bidimensional gas chromatography, GC X GC	cannabinoids and terpens at the same time, in 2 sets of retention data
High Performance Liquid Chromatography, coupled with mass spectrometry or ultraviolet detection or diode array detection, HPLC-MS/UV/DAD	both acid and neutral forms of major and minor annabinoids, even flavones, but not terpenes; DAD improves specificity for acid and neutral cannabinoids
High-performance liquid chromatography with electrospray ionization-quadrupole time of flight, HPLC-ESI-qTOF	large spectrum of cannabinoids, can identify the main component of the sample in addition to enhancing the signal to noise ratio in the peaks
High-performance liquid chromatography - tandem mass spectrometry, HPLC-MS/MS	in analyze of co-eluting cannabinoids
liquid chromatography-tandem mass spectrometry and atmospheric pressure chemical ionization, LC-MS/MS and APCI	simultaneously detect five cannabinoids in human plasma and urine; APCI in comparison with ESI methodes produced fewer matrix effects
ultra performance liquid chromatography coupled with a hybrid quadrupole orthogonal time-of-flight mass spectrometer, UPLC-QTOF-MS	better separation with higher speed than conventional HPLC; identification of unknown minor cannabinoids; acid forms (ex. THCA) and their metabolites in urine
Matrix-Assisted Laser Desorption Ionization Mass Spectrometry, MALDI-MS	sample preparation is simpler, a narrower time frame of drug can be detected, and the sample amount is reduced.
Thin-Layer Chromatography, TLC	rapid screening of many samples for the existence of cannabinoids, but lower performance and the reproducibility depends relative humidity
Fourier transform infrared spectroscopy, FTIR	identifies and measures ppb concentration of cannabinoids from unprocessed samples, shorter analysis time and with much lower costs than GC or LC techniques; it does not require a highly qualified operator. It allows the result in the field.
Nuclear magnetic resonance spectrometry, NMR	is not sensitive to impurities in the sample, unlike GC and HPLC; does not require chromatographic purification; several minutes analyze time; reference standards are not required, but very expensive
Hyperspectral coherent anti-stokes Raman scattering, HCARS	was used to identify and localize THCA or CBDA and myrcene in the secretory cavities of drug-type and fiber-type glandular trichomes

As to the quantification of cannabinoids only in hemp extracts, this can be achieved in these days through one of the 2 methodes:

1. liquid chromatography of the diluted extract,
2. gas chromatography of the derivatized extract.

The literature suggests that HPLC-MS/MS using ESI and APCI methods provide enough specificity and sensitivity to quantify cannabinoid content in all cannabis extracts.[67–70]

As to the simultaneous quantification of terpenes and cannabinoids in hemp extracts, this benefit of:

– a very detailed methode, useful in advanced research;[71] sorptive extraction and thermal desorption sampling, two-dimensional gas chromatography and mass detection;

– a routine, economic GC-FID methode.[72]

Among huge achievements of the cannabis laboratory, we should mention, not at last, the standard in use United Nations procedure for identification of Cannabis plants and plant products (of both medical and recreational types), summarized in Fig. 2.[73]

It was and still is the analytical laboratory that provides the identification of cannabinoid based chemovars in raw plant materials, as well as in plant products, present on the market, based on the CBD: THC ratios, given by the ratio of the chromatographic peak areas (Fig. 2).

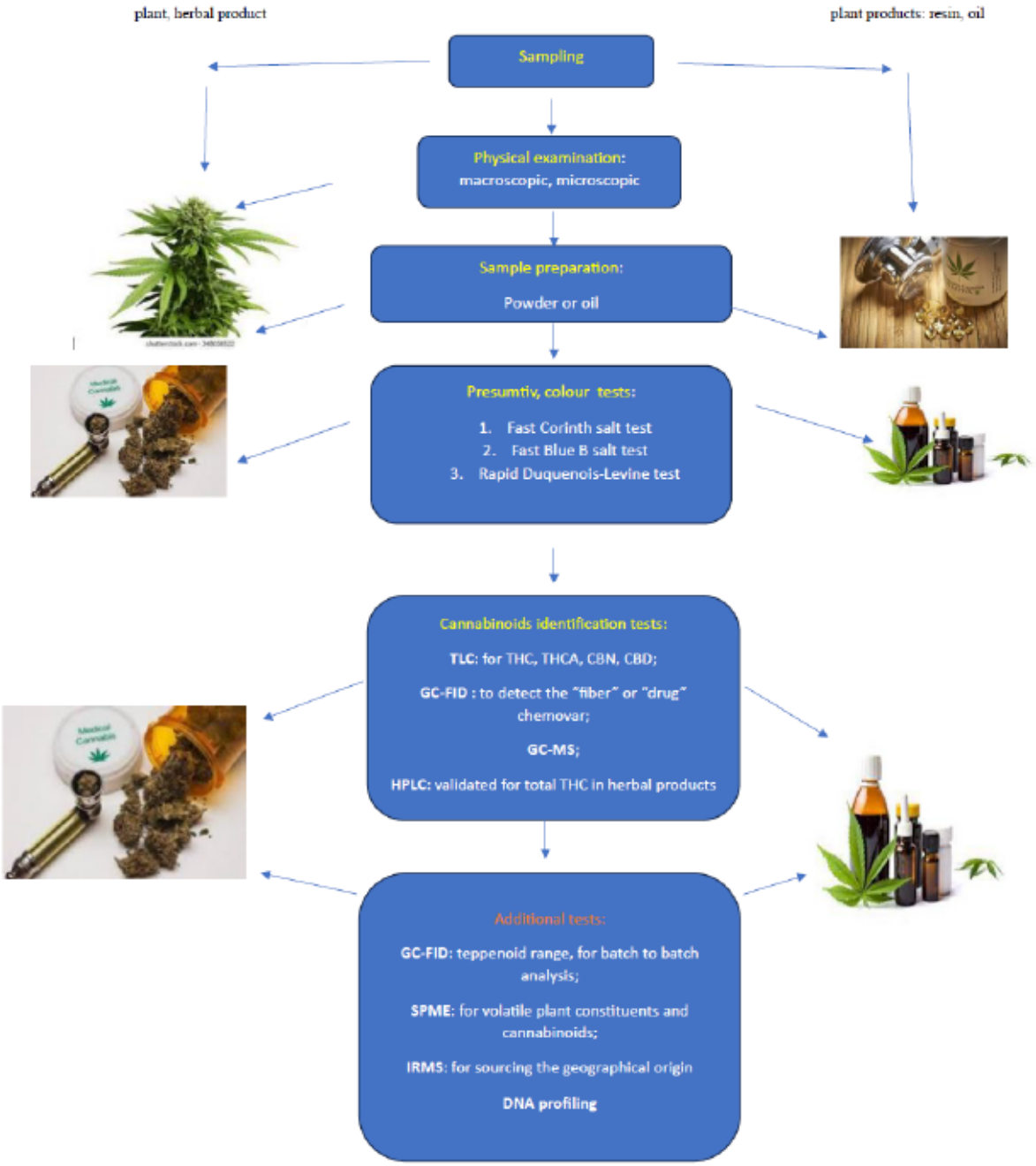

Fig. 2 – Standard analytical sequence of Cannabis plant and derivated products.

Legend: TLC *Thin-Layer Chromatography*, GC-FID *Gas chromatography coupled with flame ionization detection*, HPLC *High-performance liquid chromatography*, GC-MS *Gas chromatography coupled with mass spectrometry*, SPME *Solid phase-micro extraction, followed by GC-MS detection*, IRMS *Isotope-ratio mass spectrometry*, THC *Tetrahydrocannabinol*, THCA *Tetrahydrocannabinolic acid*, CBN *Cannabinol*, CBD *Cannabidiol*, DNA *Deoxyribonucleic acid*

Some near future expectations for the laboratory in medicinal cannabis and its products:

- a new **definition** of medicinal Cannabis chemovars is seen as possible and necessary, based not only on the profile of cannabinoids, but on the profile of cannabinoids and terpenes contained in the plant; this perspective is introduced by the publication in 2022 of the first study that reached this target. Analyzing profiles of cannabinoids, terpenes, and the combination of these substances using the partial least

square-discriminant analysis multivariate (PLS-DA) technique, this research found 11 cannabinoids and terpenes might serve as bio-indicators for 32 different active compounds. This type of research in medicinal Cannabis brings to attention that advanced laboratory techniques on Cannabis plant samples could be better utilized by using advanced statistical techniques;[74]

- **comparing the effectiveness** of the various extraction methodes published;
- the **use of statistical instruments** in such comparisons, combined or not with laboratory means;
- gas chromatography (GC) techniques **need optimization**, in order not to mislabel the cannabinoid profile of the samples (under rapid GC conditions, Δ9-THC and CBD-A showed identical retention times); besides derivatization, such notice makes GC more time-consumming technique, in comparison to liquid chromatography, but often less expensive;[75]
- the present and nearfuture of analysing the complex profile of bioactive compounds of cannabis, "at a glance" and with satisfactory resolution is the **2 or multidimentional chromatography**; examples of recent gains:
  - two-dimensional gas chromatography equipped with time-of-flight mass spectrometry, flame ionization detection, and sulfur chemiluminescence allowed the discovery of a new family of volatile sulfur compounds (VSCs), containing the prenyl (3-methylbut-2-en-1-yl) functional group, responsible for the specific cannabis scent, and the resemblance to the flavouring compounds of garlic, that oped the way to further research regarding potential beneficial health effects of such odor compounds from cannabis.[76]
  - diferentiation between 2 strains of industrial hemp was possible through a LC × LC-HRMS analize, concluding for some strain – specific compounds: CBDA or its isomer, varinic acid-C3 type, and neutral-C4 form type phytocannabinoids, respectively Procyanidins and diosmetin or chrysoeriol glycosidic derivates , with benefits for pharmaceutical, food, or cosmetic applications.[77]
- making **accessible** the HPLC-MS/MS using ESI and APCI methods, as the most specific and sensitive methode to quantify cannabinoids in cannabis raw plant, used in medicine production.
- developing and standardizing **combined analytical methodes** – a start in this direction is the achievement: spectral analysis of dried, homogenised C. sativa inflorescences, by near infrared spectroscopy (NIRS), together with chromatographic data on cannabinoids showed good quantification, rapidity, accuracy and cost-effectivness.[78]

Individual variation of the medicinal cannabis treatment efficiency influenced by genetic and epigenetic factors

It is well-known the fact that the same dose of phytocannabinoids may induce different effects from one person to another, mainly due to genetic and epigenetic factors. As phytocannabinoids act upon the human body through the endocannabinoid system, just like the cannabinoids produced by the body (endocannabinoids), the variability of genes controlling the cannabinoid receptors in the body (mainly CB1 and CB2) leads to a variability of the response to medicinal cannabis treatment.[79–82]

Variability to the reaction in the medicinal cannabis treatment may also be influenced by the endocannabinoid system (ECS) under different physiological, pathological or epigenetic conditions. For example, ECS deficiencies proved to be caused by irritable bowel syndrome (IBS), migraine, schizophrenia and fibromyalgia, and therefore, people suffering from these illnesses responded positively to exogenous cannabinoid treatment.[83–84]

Moreover, the human ECS tonus proved to be under an epigenetic modulation, as studies performed on subjects with Alzheimer's disease, glioblastoma, colorectal cancer showed.[85] CB1 gene and FAAH (fatty acid amide hydrolase) gene expressions are modulated through such epigenetic mechanisms, consisting in chemical modifications of DNA and histones tail. The changes in chromatin architecture modifies the transcription. Also, methylation of the DNA in the gene promoter region results in inactive transcription. This methylation is transferred to descendants.[86–89]

Modifications in the DNA or histone chemical modifications have been proven by studies: alcohol and exercise create opposite DNA methylation patterns;[90] binge-eating is associated with downregulation of FAAH gene expression;[91] THC and tobacco smoking was correlated with decreased CB1 expression in peripheral blood cells, by methylation at CB1 gene promoter;[92]

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,[93] while maternal high fat diet over expressed CB1 in rat hypothalamus, resulting in overweight, by histone acetylation rate.[94] There is an obvious of individualizing the therapy with medicinal cannabis, which should be performed only by doctors specialized in the field. Meanwhile, there is a need for research regarding the relationship between genes or epigenetic factors and endocannabinoids or regarding the effects of cannabinoids on people with various pathologies.

Individual variation of the medicinal cannabis treatment efficiency influenced by age, sex or metabolic factors

There are studies suggesting the presence of different reactions to the medicinal cannabis treatment in adults.[95] Thus, due to the estrogen that may influence the density of CB1 receptors and may modulate the FAAH activity, women may be more sensitive to develop an addiction to cannabinoids in comparison to men.[96,97] More studies on this subject are required in order to ensure a different cannabis therapy according to sex.

Age is another major factor influencing medicinal cannabis treatment. The older population is a growing part of medicinal cannabis users.[98–100] Although there is clear evidence that this therapy is safe and efficient for the elderly, it should be taken into consideration that they often have kidney, liver or heart problems, and, thus, a slower cannabinoid metabolization, making these individuals more sensitive to the psychoactive, neurological or hypotensive effects, compared to the youth population. On the other hand, the muscle mass decreases by age, and it is replaced by adipose mass, thus increasing the volume of lipophilic drugs distribution, like the ones based on cannabis.[102,103] There is still an extremely low number of studies regarding the pharmacokinetics of these drugs in the elderly.[104–106] The consequences of the most frequent adverse effects reported for the medicinal cannabis treatment, namely dizziness, euphoria, drowsiness, confusion and disorientation,[107,108] should particularly be investigated in the elderly, known for their common problems of mobility, sight or various forms of dementia.[109,110]

During childhood and adolescence, ECS undergoes important changes, including the increase of the CB1 receptors, increase of anandamide level, simultaneously with the decrease of the 2-arachidonoylglycerol (2-AG) effect, changes that make the individual more vulnerable to the administration of (THC).[111–113] Therefore, although it is well-known the therapeutical potential of cannabidiol in various forms of epilepsy in this age groups[114,115] or in schizophrenia[116–118] whose onset is usually at the end of adolescence, it is recommended to continue research upon the possible negative effects of medicinal cannabis on the still developing brain of children and adolescents, simultaneously with the necessity of performing the treatment only under the supervision of a doctor specialized in this type of therapy.[119–121] The scientific community supports the idea that it is imperative to gather more evidence-based data, including data from double-blind randomized-controlled trials in these special individuals. Still, the most particular individual variation in the efficiency of medicinal cannabis treatment is considered to be in relation to the metabolic differences, taking into consideration that fast metabolizers will convert the active compounds into inactive compounds more rapidly, this being one of the research directions with great impact on the analyzed treatment. It is already stated that the measurement of cytochrome CYP450 activity may be one of the tests certifying a one-time efficient dose, at the same time.[8]

Research on dosage, administration, drug interaction and side effects

Research should be performed in order to also explain the interindividual differences regarding the proper dose and plasma level concentrations obtained from various routes of administration. Individual variations of cannabinoid metabolization also lead to future areas of research, like the effect of cannabinoids in the patients with liver or kidney problems. Research should also aim at the interaction between drug-based cannabis and other drugs, but also with diet, alcohol, smoking and other epigenetic factors.[121–125] Due to this reasons, in a patient who never used medicinal cannabis, it is recommended that the dosage should be made according to the "start slow and go slow" principle.[126]

One of the most important research directions is the one related to the study of pharmacokinetics and pharmacodynamics of cannabis-based drugs and the route of administration. At present, the most used administration routes are oral, sublingual, rectal, and transdermic. The sublingual and rectal

administrations lead to a more rapid onset of effects, because they bypass the GI tract and first pass metabolism associated with oral ingestion. Moreover, for every route of administration there should be known whether there are variations according to the profile of cannabinoids found in different chemovars. Regarding oral administration, there should be brought to discussion the problem of cannabidiol food destined to treat pediatric pathologies. The purpose of these dosage forms is to provide a higher rates of adherence to treatment in very young ages. Still, they raise major barriers, like the accuracy of cannabinoid dosage in complex matrices, like food. For the analysis of this type of food, as well, it is raised the question of standardizing the analysis and control methods. Cannabis research from a food science perspective has largely been absent.[127,128] In the European Union, some products derived from the Cannabis sativa plant or plant parts, such as seeds, seed oil, have a history of consumption and therefore, are not "novel food", but are acknowledged as food or ingredients. In contrast, "extracts of Cannabis sativa L. and derived products containing cannabinoids, as well as synthetically obtained cannabinoids" are considered "novel foods" (NF), namely food that had not been consumed on a large scale before May 15th 1997. Their access to the market is subject to the Novel Food Regulation (EU) 2015/2283. Novel food based on Cannabis sativa, if authorized in the UE, will be published in the EU NF list.

Research on the long-term effects of medical cannabis treatment; the need for clinical data

Although we may state that there are already countries with experience in using medical cannabis (*e.g.* in Israel cannabis has been legal to use for medical purposes since the 1990s), there are still necessary a large number of studies in order to cover the gaps of scientific knowledge pertaining to long-term medical cannabis use. Moreover, it is still felt the need for data from clinical studies in order to enhance the knowledge regarding the impact of the medical cannabis treatment on various target populations, especially pregnant women, the elderly, children and adolescents, regarding the efficiency range of this therapy, as well as the details about the optimal treatment diagrams.

CONCLUSIONS

At present, medicinal cannabis is legalized in over 42 countries all over the world; in Roumania, the procedure is on the roll, while more and more individuals start using the medicinal cannabis-based therapy, most of the time without any medicinal supervision. In this context, it is increasingly ardent the need for knowledge in this field of research, which proves to have a great medical potential. The international scientific community already asks questions about synthesizing evidence-based knowledge, in order to establish the prioritized directions of research in the area of using medicinal cannabis. At the same time, it is taken into consideration the problem of the appropriate conditions for providing a high-quality research process into a medical practice based on evidence. The present paper shortly presents a synthesis of these debates from the literature. Information in the field is useful, even more there are required great efforts not only from specialists in public health, but also from doctors in any specialty in order to provide a proper education for the population regarding medicinal cannabis therapy and also regarding the major difference between medical and recreational cannabis.

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