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CONSIDERATIONS ABOUT NON-PSYCHOTROPIC CANNABINOIDS AND THEIR POTENTIAL APPLICATIONS

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Rezumat. *Canabinoizii non-psihotropi, alături de canabinoizii psihotropi, extractele din Cannabis sativa L. și produsele derivate ce conțin canabinoizi, au dobândit statutul de alimente noi la nivelul Uniunii Europene/UE, începând din ianuarie 2019, necesitând astfel autorizare în vederea punerii pe piața UE. Odată cu acest statut, se produce și consolidarea unei piețe emergente. În același timp, trebuie avut în vedere faptul că, de cel puțin câteva decenii de știință modernă deja, canabinoizii au făcut obiectul cercetării, al studiilor și al utilizărilor, demonstrând astfel proprietăți comprehensive și extraordinare în vederea folosirii ca agenți terapeutici. Scopul prezentei lucrări este de a furniza o analiză asupra principalilor canabinoizi non- psihotropi și a profilurilor lor farmacologice, cu obiectivul de a se constitui într-o argumentare pentru continuarea cercetării privind potențialul acestora pentru diferite aplicații, în principal ca agenți terapeutici, și, foarte important, într-o argumentare pentru parcurgerea procesului de inovare până la ajungerea pe piață a produselor inovative ce fac astfel obiectul cercetării.*

Abstract. *Non-psychotropic cannabinoids, as well as psychotropic cannabinoids, extracts of Cannabis sativa L. and derived products containing cannabinoids have gained the status of novel foods within the European Union/EU, starting January 2019, thus requiring authorization for the placing on the EU market. With this status comes also the consolidation of an emerging market. At the same time, it should be noted that cannabinoids have already been the object of research, study and applications, for at least decades of modern science, showing comprehensive and extraordinary properties for use as therapeutic agents. The purpose of present paper is to provide an overview of the main non-psychotropic cannabinoids and their pharmacological profiles, with the aim of advocating further research into their potential for various applications, mainly as therapeutic agents, and most importantly with the aim of advocating for pursuing the innovation process all the way to the market uptake of related innovative products.*

Keywords: Non-psychotropic phytocannabinoids, Cannabis sativa L., cannabidiol/CBD

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1. Introduction

Natural plant compounds have always presented great interest for science in terms of study and use in various biological and non-biological applications. Plant extracts are a main source for the development of medication, agrochemicals, cosmetics and food etc. [1]. Plant-derived cannabinoids are now a focus for research, representing lipid-soluble compounds isolated mainly from the resin which is secreted from the trichomes of the female *Cannabis sativa* L. plants [2].

Varieties of *Cannabis sativa* L., i.e. industrial hemp (Fig. 1), can be legally grown in the European Union/EU as long as they are registered in the EU Plant variety database – Common catalogues comprising of all agricultural and vegetable plant varieties regulated in the EU – and their tetrahydrocannabinol content does not exceed 0.2% [3]. Starting January 2019, it should be further noted that cannabinoids, extracts of *Cannabis sativa* L. and derived products containing cannabinoids are considered novel foods by the European Commission through the European Food Standards Agency and require authorisation by each Member State before placing such products on the EU market [4]. On the other hand, it should be emphasized that the EU market of products containing cannabidiol (CBD), i.e. the main non-psychotropic cannabinoid isolated from *Cannabis sativa* L., is estimated to show a strong growth over the next five years, with a value of up to 8.3 billion Eur by the end of 2020 and up to 13.6 billion Eur by the end of 2025, current largest EU market being Germany with a value of around 1.83 billion Eur [5].

Over 100 phytocannabinoids are produced by *Cannabis sativa* L., this group of naturally-occurring molecules comprising both of psychotropic (e.g. Δ^9-tetrahydrocannabinol/Δ^9-THC) and non-psychotropic phytocannabinoids (e.g. cannabidiol/CBD, cannabigerol/CBG, cannabidivarin/CBDV, Δ^9-tetrahydrocannabivarin/THCV) and cannabichromene/CBC, all having shared chemical structure [2]. Alongside cannabinoids, *Cannabis sativa* L. plant, also known as Indian hemp, contains other chemically active compounds, such as terpenes, flavonoids and alkaloids [6]. Among the psychoactive cannabinoids, including the aforementioned Δ^9-THC which is the most important one, there are also found others such as cannabinol (CBN), and cannabinodiol (CBND) [7].

While initially the focus of research was mostly on the psychoactive compound THC, the study and use of the non-psychotropic cannabinoids has been taking main stage in recent years, primarily in terms of cannabidiol (CBD) which is the most abundant non-psychotropic phytocannabinoid isolated from *Cannabis sativa* L. The chemical structures of non-psychotropic phytocannabinoids are as shown below (Fig. 2) [2].

Fig. 1. Legally grown plantation of *Cannabis sativa* L. in Romania, 2020 crop.

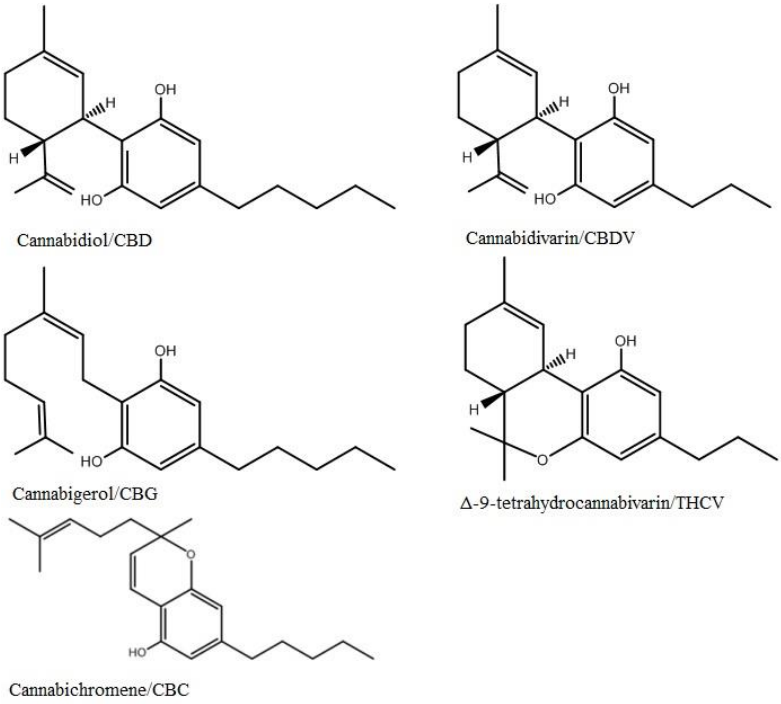

Fig. 2. The chemical structures of non-psychotropic phytocannabinoids [2]

2. Methodology

Present research was performed by reviewing relevant literature and studies on *Cannabis sativa* L. plant and non-psychotropic cannabinoids, particularly on CBD. Furthermore, a review of the main applications of non-psychotropic cannabinoids was performed. The purpose of present research is to provide a case like evaluation of the main non-psychotropic cannabinoids and their pharmacological profiles, with the aim of advocating further research and development into their potential for various applications, mainly as therapeutic agents.

3. Results/main findings and contribution

While generally classified as neutral cannabinoids and cannabinoid acids, i.e. without and with carboxyl group, the cannabinoids produced by *Cannabis sativa* L. are biosynthesized and accumulated as cannabinoid acids which must be decarboxylated into neutral forms [7, 8]. The cannabigerolic acid/CBGA is produced by alkylation of olivetolic acid with geranyl-pyrophosphate by a prenyltransferase, while the cannabidiolic acid/CBDA), cannabichromenic acid/CBCA and Δ-9-tetrahydrocannabinolic acid/D9-THCA are generated by CBGA due to the action of cannabinoid synthase enzymes, the biosynthesis of the main phytocannabinoids being synthetized below (Fig. 3) [8].

As explained by [8], in terms of the biosynthesis of the main phytocannabinoids, it should be noted that, on one side, geranyl diphosphate and olivetolic acid are converted in CBGA by synthase, being the main precursors of D9-THCA, CBDA and CBCA, which contain an n-pentyl side chain (C5-phytocannabinoids). Furthermore, by decarboxylation of said precursors, Δ-9-tetrahydrocannabinol/ D9-THC is formed, as well as its metabolite cannabinol/CBN, cannabidiol/CBD is formed, cannabichromene/CBC is formed, as well as its chemical artefact cannabicyclol (CBL). On the other side, geranyl diphosphate and divarinic acid are converted into cannabigerovarinic acid/CBGVA, which is an n-propyl side chain (C3-phytocannabinoids), and from latter, Δ-9-tetrahydrocannabivarin acid/D9-THCVA, cannabidivarin acid/CBDVA) and cannabichromevarin acid/CBCVA are synthesized. Furthermore, the cannabinoids D9-THCV, CBNV, CBDV, CBCV and CBLV are formed by their decarboxylation. The phytocannabinoids are mainly divided into 10 subclasses, i.e. cannabigerols(CBGs), cannabichromenes (CBCs), cannabidiols (CBDs), (−)-Δ^9-trans-tetrahydrocannabinols(Δ^9-THCs), (−)-Δ^8-trans-tetrahydrocannabinols (Δ^8-THCs), cannabicyclols (CBLs), cannabielsoins(CBEs), cannabinols (CBNs),

cannabinodiols (CBNDs), cannabitriols (CBTs), and the miscellaneous cannabinoids [9].

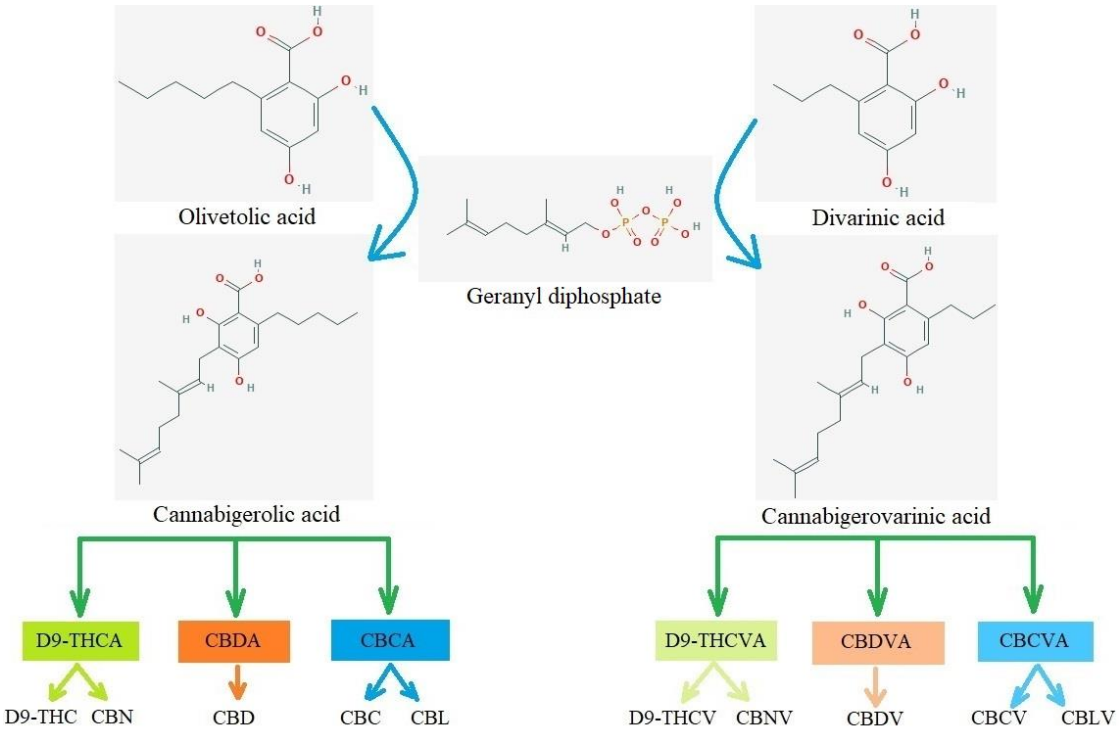

Fig. 3. Biosynthesis of main phytocannabinoids [8].

CBDs are present in abundance among the non-psychotropic phytocannabinoids isolated from *Cannabis sativa* L. (i.e. the fiber-type hemps), becoming more and more the object of research, while being the second most important in the drug chemotypes after THCs. Studies show that CBD presents numerous and various pharmacological effects via specific molecular targets, e.g. adenosine receptors, glycine receptors, opioid receptors, serotonin receptors, non-endocannabinoid G protein-coupled receptors, nicotinic acetylcholine receptors, proliferator-activated receptors; while CBD also presents anticonvulsant, anti-spasmodic, anxiolytic, antinausea, anti-rheumatoid arthritis, and neuroprotective properties and furthermore shows therapeutic results for Alzheimer's disease, Parkinson's disease, cancer, and infertility [8].

Terpenes represent another important group of chemically active compounds contained in *Cannabis sativa* L. plant, particularly in the flower and leaves, being responsible for the strong fragrance of the plant. Most present and highly volatile terpenes are limonene, myrcene, and pinene, while more than 200 terpenoids have been identified and characterised [10]. They are lipophilic

molecules capable of interacting with cell membranes of mammals, both at cerebral and peripheral level, having complex and further promising pharmacological profiles [8]. While industrial hemp has various applications, ranging from agronomy, food industry, cosmetic industry, constructions, animal production and broiler meat and chicken egg production, and very importantly pharmacotherapy [6, 10], it is the phytocannabinoids isolated from the plant that present a continuously increasing interest for research and applications.

The pharmacological profiles of phytocannabinoids have been object to research and continue to be so, showing comprehensive and applicable results. Main biological properties of cannabinoids are relevant due to their interaction with the endocannabinoid system/ECS in humans [6, 11, 12]. ECS represents a group of neuromodulatory lipids and their receptors which are found in mammalian tissues, having the role of regulating various cardiovascular, nervous, and immune system functions inside cells [13]. ECS includes two G protein-coupled cannabinoid receptors, i.e. CB1 and CB2, and two endogenous ligands, i.e. anandamide and 2-arachidonylglycerol. Endocannabinoids are believed to either modulate or play a regulatory role in various physiological processes, such as appetite, pain-sensation, mood, memory, inflammation, insulin regulation, sensitivity and fat and energy metabolism [6, 11, 12, 14-16].

While THC, i.e. the most important psychotropic cannabinoid, held the main stage in research for its pharmacological profiles, the non-psychotropic phytocannabinoids are increasingly showing their therapeutic potential via various mechanisms as a result of intensified research. Their pharmacological profiles, uses and potential uses as therapeutic agents are synthesized below (Table 1).

Table 1. Non-psychotropic phytocannabinoids - pharmacological profiles, uses and potential uses as therapeutic agents

Non-psychotropic phytocannabinoids	***Pharmacological profiles***	***Uses and potential uses as therapeutic agents following preclinical and clinical trials and studies***	***References***
Cannabidiol/CBD	anticonvulsant; anti-spasmodic; antinausea; analgesic; anti-inflammatory; anti-rheumatoid arthritis properties; anxiolytic; antipsychotic; anti-proliferative/pro-apoptotic effects in cancer cells; neuroprotective properties; reducing the side effects of THC; immunomodulatory properties; anti-fungal and	eating disorders; vomiting and nausea; pain management; rheumatoid arthritis; psoriasis; gut inflammation/ inflammatory bowel disease, Crohn's disease; sleep disorders; anxiety; depression; cancer; cerebral and myocardial ischemia; neuro-inflammation; epilepsy and hyperexcitability	[6, 8-22]

	anti-bacterial properties, bactericidal effect against Gram-positive staphylococci and streptococci, significant antibiotic activity against methicillin-resistant Staphylococcus aureus/MRSA; potent antioxidant activity; beneficial effects on bone formation and fracture healing/stimulant;	disorders; neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease), schizophrenia; autoimmune diseases, graft-versus-host-disease; oxidative injury, diabetic complications; bone formation and fracture healing, skin conditions, including but not limited to Acne Vulgaris, Kaposi Sarcoma;	
Cannabichromene/ CBC	anti-inflammatory; protective effect against intestinal inflammation; analgesic; sedative; anti-proliferative/pro-apoptotic effects in cancer cells; anti-bacterial and anti-fungal properties, significant antibiotic activity against methicillin-resistant Staphylococcus aureus/MRSA;	inflammatory bowel disease; cancer; skin conditions, including but not limited to Acne Vulgaris;	[6, 8-10, 16, 18-20, 23]
Cannabigerol/CBG	anti-proliferative/pro-apoptotic effects in cancer cells; antibacterial properties; significant antibiotic activity against methicillin-resistant Staphylococcus aureus/MRSA;	cancer; murine colitis;	[6, 9, 10, 16, 18-20]
Cannabidivarin/ CBDV	beneficial effects on bone formation and fracture healing (stimulant); anticonvulsant;	bone formation and fracture healing; epilepsy; skin conditions, including but not limited to Acne Vulgaris;	[12, 16, 18]

In terms of topical applications, research focused early on actually developing preparations from *Cannabis sativa* L., i.e. in the 1950s around the time science rediscovered cannabinoids, extensively investigating the cannabinoids as highly active topical antiseptic agents for the oral cavity and skin [18]. The topical and transdermal route of administering cannabinoids as therapeutic agents,

including non-psychotropic cannabinoids, especially CBD, is still at research stage or mostly under study in limited and small clinical studies [14].

Although they show remarkable properties, cannabinoids (including non-psychotropic cannabinoids) having the potential to treat various skin conditions, such as acne vulgaris, allergic contact dermatitis, asteatotic dermatitis, atopic dermatitis, hidradenitis suppurativa, Kaposi sarcoma, pruritus, psoriasis, skin cancer, and the cutaneous manifestations of systemic sclerosis, the formulation of topical cannabinoid products in dermatology is yet to formally and widely take place [15, 16]; thus the complete walk to market uptake of the innovative related products is still to be taken.

As emphasized in Table 1, main non-psychotropic cannabinoids present pharmacological profiles such as anti-inflammatory, anti-fungal, antibacterial and targeted antibiotic properties. Present review of the state-of-the-art research on non-psychotropic cannabinoids shows that their pharmacological profiles were not extensively investigated, identified and developed for use in topical applications. Furthermore, there is little body of work on researching the full-spectrum *Cannabis sativa* L. extract and its pharmacological profile or the mixture of non-psychotropic cannabinoids in same ratios as they naturally occur in the plant. Full-spectrum *Cannabis sativa* L. extract contains also terpenoids. Considering that antimicrobial properties were also determined for terpenoids, especially observed in pinene against both Gram + and Gram – bacteria and fungi such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Methicillin-Resistant Staphylococcus Aureus/MRSA* and *Candida albicans* [10], there is a clear indication that full-spectrum *Cannabis sativa* L. extract should be extensively researched as therapeutic agent for, but not limited to, topical applications. Various properties of each compound contained in *Cannabis sativa* L. should be considered working together, thus having the potential of increasing the effectiveness of one single comprehensive therapeutic agent.

There is also insufficient study on full-spectrum *Cannabis sativa* L. extract and on non-psychotropic cannabinoids and their applications as functional foods and functional food ingredients, as well as natural food preservatives. Current state of the art already shows some important properties of full-spectrum Cannabis sativa L. extract and of non-psychotropic cannabinoids (especially CBD) as functional foods and functional food ingredients, e.g. *Cannabis sativa* L. contains polyunsaturated fatty acids, optimum Omega-6 and Omega-3 ratio, fibres and amino acids, as well as natural food preservatives [10]. Moreover, in terms of antimicrobial activity, it looks like the actual whole plant (i.e. various solvent extract of the whole plant) and different parts of the *Cannabis sativa* L. plant (i.e. various solvent extract of different parts, such as leafs, seed's oil, stem and whole buds) show important antimicrobial activity against different organisms [19], proving the extensive potential of this plant and related extracts.

A very important issue to be considered for the non-psychotropic cannabinoids to be effectively used as therapeutic agents is to be developed into reliable drug delivery systems. Feasible methods of cannabinoid administration are under research and study, such as transdermal route, intranasal administration and transmucosal absorption, as response to the low oral bioavailability of cannabinoids. Cannabinoids are considered as suitable candidates for advanced nanosized delivery systems via numerous routes due to their highly lipophilic nature. Although several innovative non-psychotropic cannabinoid (i.e. CBD) delivery systems are currently available on the market, the results of scientific development are yet to come [14, 21, 22].

Conclusions

Current state of the art presents *Cannabis sativa* L. as having an extraordinary potential to be used as an alternative natural agent in numerous fields. It has been clearly shown that non-psychotropic cannabinoids, especially CBD, have complex and various pharmaceutical profiles, thus having a strong potential to be developed into powerful therapeutic agents. Formulation of non-psychotropic cannabinoids into reliable drug delivery systems can overcome their shortcomings, on one hand in terms of their properties, such as their high lipophilicity, and on the other hand in terms of openness of the medical community to prescribe them as effective medication. Research should also focus on identifying the pharmacological profiles of full-spectrum *Cannabis sativa* L. extracts in order to determine the combined potential of non-psychotropic cannabinoids, i.e. synergetic agent. Furthermore, considering important pharmacological profiles of the non-psychotropic cannabinoids, especially CBD, such as anti-fungal and anti-bacterial properties, bactericidal effect against Gram-positive staphylococci and streptococci, significant antibiotic activity against MRSA, potent antioxidant activity, research and study should also be orientated/refocused towards the *actual* development of topical applications, broad-spectrum or narrow-spectrum.

Nutraceuticals should also be extensively considered in order to determine their safety and efficiency, as alternative and potentially less aggressive forms of treatment. Moreover, considering the novel foods status at European Union/EU level of cannabinoids, extracts of *Cannabis sativa* L. and derived products containing cannabinoids, there is a legal framework and compulsory need to extensively develop new products containing the aforementioned novel foods and show their safety and efficiency for the EU market and beyond.

Finally, considering all the above, innovative products must be brought forward, as the market uptake of innovation in this field is long overdue.

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