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Potential of Cannabidiol (CBD) in dermatology: Efficacy, Safety, and Current Regulation

Elsa Marina dos Santos Lopes

Dissertation supervised by Professor Helena Margarida Oliveira Marques Ribeiro and co-supervised by Professor Joana Marques Marto

Master in Regulation and Evaluation of Medicines and Health Products

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Acknowledgements

Dedico este trabalho à minha família, ao meu porto seguro nos bons e maus momentos, que sempre me apoia em cada projeto no qual me envolvo. O meu obrigada pelo conforto e coragem nos momentos de maior fraqueza e indecisão, durante o desenvolvimento deste trabalho.

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Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

"Nature is the source of all true knowledge."

Leonardo Da Vinci

Abstract

Numerous studies have been described on how the *Cannabis sativa* L. plant can be used for chronic pain, spasticity, anorexia, nausea and a host of other conditions and symptoms, including dermatological disorders (MARTINS AM et al., 2022). However, there is no harmonization of legislation in the European Union regarding the use of cannabis and medicinal products. At the international level, the United Nations treaties for the control of illicit substances impose certain requirements on signatory countries to consent to the use of cannabis and derived products for medicinal purposes. In these countries, the authorization for the use of cannabis preparations through these programs is limited to a narrow set of clinical conditions (MEDICAL USE OF CANNABIS AND CANNABINOIDS, 2018). In the case of Portugal, the use of the cannabis plant has been allowed for medicinal purposes since July 2018 by submitting an ACM (a specific and simplified authorization regime for preparations and substances based on the cannabis plant). Pursuant to the provisions of number 3 of article 9th of Portuguese Law n.º 33/2018 of 18 July, the therapeutic indications considered appropriate for medicines, preparations and substances based on the cannabis plant intended for human use are approved by INFARMED, I.P. (Law n.º 33/2018, de 18 de JULHO). These are restricted to seven therapeutic indications, excluding any dermatological application. The activity of cannabinoids in the skin is a relatively recent area of research, although cannabis and its preparations for topical use are described in the older medical literature (MARTINS AM et al., 2022). The relevance of this study is related to the importance of highlighting the increasingly expressive therapeutic interest of CBD in Dermatology, due to its anti-inflammatory, antibacterial, antipruritic effect and its antinociceptive properties. Through several preclinical studies, evidence suggests that topical applications of CBD may be effective. With this study, an update will be made on the state of advances in research in this area, focusing on its potential for future exploration of the theme in regulatory terms.

Key words: Cannabidiol, CBD, cannabis, dermatology, regulation.

Resumo

Numerosos estudos têm vindo a ser descritos sobre como a planta de *Cannabis sativa* L. pode ser usada para a dor crónica, espasticidade, anorexia, náusea e uma série de outras condições e sintomas, incluindo afeções dermatológicas (MARTINS AM et al., 2022). No entanto, não existe na União Europeia uma harmonização da legislação relativamente à utilização de canábis e produtos derivados para fins medicinais. A nível internacional, os tratados das Nações Unidas para o controlo de substâncias ilícitas impõem aos países signatários determinados requisitos de modo a consentir a utilização para fins medicinais da canábis e produtos derivados. Nestes países, a autorização para a utilização dos preparados de canábis através destes programas é limitada a um conjunto restrito de condições clínicas (MEDICAL USE OF CANNABIS AND CANNABINOIDS, 2018). No caso de Portugal, o uso da planta de canábis é permitido para fins medicinais desde julho de 2018, através da submissão de uma ACM (um regime de autorização específico e simplificado para preparações e substâncias à base da planta de canábis). Nos termos do disposto no n.º 3 do artigo 9.º da Lei Portuguesa, n.º 33/2018, de 18 de julho, as indicações terapêuticas consideradas apropriadas para os medicamentos submetidos por ACM, preparações e substâncias à base da planta canábis destinados a uso humano são aprovadas pelo INFARMED,I.P. (LEI n.º 33/2018, de 18 de JULHO). Estas restringem-se a sete indicações terapêuticas excluindo qualquer aplicação de caráter dermatológico. A atividade dos canabinóides na pele, é uma área de investigação relativamente recente, apesar da canábis e as suas preparações para uso tópico estarem descritas na literatura médica mais antiga (MARTINS AM et al., 2022). Através de uma série de estudos pré-clínicos, a evidência sugere que as aplicações tópicas do CBD poderão ser eficazes. A pertinência deste estudo prende-se com a importância de destacar o cada vez mais expressivo interesse terapêutico do CBD em Dermatologia, devido ao seu efeito anti-inflamatório, antibacteriano, antipruriginoso e suas propriedades antinociceptivas. Com este estudo, será feito uma atualização do estado dos avanços na investigação desta área, com foco no seu potencial para uma futura exploração da temática em termos regulamentares.

Palavras-chave: Canabidiol, CBD, canábis, dermatologia, regulamentação.

Acronyms and Abreviations

2-AG – 2-arachidonoyl-glycerol

A2 – Adenosine receptor-dependent

ACM – Autorização de Colocação no Mercado

AEA – Anandamide

AI – Artificial intelligence

AIM – Autorização de Introdução no Mercado

API – Active pharmaceutical ingredient

CB1 – Cannabinoid Receptor type 1

CB1R – Cannabinoid Receptor type 1

CB2 – Cannabinoid Receptor type 2

CB2R – Cannabinoid Receptor type 2

CBD – Cannabidiol

CBG – Cannabigerol

CBMP – Cannabis based medicinal products

CBN – Cannabinol

CBR – Cannabinoid receptor

CNB – Cannabinoid

COVID – Coronavirus disease

DAGL – Diacylglycerol lipase

DCP – Decentralized procedure

DEA – Drug Enforcement Administration

DL – Decreto-Lei

ECS – Endocannabinoid System

EEA – European Economic Area

EFSA – European Food Safety Authority

EMA – European Medicines Agency

EMCDDA - European Monitoring Centre for Drugs and Drug Addiction

EU – European Union

EUR – EURO; European Union official currency

FDA – Food and Drug Administration

GACP – Good Agriculture and Collective Practices

GMP – Good Manufacturing Practices

HIV – Human immunodeficiency virus

HLAC – Histocompatibility complex

HMPC – Committee on Herbal Medicinal Products

HRB – Health Research Board

IAPMEI – Agência para a Competitividade e Inovação

IFN – Interferon

INCB – International Narcotics Control Board

INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde

INFOMED – Base de dados nacional de medicamentos

MA – Marketing Authorization

MHRA – Yellow Card Reports

MRP – Mutual Recognition Procedure

NHS – National Health Service (United Kingdom)

NRIP1 – Nuclear Receptor Interacting Protein 1

PPAR – Peroxisome proliferator-activated receptor

PUVA – Psolareno + UVA

RCT – Randomized Clinical Trials

RNA – Ribonuclec acid

ROS – Reactive oxygen species

RWE – Real World Evidence

SG – Sebum Gland

SOC – Skin organ culture

THC – Tetrahidrocannabinol

TNF – Tumor necrosis factor

UK – United Kingdom

UN – United Nations

US – United States

USA – United States of America

USD – United States Dollar

WHO – World Health Organization

Table of Contents

List of Figures

List of Tables

1. Introduction

Cannabis sativa L. is a plant with medicinal properties that have been known for thousands of years. The interest of the scientific community in the medicinal properties of this plant, has been growing in recent decades, and among its compounds with therapeutic effects are phytocannabinoids, substances biosynthesized by the plant and capable of modulating the endocannabinoid system (BASWAN S.M. et al., 2020).

The major phytocannabinoids in the cannabis plant are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). CBD is a non-psychoactive compound, and has been receiving special attention in recent years due to its therapeutic potential in terms of various pathologies, including skin pathologies (BASWAN S.M. et al., 2020), namely, in the case of psoriasis, atopic dermatitis, dermatomyositis, epidermolysis bullosa, pyoderma gangrenosum, acne vulgaris and in some types of skin cancer such as melanoma.(RAMER R. et al., 2022).

The potential of CBD is extremely significant and covers several areas, such as medicines, cosmetics, food, etc., however, only its therapeutic effect will be focused, specifically in dermatological affections, where is already a scientific evidence base, that allows us to continue in the process of research and development.

There are currently several ongoing clinical studies on the administration of CBD through the skin and there is still no consensus on the use of CBD in dermatology. However, and considering the sharp increase in scientific and clinical studies on the pharmacological mechanisms and efficacy of phytocannabinoids, the use of non-psychoactive phytocannabinoids such as CBD as a promising tool in the treatment of skin diseases, should be evaluated. (MARTINS A.M. et al., 2022).

The CBD global interest is presently growing exponentially, as research into the therapeutic benefits of CBD expands. This expansion could be related to the increasing consumer demand for natural and sustainable treatments for skin conditions since being a plant-derived compound with therapeutic properties, has captured the interest of consumers seeking alternative remedies for dermatological issues. The consumers awareness about CBD's potential and this growing

knowledge base about this skin benefits and properties, encourages by itself, further scientific exploration.

There is still, however, some difficulty in implementing research and development measures in this area, due to the lack of legal uniformity among the various regulatory entities and the respective laws of the countries interested on advancing in this field.

It is essential to understand and follow the diversity of regulatory considerations – as more states and countries decriminalizes cannabis, interest in the medicinal properties and benefits of cannabinoids continues to grow in tandem.

An increasing number of studies are addressing gaps in the understanding and use of these Phyto agents. Although their efficacy in specific dermatologic applications requires further research, dermatologists and other physicians, are well positioned to be pioneering in using cannabinoids to understand and treat several inflammatory and autoimmune skin conditions. (FRIEDMAN A. and WEISS M., 2019).

2. Objectives

This dissertation aims to deepen the *state-of-the-art* in the area of potential research Cannabidiol therapy in various fields of dermatology, and to try to identify the current gaps in the regulation, especially the Portuguese one, in its limitation of authorization of the use of compounds derived from *Cannabis sativa* L., to a restricted set of clinical conditions, and which exclude to date, indications of dermatological field.

In this way, following the lifting of the various regulations, both national and international, related to the Cannabis plant and more specifically to one of its major cannabinoids – CBD – regulatory changes will be proposed, at the level of the Portuguese scope of dermatological treatments based on CBD products.

This adaptation applicable to the extension of the authorization of CBD in dermatological therapy, permanently takes into consideration the quality, safety and efficacy of the CBD-based products, considering the specifications of the Herbal substances, preparations, or medicines for marketing authorization approval processes, intended to be executed.

3. The *Cannabis sativa* L. plant.

Cannabis sativa L. is a widespread species in nature. It is found in various habitats ranging from sea level to the temperate and alpine foothills of the Himalayas, from where it was probably spread (ZUARDI A.W., 2006; TROFIN I.G. et al., 2012). The age-old cultivation makes its original distribution difficult to pinpoint (GAONI Y. et al., 1966). Cannabis has a long history of medicinal use in the Middle East and Asia, with references as far back as the 6th century BCE, and it was introduced in Western Europe as a medicine in the early 19th century (ADAMS R. et al., 1940; WATANABE K. et al., 2007).

The great morphological and chemical diversity of *Cannabis sativa* L. is the result of 6000 years of selection and domestication, with different uses by humans in different geographical regions of the world. Domestication and crossbreeding took place in two directions: first, with the aim of obtaining cannabinoid-rich plants; and second, with the aim of obtaining plants that have low cannabinoid content and are well suited for fiber production or whose seeds produce a high oil yield. As a result, enormous genomic differences have arisen between the resulting plant groups (ZIEGLER A., 2024).

Cannabis is a genus of angiosperms, dioecious and manifests an annual life cycle consisting of growth, blossoming, reproduction, and death in an interval of approximately one year (RANALLI P., 1999; MOLITERNI V.M.C. et al., 2004; GUPTA R.C., 2016; DOS SANTOS N.A. et al., 2023).

The genus Cannabis belongs to the family Cannabaceae. The taxonomic classification of Cannabis sativa has long been the subject of debate and differences of opinion. However, there is now a broad consensus among taxonomists to regard Cannabis sativa as monospecific – that is, as a species with subspecies (ZIEGLER A. et al., 2024).

Taxonomically, exists three distinguished Cannabis subspecies – sativa, indica and ruderalis (figure 1).

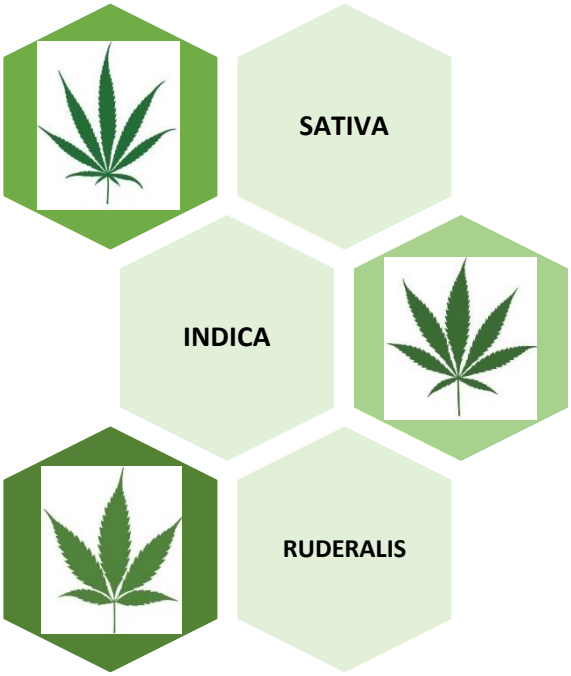


Figure 1-Representative image of *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis* leaves.

In **Botanical** aspects, Cannabis plants can be male, female or hermaphrodite (containing both male and female reproductive parts). Figure 2 illustrates the aerial parts of the Cannabis plant including the male and female parts – hermaphrodite version.

Cannabis is wind-pollinated, where male plants produce vast amounts of pollen that can spread over large geographical areas, allowing the pollination of female flowers of plants growing very far from pollen bearing flowers (POLLIO A., 2016).

The female flower is the largest reservoir of cannabinoids, usually stored in the glandular trichome spiked on the leafy surface of the flower. The male flower is responsible for the fertilization process by pollination, from which the female flower grows to seed.

Cross-pollination can affect the quality of secondary metabolites. To overcome such situations, male plants are removed, and the desired female plants are selected for adequate secondary metabolite production (PATTNAIK et al., 2022).

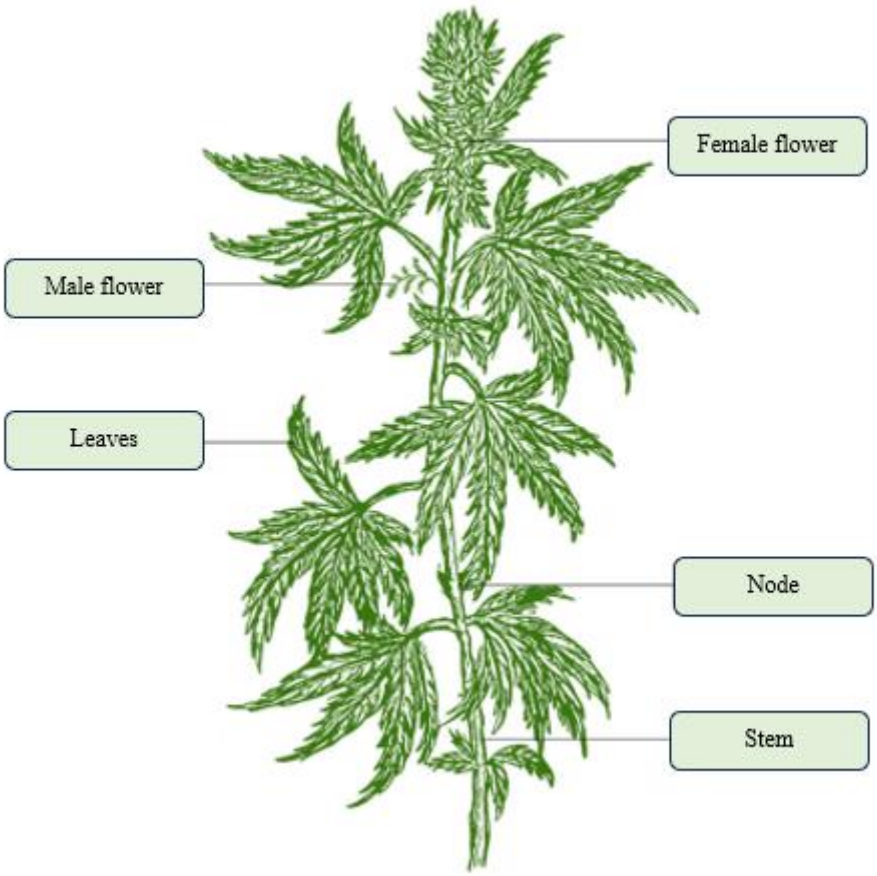


Figure 2 – Anatomy of a *Cannabis sativa* L. plant showing male and female flowers, in a hermaphrodite version. (Adapted image from a hand-draw sketch made by Dr. Sonil Nanda)

Morphologically, *Cannabis sativa* L. presents green and palmate (seven lobes leaves). Their size and shape differ markedly, according to the genetic origin. The leaf arrangement may be either opposite or alternate or spiral. The leaflets are 6–11 cm (length) and 2–15 mm (width). Leaf margins are coarsely serrated (figure 2). The stems are typically angular, furrowed, branched, with a woody interior, sometimes hollow in the internodes, and vary from 1 to 6 m in height. The branching is either opposite or alternate. The roots are advantageous, with branched taproot, generally 30–60 cm deep, up to 2.5 m in loose soils, very near to the surface, and more branched in wet soils. Inflorescences comprise numerous flower heads that may be found on long, leafy stems from each leaf axil. Male flowers have five pale-green, hairy sepals about 2.5–4 mm long,

and five pendulous stamens, with slender filaments. The pistillate (female flowers) are almost sessile and in pairs (figure 3) (SPITZER-RIMON, B. et al., 2019).

Figure 3- Example of a female and a male plant (From Freepick free images bank, accessed 29th April 2024).

Trichomes (Figure 4), are the part of the plant where the phytocannabinoids production happens. There are different types of trichomes, but the main type is the one represented below.

They are located on the flowers and the small leaves around ("sugar leaves").

Metabolically, *C. sativa* L. produces numerous chemicals via secondary metabolism. More than 545 bio compounds are known, including phytocannabinoids, non-cannabinoid phenols, terpenes, terpenoids, flavonoids, phenylpropanoids, steroids and fatty acids. Cannabis has approximately 140 different terpenes, predominantly monoterpenes such as β-myrcene, α- and β-pinene, α-terpinolene, but also sesquiterpenes including β-caryophyllene, di- and triterpenes (FLORES-SANCHEZ, I.J. et al., 2008; SOLYMOSI, et al., 2016; ELSOHLY, MA et al., 2017; GONÇALVES-PINHO, M. et al., 2020).

Figure 4. Cannabis flower trichomes in a macro view (From Unsplash free images bank, accessed 29th April 2024).

3.1 An historical approach of the use of *Cannabis sativa* L.

The history of medicinal cannabis goes back to ancient times. The use of cannabis as a medicine was firstly reported by ancient Chinese (5000 BC), using mainly the plant seed to treat rheumatic pain, intestinal constipation, disorders of the female reproductive system, malaria, and other diseases (ZUARDI A.W. et al., 2006; TOUW M., 1981). Followed by India (1000 BC) and Africa (1000 AC), where the plant seed and flower were used for several functions, such as analgesic (neuralgia, headache, toothache), anticonvulsant (epilepsy, tetanus), hypnotic, tranquilizer (anxiety, mania, hysteria), anesthetic, anti-inflammatory (rheumatism and other inflammatory diseases), antibiotic (topical use on skin infections, erysipelas, tuberculosis), antiparasitic (internal and external worms), antispasmodic (colic, diarrhea), digestive, appetite stimulant, diuretic, aphrodisiac, antitussive and expectorant (bronchitis, asthma) (ZUARDI A.W. et al., 2006; MIKURIYA T.H., 1969). Also, in 1464, was reported the first case of an epileptic child treated with plant's resin, which according to literature, the child fully recovered (ZUARDI A.W.

et al., 2006; MATHER L.E. et al., 2013). In Europe (19th century) cannabis in the format of tinctures, powders and syrups were used for the treatment of rheumatism, convulsions, and mainly for muscular spasms of tetanus and rabies (MIKURIYA T.H., 1969). However, by the twentieth century, medical use of cannabis had largely declined, and its consumption for medical purposes was already very limited when in 1961 cannabis was included in the United Nations Single Convention on Narcotic Drugs and classified as a drug that had no medical uses, due to THC psychoactive effects.

In the past 30 years, however, there has been a resurgence of patient interest accompanied by renewed scientific attention in the medical use of cannabinoids (MATHER L.E. et al., 2013). With this resurgence, the cannabis medicinal industry started to expand. Nowadays, the extracted cannabinoids, in the form of oil, are used to treat a variety of conditions, including chronic pain, cancer pain, depression, anxiety disorders, sleep disturbances and neurological disorders. The first prescription of medicinal cannabis was in the form of dried flower doses intended for vaporization (MATHER L.E. et al., 2013). Though only two medicinal products are approved by FDA and EMA and they are SATIVEX (50% THC and 50% CBD) and EPIDIOLEX (100% CBD) (MATHER L.E. et al., 2013; GROCE E.C., 2018). Currently, most EU countries allow, or are considering allowing, the medical use of cannabis or cannabinoids in some form. However, the approaches taken vary widely in terms of both the products allowed and the regulatory frameworks governing their provision.

3.2 The plant as a medicinal source

The diversity of Phytocannabinoids production

Cannabis sativa L. is a versatile plant. The success key of its medicinal purpose is the capability to produce many different types of chemical compounds.

Cannabis contains several secondary metabolites belonging to different chemical classes including cannabinoids, terpenoids, flavonoids, and steroids among 545 identified compounds

(CHANDRA S. et al., 2017; CITTI C. et al., 2019; GILL EW. et al.,1970; HANUŠ LO. et al., 2016; JIN D. et al., 2020; MCPARTLAND JM. et al., 2001; MECHOULAM R. et al., 1967; PAVLOVIC R. et al., 2019).

The term “variety” is the adaptation of a species resulting from changes in its habitat due to accidental factors such as climate change, soil changes, diseases , insect attacks, nematodes, and other similar influences (ARÉVALO RA. et al., 2006).

The term “cultivar” is a combination of “cultivated variety,” abbreviated to “cultivar” (ARÉVALO RA. et al., 2006). Unlike varieties, cultivars are not products of natural evolutionary processes. Instead, they are bred through deliberate breeding or agricultural techniques for improved, uniform characteristics (TOOKER JF. et al., 2012).

Hundreds of Cannabis cultivars and hybrids exist worldwide, each with a unique and distinct chemical profile. (PROCACCIA S. et al., 2022)

The main active ingredients that are used for medical purposes are tetrahydrocannabinol (THC) and cannabidiol (CBD).

THC is the psychoactive part of cannabis, and it has been used to treat symptoms such as nausea, pain and muscle spasticity. CBD has no psychoactive properties and has been used to treat several inflammatory disorders. (Royal Australian College of General Practitioners, 2016)

Phytocannabinoids, are C21 terpene phenolic or C22 for the carboxylated forms, compounds with physiological and often psychotogenic effects, possessing monoterpene and alkyl resorcinol component in their molecules, they include alkanes, sugars, nitrogenous compounds. The most well-known and widely documented compounds within the Cannabis plant include the phytocannabinoids: trans-Δ-9-tetrahydrocannabinol (THC), and cannabidiol (CBD), which molecular structure is illustrated on Figure 5.

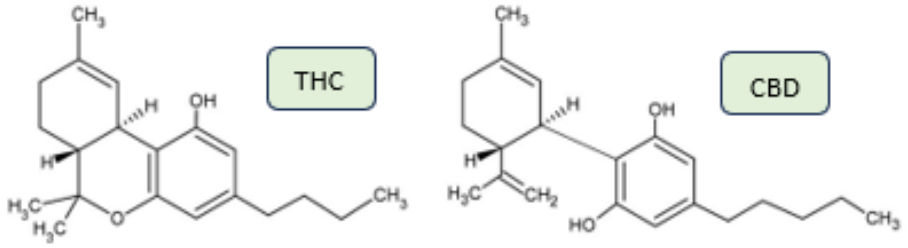


Figure 5. Molecular structure of the two main *C. sativa* L. cannabinoids – THC and CBD.
Adapted image from "Cannabis-Based Products for the Treatment of Skin Inflammatory Diseases: A Timely Review" (MARTINS AM. Et al., 2022)

Most studies focus on THC and CBD, but these are just two of over 140 phytocannabinoids found in the plant in addition to a milieu of terpenoids, flavonoids and other compounds with potential therapeutic activities. (PROCACCIA S. et al., 2022)

Different plants contain a very different array of these metabolites in varying relative ratios, and it is the interplay between these molecules from the plant and the endocannabinoid system in the body that determines the ultimate therapeutic response and associated adverse effects. (PROCACCIA S. et al., 2022).

This distinction is crucial as it highlights the human intervention in developing specific plant traits and characteristics. These genetic differences result in variations in plant morphology, cannabinoid content (e.g., THC and CBD levels), and terpene profiles, leading to different effects and uses.

For medical applications, researchers largely adopt a chemotaxonomic perspective that describes three chemical phenotypes or chemotypes based on the content of two main cannabinoids: psychoactive tetrahydrocannabinol (THC) and non-psychoactive cannabidiol (CBD) (DE MEIJER EPM et al., 2003). THC-dominant strains have a THC/ CBD ratio > 1, intermediate strains have THC/CBD ≈ 1, and CBD-dominant strains have THC/CBD ratio < 1.

Continued exploration of the pharmacological effects and mechanisms of action of individual cannabinoids, including the *major* cannabinoids, THC and CBD, as well as some other *minor* ones such as CBG (Cannabigerol) has showed relevant conclusions.

CBD has been extensively studied for its vast pharmacological properties, knowing that it has the advantage of not having adverse psychoactive effects like THC.

On the skin field, CBD is being investigated for its potential in treating various skin conditions, such as acne, eczema and psoriasis, due to its anti-inflammatory and sebostatic properties, and that subject will be explored in detail during this dissertation.

Many studies have been conducted with an expressive growth, especially during the last decade, to explore the potential medicinal properties of the *Cannabis sativa* L., and particularly the production of the cannabinoids – the active compounds of the plant.

A survey in the period 2012-2022 performed on the Pubmed platform, using the keywords "Cannabis" and "CBD", noticed the exponential growth in interest and scientific study in this area. (Figures 6 and 7, respectively.)

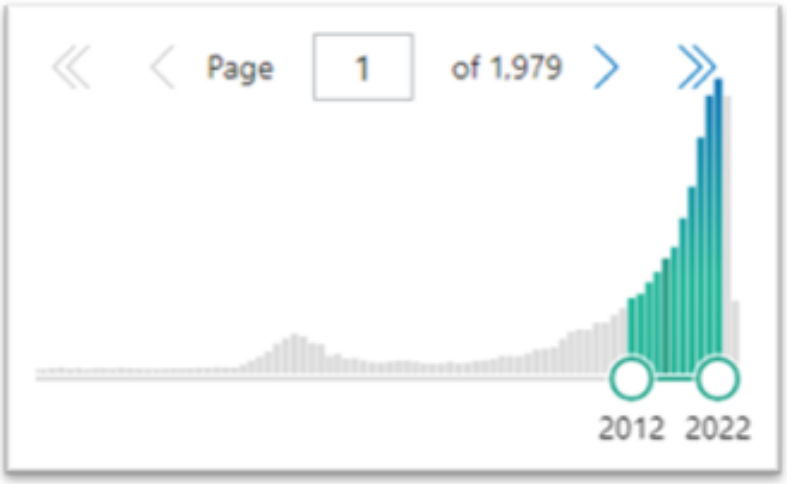


Figure 6 - Publication by Keyword "Cannabis" (2012 - 959 studies; 2022 - 3945 studies), accessed on November 2023. Adapted from www.Pubmed.gov

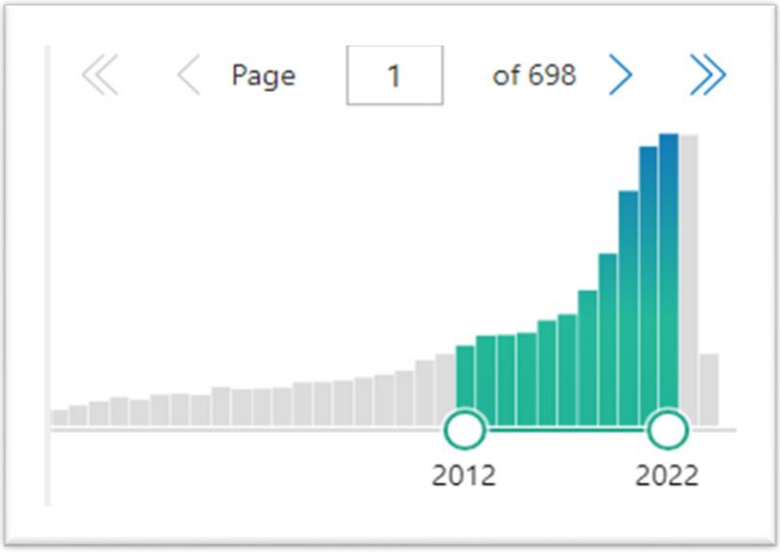


Figure 7 - Publication by Keyword “CBD” (2012 - 365 studies; 2022 - 1398 studies), accessed on November 2023. Adapted from www.Pubmed.gov

4. The endocannabinoid system

The medicinal applications of the *Cannabis sativa* L. plant are closely tied to its interactions with the Endocannabinoid System (ECS) in the human body.

The ECS is a complex structure that was discovered in 1988 by scientists Allyn Howlett and W.A. Devane (KALANT H., 2001; DEVANE W.A., et al., 1988) and plays a crucial role in maintaining homeostasis, in various physiological processes, and for that, it is currently at the center of renewed international research and drug development.

The ECS regulates and controls many of our most critical bodily functions such as learning and memory, emotional processing, sleep, temperature control, pain control, inflammatory, immune responses, and eating.

The ECS plays critical roles in multiple physiological processes, and it offers promising opportunities for the development of novel cannabinoids-based therapeutic drugs that may be designed to target different components and/or cell-signaling pathways of the ECS, which may ultimately be of therapeutic benefit. (LOWE H. et al., 2021)

The two main types of receptors in the ECS are CB1 receptors (CB1R), primarily found in the central nervous system, and CB2 receptors (CB2R), primarily found in the peripheral tissues and immune cells, like it is illustrated in figure 8.

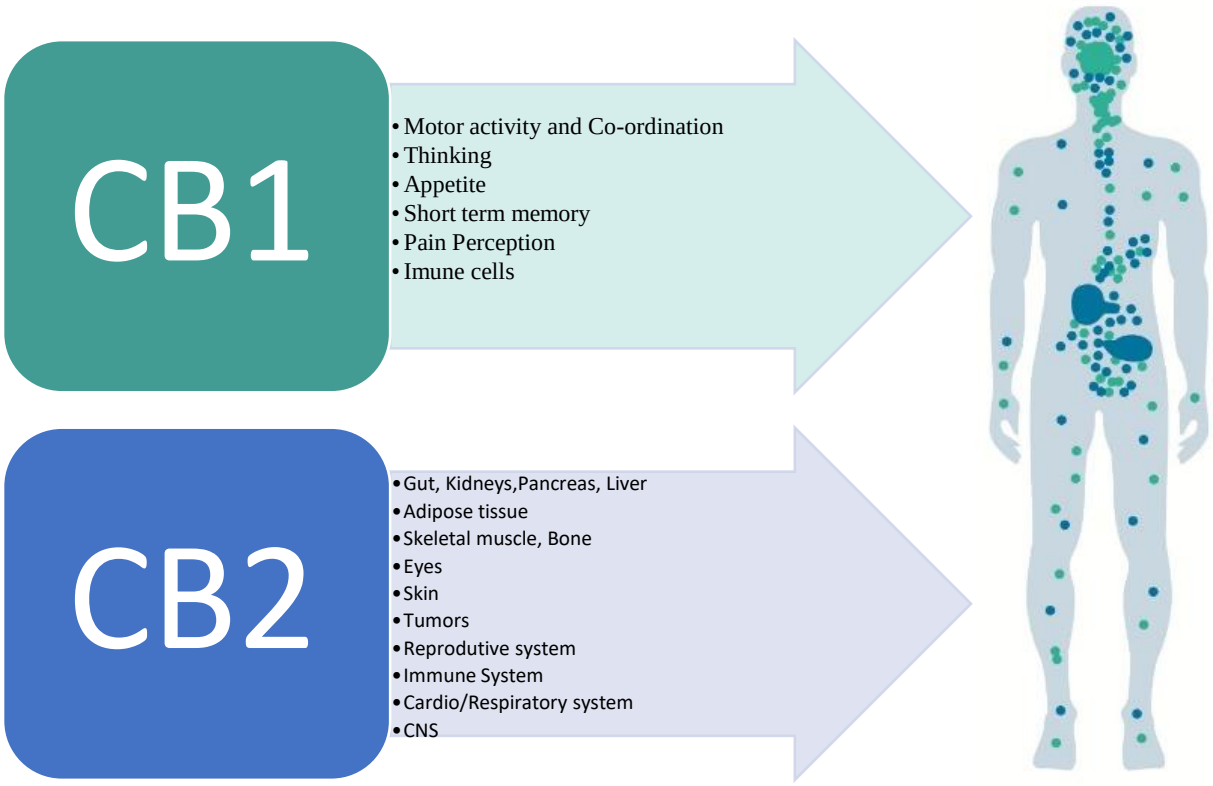


Figure 8: Distribution of CB1 and CB2 receptors over the human body. Adaptation from: https://cdn.shopify.com/s/files/1/0255/7598/1141/t/30/assets/pf-8ccb4e54--CBD101ECSExplained.jpg?v=1596498021, accessed on 12th February 2024

Cannabimimetic drugs such as small-molecule cannabinoid receptor agonists and antagonists may be designed to target the ECS and its enzymes and either enhance the bioactivity or activation of endocannabinoids or inhibit their inactivation (DI MARZO V., et al., 2004; DI MARZO V., 2008).

Understanding the interactions between cannabinoids and the ECS is crucial for harnessing the medicinal potential of the *Cannabis sativa* L. plant. However, it´s important to note that the effects can vary based on individual differences, the specific cannabinoids present, and their concentrations in different cannabis cultivars (LOWE H. et al., 2021).

The ECS comprises a vast network of chemical signals and cellular receptors that are densely packed throughout our brains and bodies. The "cannabinoid" receptors in the brain — the CB1R — outnumber many of the other receptor types on the brain. They act like traffic cops to control the levels and activity of most of the other neurotransmitters. This is how they regulate things: by immediate feedback, turning up or down the activity of whichever system needs to be adjusted, whether that is hunger, temperature, or alertness.

The CB2 receptor, exists mostly in our immune tissues (Figure 9) and is critical to helping control our immune functioning, playing a role in modulating intestinal inflammation, contraction, and pain in inflammatory bowel conditions. CB2 receptors are particularly exciting targets of drug development because they don't cause the high associated with cannabis that stimulating the CB1 receptors does.

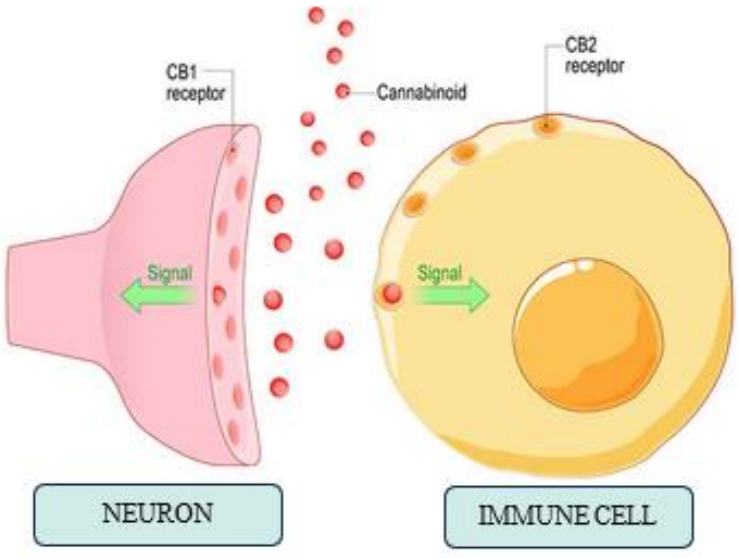


Figure 9 – The cannabinoid interaction between different types of cells, namely Neurons, with CB1 receptors, and Immune cells, with CB2 receptors. Adapted from: https://domf5oio6qrcr.cloudfront.net/medialibrary/11419/conversions/856e427f-4396-41f7-b18e-771c4d02596e-thumb.jpg, Accessed on 12th February 2024.

In recent years, genetic and pharmacological manipulation of the ECS has gained significant interest in medicine, research, and drug discovery and development. It's important physiological and pathophysiological roles offer promising opportunities for the development of novel cannabinergic, cannabimimetic, and cannabinoid-based therapeutic drugs that, genetically or pharmacologically, modulate the ECS via inhibition of metabolic pathways and/or agonism or antagonism of the receptors of the ECS. This modulation results in the differential expression/activity of the components of the ECS – beneficial in a number of diseases (LOWE H. et al., 2021).

4.1 ECS in Human Skin

The skin is our largest organ, and its primary role is as a first line defense against external agents. All components of the ECS are found in the skin (Medical Cannabis Oil for Inflammatory Skin Disease, 2021) as it is illustrated in Figure 10, further establishing the role of the ECS in healthy and diseased skin and general homeostasis (TRUSLER A.R. et al., 2017; DEL RÍO, C. et al., 2016).

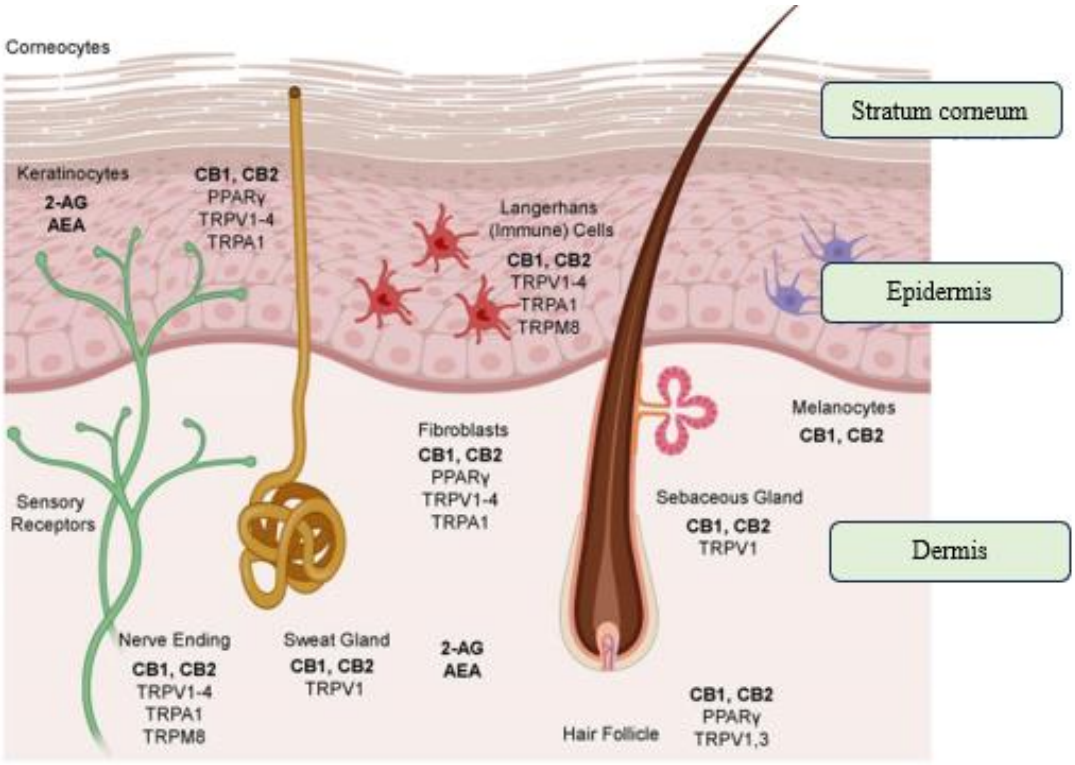


Figure 10. Schematic representation of the key components of the ECS in different cellular compartments of the skin. Adapted from "Therapeutic Potential of Cannabidiol (CBD) for Skin Health and Disorders (BASWAN S., 2020)."

The endocannabinoid system plays an important role in skin homeostasis, and its dysregulation has been linked to dermatologic diseases (TÓTH K.F. et al., 2019).

The discovery of a skin ECS led to the investigation of its role in the functions of this organ, and how disturbances in its regular actions can contribute to the development of pathological skin disorders (BÍRÓ, T. et al., 2009).

Studies with cannabinoid receptors, selective agonists, antagonists, and other regulatory agents that can regulate the levels and actions of endocannabinoids during inflammatory processes have provided extensive evidence on the numerous immunomodulatory and anti-inflammatory effects of the ECS (SHERIFF, T. et al., 2020).

The most well-known endocannabinoids are 2-arachidonoyl-glycerol (2-AG) and anandamide (AEA). They are derived from cell membrane phospholipids and are the natural ligands for their receptors, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) (NIKAN M. et al., 2016). CB1 and CB2 are G-protein coupled receptors that comprise the endocannabinoid system.

The skin's cannabinoid tone constantly affects all compartments of the skin, as endocannabinoids act on various cell types and contribute to their healthy physiological function.

Activation of cannabinoid receptors by endocannabinoids on epidermal cells regulates normal function of the skin as a barrier. Previous studies suggest that both CB1 and CB2 receptors are present in keratinocytes, mast cells, hair follicles, and sensory nerve fibers in the skin. In epidermal keratinocytes, hair follicles, and sebaceous glands, CB1 and CB2 receptors show a complementary distribution pattern (MACCARRONE M. et al., 2003; STÄNDER S.et al., 2005; SAMSON M.T., et al., 2003). When CB1 or CB2 are engaged, these functions of epidermal cells are modified – whether through proliferation, differentiation or apoptosis – which are all important processes for the healthy physical defense of the body. Endocannabinoids also suppress inflammation in the epidermis.

Due to their molecular and structural similarities, phytocannabinoids mimic the effects of endocannabinoids and can therefore act as ECS receptor agonists and consequently regulate skin homeostasis. Novel drugs, such as the CBD-based ones, that increase the activity of the skin's ECS may hold promise for treating inflammatory and immune-related diseases in the skin.

5. The dermatological application of CBD – evidence-based treatments

Inflammatory skin disorders such as acne vulgaris and psoriasis, are a great disease burden globally and may greatly impact an individual's self-esteem, social interactions with others and general quality of life, particularly if accompanied by pain, pruritus and permanent scarring.

Recently, numerous studies have been carried out in the dermatological field in order to discover the real potential of cannabinoids, and more specifically CBD, and the most recent conclusions point to an undeniable efficacy of this compound, and its anti-inflammatory properties have piqued the interest of researchers and clinicians because they represent promising avenues for the treatment of autoimmune and inflammatory skin disorders that may be refractory to conventional therapy.

The anti-inflammatory properties of CBD, suggest that it may have different therapeutic applications against dermatological inflammatory diseases. Due to its immunomodulatory and anti-inflammatory nature, CBD stands out as an innovative and alternative treatment for dermatological diseases such as acne, psoriasis, melanoma among many others, also described in figure 11.

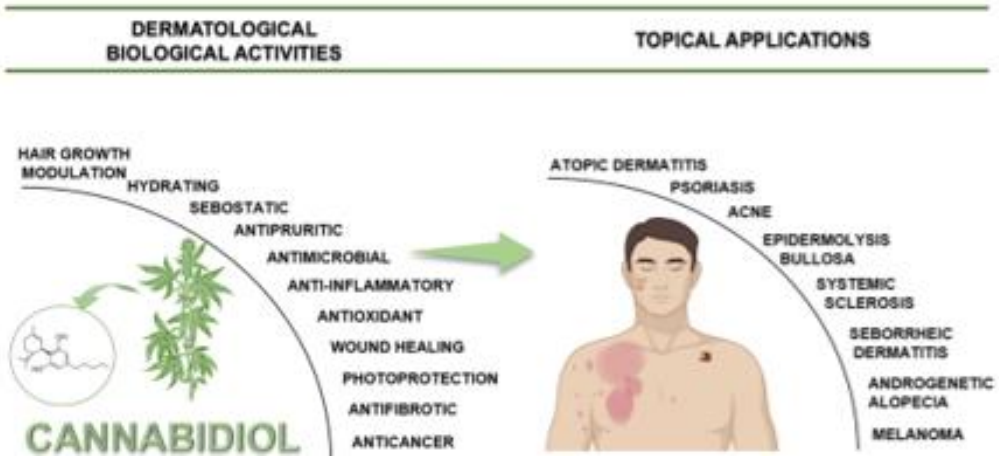


Figure 11: Topical applications of cannabidiol and its delivery systems.

Adapted from: "Skin applications of cannabidiol: sources, effects, delivery systems, marketed formulations and safety" (FERREIRA, BP. Et al 2023); Accessed on 5th March 2024

5.1 ACNE

Acne is a chronic inflammatory cutaneous disorder and is the most prevalent skin disorder, globally. It is characterized by the clogging of oil glands in the skin by oil and dead skin cells, resulting in the formation of pimples. (LOWE H. et al., 2021)

According to many dermatologists and immunologists, CBD inhibits lipid synthesis and induces cell death in human sebaceous gland-derived sebocytes and ultimately may be a safer treatment for acne rather than some traditional drugs used to treat severe acne.

Considering acne as a multifactorial disease, the onset and progression of the disease can be triggered by an interplay of many factors including stress, hormonal and nutritional alterations. (DRENO B et al., 2018; ZAENGLEIN AL et al., 2016).

Pathologically, acne is an inflammatory disease affecting the pilosebaceous units. The pilosebaceous unit consists of the hair follicle and shaft, and sebaceous gland; these sebaceous pores are found on the face, chest, and back. (MARTEL JL et al., 2021; GOLLNICK H et al., 2003). Excess sebum production (hyperseborrhea), abnormal shedding of the cutaneous cells (hyperkeratinization), accumulation of *Cutibacterium acnes* (*C. acnes*) at the pilosebaceous unit, and inflammation are elemental to the disruption of sebaceous gland activity and pathogenesis of acne (Figure 12). (DRENO B et al., 2018; GOLLNICK H et al., 2003; DRENO B. 2017).

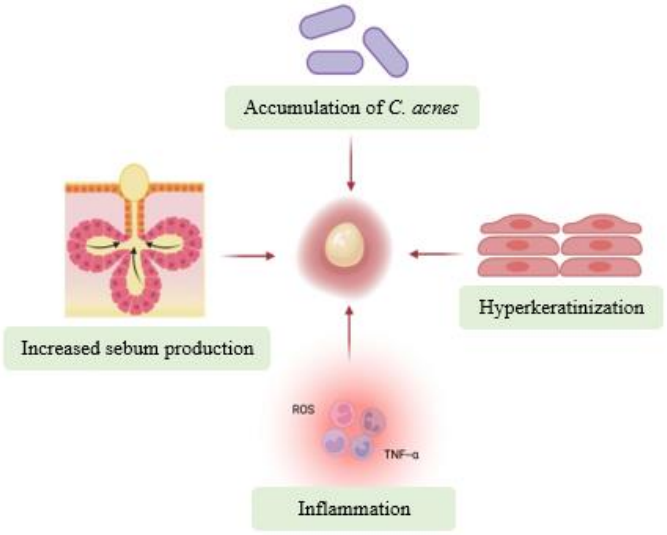


Figure 12. Acne pathogenesis.

Adapted from "The Anti-Inflammatory Effects of Cannabidiol (CBD) on Acne" (PEYRAVIAN N. et al.,2022)

Androgen hormones, particularly testosterone, stimulate sebum production and are linked to the formation of comedones (FOX L et al., 2016). Comedones are formed when the pilosebaceous units become plugged with sebum and can be classified as open comedones (blackheads) or closed comedones (whiteheads). Follicular hyperkeratinization occurs when cutaneous cells that line the sebaceous follicle, primarily keratinocytes, do not become cohesive with one another, resulting in rapid shedding of these cells, and subsequent microcomedone formation (THIBOUTOT DM., 2000). Colonization of *C. acnes* at the sebaceous follicle may also lead to comedogenesis and subsequent presentation of acne. *C. acnes*, formerly termed *Propionibacterium acnes* (*P. acnes*), is a gram-positive anaerobic commensal bacteria found as part of the skin's microbiota in all individuals to maintain skin homeostasis. (DRENO B et al., 2018; PLATSIDAKI E et al., 2018).

However, colonization of *C. acnes* at the pilosebaceous units, particularly in areas densely packed with sebaceous follicles that harbor a lipid-rich environment, is a pathological hallmark of acne. (FOX L et al., 2016) While *C. acnes* is present cutaneously in all individuals, the onset of

acne is dependent on individual immunological responses to the bacteria, triggering the formation of comedones and the release of inflammatory mediators (FOX L et al., 2016).

Detection of *C. acnes* initiate an inflammatory response by the immune system, triggering the release of inflammatory cells, such as lymphocytes and neutrophils, and their subsequent release of inflammatory chemicals, such as reactive oxygen species (ROS) and tumor necrosis factor-alpha (TNF-α) (KUROKAWA I et al., 2009). Consequently, these inflammatory mediators contribute to the inflammation and the subsequent chemical insult to the follicle epithelium and proximate dermis (FOX L et al., 2016; AKAMATSU H et al., 2003).

CBD has been suggested as a promising therapeutic agent for the treatment of acne vulgaris since it normalizes the lipogenesis of sebocyte cells (lipostatic effect, without compromising cell viability), decreases the proliferation of these cells (antiproliferative effect, without inducing sebocyte apoptosis) and decreases the levels of pro-inflammatory cytokines (anti-inflammatory effect) (OLÁH A., et al., 2014). It is interesting that CBD has an opposite effect to that of ECBs. While ECBs stimulate the lipid synthesis in SGs via the ‘classical’ signaling pathway involving CB2 receptors, CBD exerts a sebostatic (lipostatic and antiproliferative) action by activating TRPV4 receptors (RÍO C.D. et al., 2018; OLÁH A., et al., 2014).

CBD and Acne

In a study evaluating the effects of cannabidiol on human sebaceous glands, CBD was evaluated in the context of immortalized human sebocytes under "acne-like" conditions (OLAH A. et al., 2014). In this study, CBD was shown to dose-dependently inhibit excessive lipid synthesis (lipogenesis) in sebocyte cultures that were pre-treated with "pro-acne" inducing inflammatory compounds such as arachidonic acid, linoleic acid, and testosterone (OLAH A. et al., 2014). The anti-inflammatory effects of CBD were also observed in the reduction of inflammatory cytokine, TNF-α. Lipopolysaccharides (GOTTLIEB JF., et al., 2019) were used to pre-treat sebocytes to induce "pro-acne" inflammatory conditions. Subsequently, TNF-α concentrations in sebocytes were measured after 24 h with or without CBD (10 μM). Treatment with CBD was found to decrease TNF-α mRNA expression and the expression of other inflammatory cytokines including, IL-1β and IL-6 in the sebocytes (OLAH A. et al., 2014). Results from this study strongly demonstrate the clinical potential of CBD in the treatment of acne.

In another study, Dobrosi et al. (DOBROSI N. et al., 2008) performed in vitro studies using cultured human SZ95 sebocytes and observed the presence of AEA and 2-AG in the cultures, and that the cells expressed CB2 receptors but not CB1 ones. The ECBs increased lipid synthesis in a dose-dependent manner by upregulating genes involved in this process. Additionally, 2-AG and AEA induced apoptosis-driven cell death. These actions were mediated by selective CB2-coupled signaling using the MAPK pathway. The authors suggested that agents that suppress the local output of these ECBs in the ailing SGs (e.g., DAGL inhibitors), and/or that inhibit CB2R on the sebocytes (CB2R antagonists), have therapeutic potential in the management of acne and seborrhea.

Additional in vitro studies using human sebocytes and human skin organ cultures (hSOC) provided evidence that CBD inhibited the lipogenic actions of several compounds (e.g., AA, combination of linoleic acid and testosterone), and suppressed the proliferation of human sebocytes (OLÁH A., et al., 2014). The authors used hSOC to mimic the SG (sebum gland) function *in vivo* and showed that CBD completely inhibited the lipogenic action of AEA in these experimental conditions. In pharmacological terms, CBD inhibited the AEA-induced prolipogenic ERK1/2 MAPK pathway by activating the transient receptor potential vanilloid-4 (TRPV4) ion channel. Gene expression

studies showed that this led to the downregulation of genes related to lipid synthesis (NRIP1), which affects glucose and lipid metabolism, thus inhibiting sebocyte lipogenesis. Furthermore, it was observed that CBD had anti-inflammatory effects that seem to occur via upregulation of tribbles homolog 3 (TRIB3) and inhibition of NF-κB signaling, both dependent on the A2a adenosine receptor. The combined lipostatic, antiproliferative (TRPV4-dependent) and anti-inflammatory (A2a adenosine receptor-dependent) actions suggested CBD as a possible therapeutic agent for acne.

5.2 PSORIASIS

Psoriasis is an autoimmune inflammatory hyperproliferative skin disease, notable for the manifestation of lesions (‘scales’) that develop within the epidermis, originated by an extremely fast turnover of epidermal keratinocyte proliferation, accompanied by the infiltration and increased expression of proinflammatory mediators into the skin. (MARTINS A. et al., 2022)

The incidence of which is constantly increasing and affects 2–4% of the world’s population, depending on the country, with about 1% affecting children and adolescents (CHOVATIYA R., 2019; FRIEDLAND R., et al., 2022).

Psoriasis is characterized by up-regulation of the keratins K6 and K16 (MACCARRONE M. et al., 2003). Psoriasis is also accompanied by increased keratinocyte proliferation and differentiation (FRIEDMAN A., 2019), that is the result of dysregulation of Th1 and Th17 immune cells in the skin, T-cell infiltration, neutrophil infiltration, and activation of dendritic cells and macrophages (MUÑOZ E., 2021; EAGLESTON L. et al., 2018). This suggests that, as cannabinoids regulate Th1 and Th17 immune cells in the skin, the ECS might be a promising therapeutic target for psoriasis (DERAKHSHAN N. et al., 2016). The endocannabinoid AEA, and the CB1R-specific agonist, arachidonoyl-chloroethanolamide (ACEA) are also shown to inhibit epidermal differentiation and the proliferation of epidermal keratinocytes (immature skin cells) (MACCARRONE M. et al., 2003; RAMOT Y. et al., 2013) via downregulation of the expression of keratins K6 and K16 in vitro and in vivo (RAMOT Y. et al., 2013). In immortalized human keratinocytes (HaCaT) and normal human epidermal keratinocytes (NHEK), AEA demonstrated inhibition of cornified envelopes, characteristic of keratinocyte differentiation (MACCARRONE M. et al., 2003). The anti-inflammatory properties of AEA may also be due to its ability to inhibit cytokines produced by keratinocytes (MANGKORNTONGSAKUL V. et al., 2020). These immature skin cells are characteristic of psoriasis (MACCARRONE M. et al., 2003; MORRIS S.Y., 2019). This mechanism of action is via the activation of the CB1R, which inhibits human hair growth and decreases proliferation of epidermal keratinocytes (MACCARRONE M. et al., 2003).

The development of psoriasis is associated with the action of environmental factors (bacterial or viral infections, trauma, stress) mainly on genetically predisposed individuals (strong correlation with some histocompatibility complexes, such as HLACw6 or HLACw7), which leads to the activation of immune cells (GRIFFITHS C.E.M. et al., 2017; KANTOR R. et al., 2017; RENDON A. et al, 2019), resulting in chronic inflammation within most skin cells and metabolic changes throughout the whole organism. Consequently, in addition to the changes typical for Psoriasis vulgaris (PsV) (CANNAVÒ S.P. et al., 2019), 6–42% of patients with PsV develop Psoriatic arthritis (PsA), which is a progressive disease of the joints (FELQUER M.L.A. et al., 2021). The characteristic clinical features of PsA include concomitant psoriatic skin lesions with accompanying pain, stiffness and swelling of the joints with limited mobility (MEASE P.J. et al., 2014).

CBD and Psoriasis

The cutaneous ECS inhibits cell growth and angiogenesis, leading to skin cell apoptosis (BÍRÓ T. et al., 2009), thus it is not unexpected that cannabinoids have shown promising results in helping to treat psoriasis.

The inhibition of keratinocyte proliferation by diverse cannabinoids (THC, CBD, CBN and CBG) was reported by Wilkinson et al. (WILKINSON J.D. et al., 2007) in an in vitro study using a hyper-proliferating human keratinocyte cell line.

The results showed proliferation inhibition in a concentration dependent manner, independent of CBR activation, with the authors suggesting a mechanism involving the PPAR receptor.

A later study (RAMOT Y. et al., 2013), reported a different inhibitory mechanism, occurring through downregulation of keratins K6 and K16 expression by CB1R activation. The in-situ studies used organ-cultured human skin and showed that stimulation with a CB1R specific agonist decreased expression of the keratins, which are upregulated in psoriatic skin. A similar result was

obtained in in vitro studies using human HaCaT keratinocytes, with the CB1R agonist decreasing the expression of K6 at the transcription and translation levels. Cannabinoids may also be promising in psoriasis therapeutics due to their anti-inflammatory effects.

Namazi (NAMAZI M.R., 2005) reported that cannabinoids inhibited antigen processing in macrophages, macrophage/T-cell interaction, and release of pro-inflammatory cytokines (IL-2 and TNF-α) and nitric oxide from immune cells. Since psoriasis is characterized by a type 1 cytokine pattern (where IFN-γ, IL-2, IL-1 and TNF-α are predominantly expressed), which occurs following the presentation of the antigen to CD4+T lymphocytes and resulting in stimulation of keratinocyte proliferation and expression of adhesion molecules, the authors hypothesized that CNBs could have therapeutic efficacy against psoriasis, given their inhibitory effect of the inflammatory mechanisms.

Derakhshan and Kazemi (DERAKHSHAN N. et al., 2016) also suggested a possible therapeutic action of CNBs in psoriasis due to their keratinocyte antiproliferative action and the anti-inflammatory role due to vagal nerve stimulation followed by acetylcholine release and immunomodulation via inhibition of TNF-α production by cytokine-producing macrophages (EAGLESTON L.R.M. et al., 2018; DERAKHSHAN N. et al., 2016).

Still related to the antiproliferative and anti-inflammatory actions of CNBs, it was reported that the gene NRIP1, which was previously shown to be an important target gene of CBD (with lipogenic effect in acne and seborrhea disorders), was overexpressed in psoriatic skin, and that its downregulation in HaCaT keratinocytes significantly suppressed their proliferation. Furthermore, the inhibition of NRIP1 also reduced the expression of p65 NF-κB and the release of IL-17, thus suggesting that NRIP1 may be a multifaceted therapeutic target in psoriasis (LUAN C. et al., 2016).

Additionally, in the previously discussed study of the pathology of acne and seborrhea (OLÁH A. et al., 2014), it was reported that, in cultured human sebocytes, CBD negatively regulated

NRIP1 in a TRPV4-dependent pathway. Therefore, it can be hypothesized that CBD exerts its anti-inflammatory effects on psoriasis via the activation of the same signaling pathway (TÓTH K.F. et al., 2019). Norooznezhad et al. (NOROOZNEZHAD A.H. et al., 2017) suggested targeting angiogenesis, another process involved in psoriasis pathogenesis, with the synthetic cannabinoid JWH-133. This molecule has antiangiogenic and anti-inflammatory properties, inhibiting the production of several angiogenic growth factors (e.g., HIF-1 α, VEGF, MMPs, and bFGF) and cytokines (e.g., IL-8 and IL-17), thus it can target two main features of psoriasis pathogenesis, inflammation and angiogenesis. A few clinical studies have been reported for the treatment of psoriasis with cannabinoids.

In 2019, a patent was launched for the treatment of psoriasis with the application of different topical formulations (ointment, gel, liquid, spray, and powder) containing cannabinoids, mainly CBD and CBG (natural or synthetic), in concentrations of 3–20% (see Table 1). The application of the formulation in the affected areas led to a dose-dependent improvement in psoriasis, while controls that received placebo oil showed no improvement. The authors suggested a possible T cell (Th1 and Th2) rebalancing mechanism, as well as a direct CBG inhibition of keratinocyte proliferation (CHANGOER L., 2019).

In summary, these findings do support a potential role for CNBs, for CBD, on the treatment of psoriasis, possibly involving a combination of their antiproliferative, anti-inflammatory and antiangiogenesis properties.

This possibility is highly relevant, since antipsoriatic medications are often associated with adverse side effects (MARTINS A.M. et al, 2020), and so, an ongoing search for safer agents that can be used alone or in combination with current antipsoriatic drugs is imperative. The following table summarize some clinical trials developed with CBD alone or combined with CBG (a *minor* cannabinoid) in the treatment of Acne vulgaris or Psoriasis vulgaris.

Table 1 - The use of Phytocannabinoids in clinical trials. Adaptation from "Phytocannabinoids in the Pharmacotherapy of Psoriasis" (Wronski A., et al., 2023)

Phytocannabinoids	Test Products/ Time of application	Method of Application	Skin problem	Total Participants	Effects of the Preparation	Suggestion for treatment	Date of publication
CBD+CBG oil	3-20% 3 and 15% 2:1 Ratio/ Twice a day/ 6 Weeks	Topic	Psoriasis Vulgaris	2	Reduction of psoriatic lesion	Psoriasis Vulgaris	2019 Patent number: US20190060250A1
CBD	5% CBD Solution Twice a day/ 84 days	Topic	Acne Vulgaris	368	Reduction of acne lesion	Acne Vulgaris	2022
Synthetic CBD (BTX1503)/Permetrex TM Patent	5% CBD (14 and 28 days / twice a day)	Topic	Acne Vulgaris	20 healthy volunteers and 23 with moderate to severe acne	Anti-acne effect	Acne Vulgaris	2018

Skin diseases like psoriasis and acne are challenging to treat, have a significant impact on patients' quality of life, and assume high costs in the long term throughout the entire life. With annual costs of over EUR 30 billion per year in Europe and USD 5.3 billion in the USA and treatments that are trying to modulate the microbiome or innate immune response (HOUSE, W. et al. 2022). Psoriasis affects an estimated 60 million people worldwide, with country-specific prevalence being more common in high-income areas and among the elderly. (RAHARJA, A. et al. 2021)

Psoriasis, with annual costs of over USD 11.5 billion in 2008 alone in the United States, might impose a significant economic burden on taxpayers, patients, and society in general due to its high prevalence and significant direct and indirect costs. (MICHALEK, I.M. et al. 2019) Psoriasis remains a challenge for medical systems worldwide, with expensive treatments that have short-term effects or a high number of side effects (NAIR, P.A. et al. 2023) and these are only a

few examples of skin conditions that are a challenge for medical systems worldwide. The skin, as a therapeutic target for phytocannabinoids, represents a vast research area that has not received enough attention.

In the case of both acne and psoriasis, millions of people are affected worldwide. These are diseases that, in the case of acne, can be treated, and regarding psoriasis, there is a control of the disease, but no definitive treatment is yet known.

In addition, there is a considerable range of adverse effects of the drugs used in the treatment of these two diseases, and their cost is quite high.

Phytocannabinoids, more specifically CBD, should be seen as an effective, safe and more accessible therapeutic alternative in these diseases.

The Table 2 summarizes the current treatments available for Psoriasis and Acne, as well as their adverse events and related costs, that could be minimized considering a therapeutic alternative such as CBD.

Table 2 - Current treatments available for Psoriasis and Acne, their adverse effects and related costs. (Adapted from Silviu-Iulian Filipiuc et al. 2023 – "The Skin and Natural Cannabinoids – Topical and Transdermal Applications".)

Estimative Costs around the Current Course of Therapy	Current Drug Therapies		Adverse Effects (Most significant)
Psoriasis (Between USD 23.9 and USD 35.4 billion annually in the US	Topical agents	Vitamin D analogues/ corticosteroids	Poor therapy response
	Phototherapy	NB-UVB PUVA	Major risks of skin cancer
	Standard systemic	Acitretin Ciclosporin	Dry skin, hair loss, hyperlipidemia, hepatotoxicity hypertension, irreversible renal toxicity
		Methotrexate	Bone marrow suppression, liver fibrosis, teratogenicity, hepatitis
	Biologic Agents	TNF IL-17 L-23 inhibit	Individualized therapy regimen
	Small molecule inhibitors	Apremilast dimethyl fumarate	Used only in studies
Acne (acne is thought to cost the economy USD 3 billion annually)	Topical retinoids	Adapalene, isotretinoin, motretinide, retinoyl-β-glucoronide, tazaroten, tretinoin	Used in various combinations, all of these topical treatments disrupt the skin's natural barrier, requiring frequent treatment changes
	Topical antibiotics	Clindamycin, erythromycin	Disruption of the skin's natural barrier
	Diverse topical agents	Azelaic acid, benzoyl peroxide, chemical peels, corticosteroids, dapsone, hydrogen peroxide, niacinamide, salicylic acid, sodium sulfacetamide, sulfur triclosan	Specific adverse events
	Systemic retinoids	Isotretinoin	Hematological/lymphatic disorders, immune system disorders, metabolic and nutritional disorders
	Systemic antibiotics	Azithromycin, clindamycin, co-trimoxazole, doxycycline, erythromycin, levofloxacin, minocycline, roxithromycin	Specific adverse events
	Other systemic agents	Hormones, clofazimine, corticosteroids, ibuprofen, zinc sulfate	Specific adverse events

5.3 MELANOMA

Melanoma is one of the most aggressive malignancies in humans. Recently developed therapies improved overall survival rate. However, the treatment of melanoma still remains a challenging issue.

In addition to anti-inflammatory effects, cannabinoids interact with the ECS components of the skin to produce antipruritic, anti-ageing, anti-cancer (SHERIFF T. et al., 2020), and antinociceptive effects (NICKLES M.A. et al., 2020).

The knowledge about the role of cannabinoids in health and disease is still progressing. Due to encouraging results of application of the cannabinoids in various cancers and their relatively low toxicity, they began to gain interest in the field of melanoma treatment. There are couple of factors that impact the signaling of cannabinoids. They are exerting their actions through various signaling pathways, not only by widely described CB receptors.

Multiple receptors affected by CBD and various mechanisms take part in modulation of oncogenic signaling and redox homeostasis (AFRIN F et al., 2020), as it can be illustrated on the Figure 13. Recent study presents beneficial therapeutic effect of CBD in a murine model. The administration of CBD in mice with injected subcutaneously melanoma caused significant extension of survival time and decrease in tumor growth compared to the control animals without treatment (SIMMERMAN E et al., 2019). The combination of THC with CBD causes stronger inhibition of cell viability in both in vitro and in vivo studies (ARMSTRONG JL et al., 2015).

The findings indicate that cannabinoids, and in particular CBD, induce apoptosis, necrosis, autophagy, cell cycle arrest and exert significant interactions with tumor microenvironment.

CBD should be rather considered as a part of multi-targeted anti-tumor therapy instead of being standalone agent.

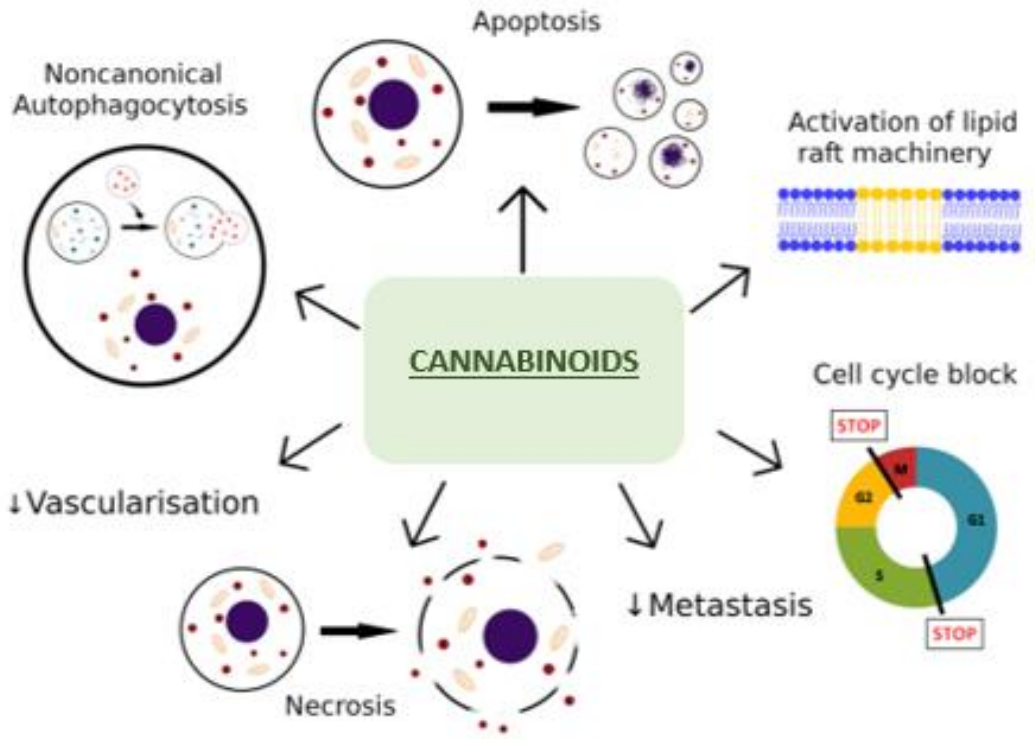


Figure 13 – Summary of destructive mechanisms of actions exerted by cannabinoid on melanoma.

Adapted from "Cannabinoids and their derivatives in struggle against melanoma" (MARZEDA P. et al., 2021)

6. Medicinal application – The prescription challenge

Medicinal cannabis and its major cannabinoids are gaining momentum for various medical purposes as their therapeutic qualities are becoming better established.

General practitioners are faced with the pressing need to help patients manage chronic and debilitating conditions (LYNCH ME et al., 2015). Many patients do not respond well to mainstream treatments for serious symptoms of illness.

With recent changes to legislation around medical cannabis and media coverage creating a perception of easy access, general practitioners may experience greater patient demand to prescribe cannabis-based medications.

Prescribing always presents challenges in balancing patient-centered care, evidence-based practice, and the legislative requirements, particularly where there is potential for misuse of medicines (Royal Australian College of General Practitioners, Prescribing drugs of dependence in general practice, Part A).

During the development of this thesis, it's been demonstrated the importance of CBD on the treatment of various dermatological conditions. However, there is a need to evaluate the quality, safety, efficacy and economic relevance of this therapeutic alternative compared to pharmacological solutions currently available on the market.

Also, raising awareness among the medical community should be a point of focus – in addition to drug development, there is a need to educate providers.

According to Friedman, a survey data of 531 dermatologists and allied health professionals suggests that most providers are open to the exploration of cannabinoids for the treatment of various skin diseases (94%) and were willing to prescribe topical cannabinoids to patients to patients (91%) (Robinson ES. Et al. 2018).

Nearly half of providers (47.5%) particularly those younger than 35 years, reported concerns about the negative perception of prescribing cannabinoids.

One concerning finding from survey was 64% of responders were not aware that CBD is not psychoactive and 29% did not know THC is psychoactive.

Providers recommending cannabis will need some form of education on the benefits, harms, and risks associated with cannabinoids, like other therapies, to ensure that patients are aware of all potential outcomes and can be informed when selecting cannabinoid-based products at dispensaries. (Robinson ES. Et al. 2018)

7. The Regulatory paradigm

It is undeniable that cannabis plant and its chemical main compounds such as CBD and THC, brings benefits in several therapeutic areas. Also, for this reason, the fact that the science surrounding cannabis has evolved exponentially in recent years reflects the importance of this matter. Despite this, there is currently a diversity of procedures and governing patterns, regarding this topic.

The legal status and regulatory frameworks for cannabis vary significantly around the world, leading to non-uniformity in laws and policies.

Some key factors contributing to this inconsistency can vary across the legalization status, where some countries have fully legalized cannabis for both medicinal and recreational purposes, while others only allow medical use, or, others maintain strict prohibition. This divergence can impact on how cannabis is regulated and acceded, creating significant differences.

Even within countries that permit medicinal cannabis, the regulations surrounding its cultivation, distribution and use can vary widely. Some jurisdictions have robust medicinal cannabis programs with extensive regulations, while others have more limited access or less stringent oversight.

For countries that have legalized recreational cannabis, like Germany, there can be substantial differences in the regulatory frameworks governing its production, sale, possession, and consumption. These variations may include restrictions on advertising, packaging requirements, age limits and allowable quantities.

Some countries, like Belgium and Austria, have opted for decriminalization rather than full legalization, which typically involves reducing or eliminating criminal penalties for possession of small amounts of cannabis for personal use. However, the specifics of decriminalization laws can vary, including the thresholds for possession and the associated penalties.

On the other side, cultural and societal attitudes toward cannabis play a significant role in shaping legislation and regulation. Countries with governments with more permissive approaches

towards drug use, may have more lenient laws, while those with more conservative views may maintain stricter prohibitions.

Within larger countries or regions, there may be further non-uniformity in cannabis laws at the sub national level – Regional Disparities. For example, in the United States, cannabis laws can vary significantly between states, with some legalizing both medical and recreational use, while others doesn't allow any kind of use.

Many countries are signatories to international obligations and drug control treaties, such as the United Nations Single Convention on Narcotic Drugs. These treaties can influence domestic cannabis policies and limit the extent to which countries can liberalize their laws without violating international obligations.

Overall, the non-uniformity of cannabis laws around the world reflects the diverse approaches that different countries and regions take in response to complex social, economic and political factors.

Regardless of the specific regulatory framework, there are common challenges in implementing cannabis legislation, such as establishing quality control standards, preventing diversion to illicit markets, ensuring public health and safety, and addressing social equity concerns. As a result, regulatory frameworks often evolve over time in response to emerging evidence, public opinion and practical considerations.

8. Current regulatory worldwide pattern

Legalization of Cannabis on the biggest worldwide players

In recent years, cannabis and products with cannabis components are one of the "hot topics" in the life sciences industry. Many countries now allow the medicinal use of cannabis to treat numerous conditions. Additionally, more and more countries have recently allowed the recreational use of cannabis. Finally, hemp, for industrial purposes (cannabis grown without mind-altering substances), is another burgeoning industry worldwide.

Some countries still consider cannabis a dangerous illicit substance. Thus, the legal landscape on cannabis and cannabis products is very fragmented and complicated, making it hard to get involved in the cannabis industry (WLG Cannabis Group, 2020).

As cannabis legalization is rising in many countries worldwide, the opinions about its use are split into supporters who believe that cannabis legalization can improve public health, stimulate the economy, and reduce criminal justice expenditure, while critics believe that legalization will increase cannabis use, which may affect health and safety, lower the educational achievement in teens, and increase crime (ZVONAREV V., et al. 2019).

8.1 FDA vs EMA

The FDA/ American Reality:

To date, the FDA has only approved one cannabis-derived drug product (Epidiolex (cannabidiol)) and three synthetic cannabis (dronabinol (Marinol and Syndros) and nabilone (Cesamet) products and did not approve any other cannabis or its derivatives. **Cannabis** is classified in **Schedule I** by the FDA, where substances that have high potential for abuse are restrictively categorized (National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Researc, 2017; TURNER, AR., et al., 2020). Cannabis being in Schedule I increases the complexity for research studies, because all researchers must follow Schedule I research registrations.

In addition, cannabis is a controlled substance, and researchers must obtain it from registered cultivators with the Drug Enforcement Administration (DEA) and licenses from the state-controlled drug authority (TURNER, AR., et al., 2020; MEAD, A., 2019).

Medical use of cannabis and cannabinoids must be supervised by medical practitioners and dispensed by prescription where the drug should be used only when necessary (European Monitoring Centre for Drugs and Drug Additions, 2018).

Although cannabis is federally illegal in the US, nine US states have legalized adult recreational use of cannabis since 2012, and under the nation, there are different status of Cannabis legislation over the United States (Figure 14).

Color	Legal Status
	Recreational and medicinal
	CBD/ low THC
	No public program
	Some form of medicinal cannabis

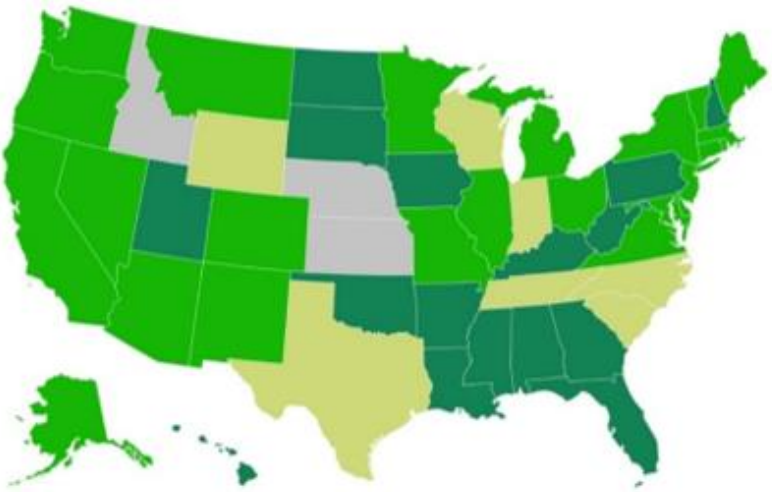


Figure 14 - Legal Status of cannabis in United States of America.
Adapted from: https://www.eupedia.com/europe/legal_maps_of_europe.shtml

The EMA/ Europe Union reality:

Cannabis products have a promising future in the European Union, as many EU countries move to decriminalize cannabis for personal use. The first medicinal cannabis product received EU-wide marketing authorization in late 2019, with cannabis product sales expected to total more than €100 billion by 2028.

Although there are some challenges for international cannabis product manufacturers in the EU market, and the laws regulating cannabis products differ in each EU member state, the regulation of medicinal cannabis, recreational cannabis, and CBD, in the EU market must evolve and assure a uniform regulatory landscape.

8.1.1 Regulation of Cannabis Products for Medicinal Use in European Union (EU)

Rules relating to medicinal cannabis and access by patients to such products vary considerably among EU member states. Each member state determines its own laws in relation to cannabis. This can pose a significant challenge for cannabis companies looking to sell their products in the EU market. Even where a product can be lawfully sold in all or some EU member states, health-care professionals and patients will be restricted in accessing and using the product in accordance with the laws of the individual EU member state.

However, a 2019 decision by the European Medicines Agency marks a shift in the direction of easier market access for some medicinal cannabis products. The EMA is responsible for scientific evaluation, supervision, and safety monitoring of medicines in the EU. The EMA granted the first EU-wide marketing authorization for a CBD-based product in September 2019 to GW Pharma. CBD and THC are some of the components of the cannabis plant being used in medicines.

Prescription medicines must hold a marketing authorization (MA) before the product can be sold and accessed by patients in the EU. Not only does a marketing authorization enable a company to sell and market its product in the EU, it will also grant certain intellectual property protections to the product.

An EU-wide (centralized) marketing authorization is the most beneficial type of authorization, as it enables the product to be marketed in all EU member states, Iceland, Norway, and Liechtenstein.

There are three different routes to obtaining a marketing authorization in the EU: centralized procedure, decentralized procedure/mutual recognition procedure, or national procedure.

Centralized Procedure

The centralized procedure involves a single application to the EMA. Some products are required to apply via the centralized procedure, including all advanced therapy medicines and medicinal products containing new active substances for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases, and orphan medicines intended for the treatment of rare diseases. The centralized procedure is optional for other specific types of medicinal products.

Decentralized or Mutual Recognition Procedure

A product that is not required to obtain a centralized marketing authorization may apply via the decentralized procedure (DCP) or the mutual recognition procedure (MRP). The DCP can be used where the product has not been authorized in any EU country to date. If the product has already been authorized in an EU member state, then the MRP can be used to seek authorization in other EU member states. For both DCP and MRP, a single application is made to one EU member state, which will coordinate the application on behalf of the other member states.

National Procedure

The third way to get a medicinal product authorized in the EU is for a company to apply to an individual EU member state to obtain a marketing authorization, under its national procedures. The national marketing authorization will only be valid in that EU member state.

Authorized Products

GW Pharma's Centralized marketing authorization permits the sale and supply of its CBD-based product Epidyolex in all EEA member states. The product can be used to treat two rare forms of epilepsy and had previously enjoyed orphan status. Medicines used to treat rare illnesses in the EU can apply for orphan status or designation and may be supplied to patients prior to obtaining a marketing authorization in certain circumstances.

Other EU-authorized medicinal cannabis products include Sativex, a medicinal product containing Delta-9 THC and CBD, which holds marketing authorizations in more than 18 EU member states. Sativex is used to treat multiple sclerosis symptoms. Nabilone, which contains synthetic CBD and THC for treating side effects associated with chemotherapy, is currently authorized in the U.K. and Austria. Marinol (Dronabinol), which contains THC, is only authorized in Germany and is used for treating chemotherapy side effects and AIDS-related weight loss.

Some companies are currently permitted to supply medicinal products with the active substance lenabasum (containing Delta-8 THC) to treat a number of conditions including cystic fibrosis, dermatomyositis, and systemic sclerosis, in the EU. The EMA has provided these products with orphan designation.

Notably, some EU member states are facilitating access by patients to products that do not hold a marketing authorization or orphan designation (non-authorized products). For example, in Ireland, currently three cannabis-based products for medical use (Aurora High CBD Oil Drops, CannEpil, and Tilray Oral Solution THC10:CBD:10, 25ml) can be supplied on the Irish market to patients under the Medical Cannabis Access Program.

Cannabis grown for medical purposes is not currently subject to a marketing authorization and is often referred to as medical cannabis as distinct from medicinal cannabis products. Cannabis grown for medical purposes and other purposes is governed by the individual laws of each EU member state. Agencies have been set up in some EU member states that govern the growth and supply of medical cannabis.

Other Regulatory Developments

Marketing authorization applications are likely to increase, as well as the supply of non-authorized products by cannabis companies in the EU. This is due to recent developments:

• Several EU countries have loosened their rules relating to medical cannabis access programs.

• Drug reimbursement programs have been extended to cover medicinal cannabis in some EU member states.

• Insurance companies in Germany, Denmark, and Italy are now covering medicinal cannabis prescriptions.

• Members of the European Parliament adopted a resolution in February 2019 to harmonize EU laws on cannabis for medical purposes. This means that the EU intends to carry out research into cannabis for medical purposes to potentially bringing in rules that would apply in all EU member states. This may simplify matters for cannabis companies placing products on the market as it would potentially avoid diverging approaches by different EU member states.

• The resolution also seeks to improve equal access in all EU member states to cannabis-based medicines and to ensure that where appropriate such medicines are covered by health insurance schemes. The European Parliament also emphasized that EU member states should ensure sufficient availability of cannabis-based medicines for patients where suitable.

• The European Commission subsequently confirmed that scientific research involving medicinal cannabis is on the 2020 EU agenda. It remains to be seen whether the Commission will progress cannabis law reform beyond the research stage.

There is an increasing demand for medicinal cannabis products (both authorized and non-authorized) in European countries and there is a clear lack of suitable cannabis products currently available to EU patients.

This gap in the European market is partially due to the absence of significant clinical studies and scientific evidence bolstering the effectiveness of cannabis as a medicine. This appears

to be the position for both authorized medicinal products and non-authorized products. However, with the projected growth in this industry, pharmaceutical companies will no doubt turn their attention to the potential to develop and exploit cannabis-based medicinal products. This may in turn lead to the availability of clinical study results and scientific research. This will hopefully provide more concrete evidence as to the benefits and uses of cannabis-based medicinal products, prompting EU member states to open their gates to additional cannabis products, making them more accessible to patients.

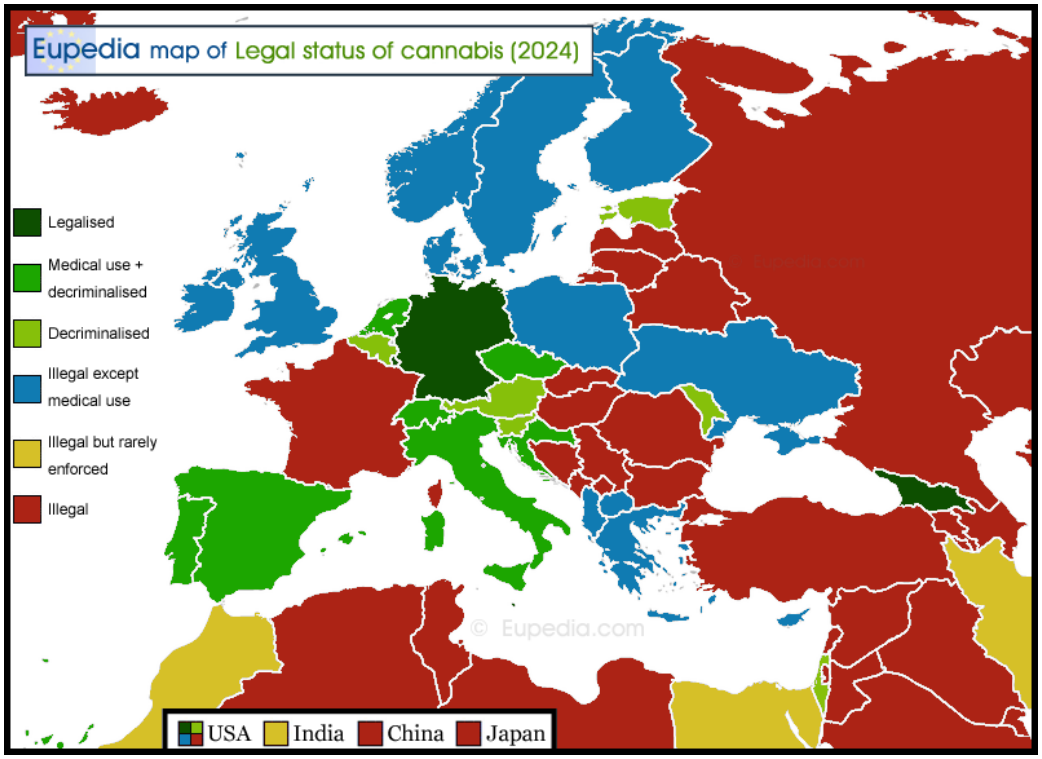


Figure 15 – Legal status of cannabis over the Europe. Accessed on March 2024 (Adapted from www.eupedia.com/europe/legal_maps_of_europe.shtml)

Perspective of European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

Complicating an already challenging policy landscape is the fact that cannabis products are becoming increasingly diverse, including extracts and edibles (high-THC content) and **CBD products**. A report from EMCDDA describes how developments are, not only taking place in the area of cannabis as a recreational drug but are also extending to the regulation of cannabis and cannabinoids for industrial, therapeutic, food or cosmetic uses.

In December 2020, following a recommendation from the World Health Organization (WHO), the UN Commission on Narcotic Drugs voted to reclassify cannabis under international law. While cannabis and cannabis resin remain under Schedule I of the 1961 UN Single Convention on Narcotic Drugs (meaning that they remain under strict international control), they were removed from Schedule IV (which lists drugs that are considered most dangerous and of little or no therapeutic benefit).

All policy approaches to drug control bring with them both potential costs and benefits. However, understanding their key objectives, quantifying the costs and benefits accordingly, and measuring change over time, calls for a robust evaluation framework, including baselines. This report reviews the elements necessary to support this process. More monitoring and research are also needed to understand the impact of policy changes on population health, crime and public safety. The EMCDDA will continue to monitor closely cannabis use, supply and policies, and provide sound information on cannabis-related issues to inform evidence-based policy and practice.

Perspective of the International Narctics Control Board (INCB)

The INCB is the independent and quasi-judicial monitoring body for the implementation of the United Nations international drug control conventions.

According to the latest report of the INCB launched in March 2023, “Legalizing the use of cannabis results in higher consumption and lowers risk perception”. The most concerning effect of cannabis legalization is the likelihood of increased use, particularly among young people, according to estimated data. In the United States, it has been shown that adolescents and young adults consume significantly more cannabis in federal states where cannabis has been legalized compared to other states where recreational use remains illegal. There is also evidence that general availability of legalized cannabis products lowers the perception of risk and of the negative consequences involved in using them. New products, such as edibles or vaping products marketed in appealing packaging have increased the trend. INCB finds that this has contributed to a trivialization of the impacts of cannabis use in the public eye, especially among young people.

INCB President Jagjit Pavadia said: "The expanding cannabis industry is marketing cannabis-related products to appeal to young people and this is a major cause for concern as is the way the harms associated with using high-potency cannabis products are being played down.”

8.1.2 Regulation of Cannabis Products for <u>Recreational Use</u>

The recreational cannabis industry in the EU is expected to grow to €65 billion by 2028. Nonetheless, there are considerable divergences among EU member states in relation to the lawfulness of recreational cannabis. Currently the following European countries (including non-EU members) have decriminalized to some degree/ eased criminal penalties relating to cannabis for recreational/personal use: Austria, Belgium, Cyprus, Czech Republic, Croatia, Estonia, France, Ireland, Italy, Luxemburg, Malta, Moldova, Netherlands, Portugal, Slovenia, Spain, Switzerland, and the U.K. On 1st April 2024, Germany has been the first European county that has legalized the recreational use of Cannabis.

<u>The European Monitoring Centre for Drugs and Drug Addiction</u> has stated that there is no objective test for de-criminalization, so it is difficult to definitively say which countries have

decriminalized the recreational use of cannabis. Certain EU countries have introduced personal possession limits, but there is little consistency in the limits they set, leaning to diverging laws, penalties, and attitudes from country to country.

The Single Convention on Narcotig Drugs 1961 and subsequent amending treaties classifies certain cannabis products (depending on the part of the plant) as controlled substances. Historically, individual EU countries have formulated their own national legislation dealing with controlled substances based on the international treaties.

The World Health Organization (WHO) in June 2019 recommended that whole plant marijuana as well as cannabis resin to be reclassified under the Treaty and removed from Schedule 4. Further, it recommended that THC and its isomers be listed under Schedule 1 of the 1961 Convention. This would essentially downgrade such elements of the cannabis plant to the less serious category and therefore could result in the loosening of laws in countries that are signatories to the Convention.

The WHO has also stipulated that CBD and CBD-focused preparations that have no more than 0.2% THC are not under international control. CBD is not currently listed as a controlled substance under the International Conventions. WHO is requesting that this must be made clearer. The U.N. Commission was due to hold a vote on the WHO submissions at the Commission on Narcotic Drugs in March 2020, but the Commission delayed this vote until Dec. 2020. It is apparent that there are numerous opposing views to adopting the WHO recommendations among different countries.

8.2 – BIGGEST WORLDWIDE PLAYERS

- *Australia*

Although there are some regulatory differences among the federal states regarding the importation of products, and the qualification required to write a prescription, medical Cannabis may be prescribed after receiving authorization from the Therapeutic Goods Administration (TGA), through the Special Access Scheme for an individual patient, or through the Authorized Prescriber Scheme for a group of patients with the same condition. Products of industrial origin are exempt from these schemes as approval for sale has already been granted (Sativex® and Epidiolex®). As well as Sativex® and Epidiolex®, indicated for the treatment of spasticity in multiple sclerosis and pediatric epilepsy, herbal Cannabis based products may also be prescribed. The most common conditions are spasticity in multiple sclerosis, nausea or vomiting caused by anti-tumoral chemotherapy, pain or anxiety in patients with terminal diseases, and refractory child epilepsy. The physician may in any case write a prescription for pathologies other than those indicated. Pharmacies are authorized to dispense medical Cannabis based products. The cost of the therapy is not subsidized by the government. (BARATTA F., et al., 2022; Alcohol and Drug Foundation, 2021; Australian Capital Territory Government, 2021; Australian Government, 2017a; Australian Government, 2017b; Australian Government, 2018; Australian Government, 2020; Australian Government, 2021; Australian Institute of Health and Welfare, 2019; CASTLE, et al., 2019; Centre for Medicinal Cannabis Research and Innovation, 2021; Health Direct, 2019; MERSIADES, et al., 2019; The Health Products Regulatory Authority, 2017; The Office of Drug Control, 2021)

- *Brazil*

Various products of industrial origin are available such as Epidiolex® and Sativex®, and the importation of Cannabis derived products is generally authorized. However, the importation of the raw plant or parts of the plant is not permitted. Products with a concentration of THC greater than 0.2% may only be prescribed when no alternative therapy is available, and the patient has reached the irreversible or terminal stage of their disease. Prescription is under the responsibility of the prescribing medical doctor. The medication may be taken either orally or by inhalation. The

cost of the treatment is generally high and is completely at the patient's expense. The dispensation may take place in a pharmacy, where Cannabis may not be processed, however. (BARATTA F., et al., 2022) (CRIPPA, et al., 2018; Marketrealist, 2019; Ministério da Saúde, 2019; Reuters, 2019; Brazilian Government, 2021)

- *Canada*

The situation in Canada is quite different, medical Cannabis (except for approved industrial products) is not considered as a medicine; hence, it is not dispensed in pharmacies. Medical doctors or nurses may prescribe it for individual patients. The patient can then acquire it from a licensed vendor; grow a quantity sufficient for personal use in residence after registering with the Ministry for Health; nominate a grower in their place (a grower can only cultivate for two people); or acquire it from a provincial or area level licensed retailer. The patient is allowed to prepare Cannabis-based products, but the use of organic solvents such as butane, benzene, methyl-chloride, or chlorinated hydrocarbons is forbidden. Regarding industrial products, Sativex® is available for sale; it is indicated for the treatment of spasticity in multiple sclerosis. Other recommended uses include additional pain relief for neuropathic pain in adult patients with multiple sclerosis, and additional pain relief for patients with late-stage cancer who experience moderate to serious pain when already undergoing palliative care with the highest tolerable dosages of opioids. Nabilone is approved for treatment of serious nausea and vomiting associated with chemotherapy, while dronabinol is approved for the treatment of AIDS-related anorexia, and for serious nausea and vomiting associated with chemotherapy. Dronabinol was withdrawn for the Canadian market by the producer in February 2012, but not for health risks. Generally, Cannabis may be used for any symptom without demonstrating the inefficacy of the previous therapies. The approved industrial products may be reimbursed by health insurance companies, while all the others are non-reimbursable. (FISCHER, et al., 2015; ABLIN, et al., 2016; Health Canada, 2016; The Health Products Regulatory Authority, 2017; ABUHASIRA, et al., 2018; Conseil fédéral, 2018; Government of Canada, 2019; Health Canada, 2022)

- *Israel*

In Israel, patients with a prescription may use a licensed pharmacy to obtain medical Cannabis. There is a list of conditions for which Cannabis may be used, but the medical doctor may also prescribe it for other pathologies: in any case, it may only be used when other therapies have proved ineffective. The list includes neuropathic pain, serious cachexia in AIDS patients, spasticity from multiple sclerosis, pain associated with Parkinson's disease, Tourette's syndrome, treatment of metastatic cancer or chemotherapy-induced symptoms, inflammatory intestinal diseases and post-traumatic stress disorders. In general, the products available are Cannabis inflorescences, Sativex® and Epidiolex®. The number of medical Cannabis patients among the Israeli population is one of the highest in the world (on February 2022 about 100,000 Israelis - about 1% of the population were allowed to consume medical Cannabis). Sativex® is recommended for spasticity from multiple sclerosis unresponsive to other treatments, or as an additional analgesic therapy in adult patients with advanced stage cancer with moderate to severe pain despite being administered the highest tolerable dosage of opioids; Epidiolex® is used to treat convulsions in Dravet syndrome, and Lennox-Gastaut syndrome. As for herbal Cannabis, a government-run program produces and distributes this product. Medical Cannabis is supplied in two forms: as an oil extract for oral administration or sub-lingual deposition, and as the inflorescence which may be smoked or inhaled with vaporizers. The cost of the therapy is reimbursed in part by some private and state health insurance schemes. (abcNEWS, 2022; ABLIN, et al., 2016; ABUHASIRA, et al., 2018; KRCEVSKI-SKVARC, et al., 2018; State of Israel - Minister of Health, 2017; State of Israel - Minister of Health, 2022; The Health Products Regulatory Authority, 2017)

- *United States of America*

There are significant legislative differences among the states concerning Cannabis in the United States. In some states the legislation in force is extremely limiting, in others significantly less restrictive. Therefore, the state laws may not be completely harmonized with federal laws. Regarding industrial products, the FDA has approved the prescription of Dronabinol and Nabilone for the treatment of chemotherapy-induced nausea and vomiting. Dronabinol may also be used for the treatment of appetite and weight loss in HIV patients. Epidiolex® may be prescribed for the

treatment of epileptic disorders, Lennox-Gastaut syndrome and Dravet's syndrome. Concerning herbal Cannabis, only 36 states have legalized or decriminalized its use. In general, in those states which have authorized the use of medical use Cannabis, there are restrictions on its prescription. Depending to the local laws, therefore, Cannabis may be prescribed for pain, anxiety, epilepsy, glaucoma, appetite and weight loss associated with AIDS, inflammatory intestinal disturbances irritable intestine syndrome, motor disturbances due to Tourette's syndrome or multiple sclerosis, nausea and vomiting caused by chemotherapy, sleep disorders, and posttraumatic stress disorders. Some states allow the addition, at the prescribing medical doctor's discretion, of pathologies other than those expressly stated. Generally, medical doctors do not need specific training to prescribe Cannabis, but in many states, it is necessary to register before doing so. In other states, medical doctors must attend a short training course to be able to register. In some states, it is enough that the medical doctor gives advice verbally to take medical Cannabis, or its use may be recommended by a health care professional who is not a medical doctor. On the other hand, in some states, it is necessary that two medical doctors confirm the need for a Cannabis-based treatment for a patient. Depending on the state, Cannabis may be supplied to the patient by licensed dispensaries, or it may be grown at home by the patient or by a caregiver. Smoking medical Cannabis is prohibited in some states. Similarly, even the edible forms are prohibited in some states. Generally, the administration is performed orally or by vaporizer. Patients are generally registered so that the possession and use of medical Cannabis is not prosecuted.

(ABUHASIRA, et al., 2018; ALHARBI, 2020; CARLINER, et al., 2017; CHOO and EMERY, 2017; CORROON and KIGHT, 2018; JOHNSON, et al., 2021; MEAD, 2017; National Conferences of State Legislatures, 2022; PROCON, 2022; RYAN, et al., 2021; The Health Products Regulatory Authority, 2017)

- *Switzerland*

The prescription and use of Cannabis-based magistral preparations is authorized for spasticity (multiple sclerosis), chronic pain, appetite loss in AIDS and nausea, pain, and appetite loss from cancer. The magistral preparations are prepared in a pharmacy. Medical doctors may prescribe Cannabis-based medicines only after receiving authorisation from the Federal office of the Public Health System. The cost of the therapy is not reimbursed systematically, but on a case-

by-case basis. As well as the inflorescence, it is possible to use dronabinol and Epidiolex®. Sativex® is also authorized for use and available for treatment of spasticity from multiple sclerosis.

(ABUHASIRA, et al., 2018; KRCEVSKI-SKVARC, et al., 2018; Swiss Confederation, Federal Office of Public Health, 2020; Swiss Confederation, Federal Office of Public Health, 2021a; Swiss Confederation, Federal Office of Public Health, 2021b; Swiss Confederation, Federal Office of Public Health, 2021c)

- *United Kingdom*

In the United Kingdom, medical Cannabis is generally prescribed to adults and children with rare and serious forms of epilepsy, adults suffering from nausea or vomiting from chemotherapy, and adults with muscular stiffness or spasms from multiple sclerosis. This therapy is considered only in cases in which no alternative treatment is available, or other treatments have been inefficacious. The available products are Epidiolex®, prescribed to patients with Lennox-Gastaut syndrome or Dravet syndrome; nabilone, which is authorised for nausea and vomiting associated with chemotherapy; dronabinol is also available, but it has no marketing authorization; and Sativex®, which is prescribed for muscular spasms in multiple sclerosis unresponsive to other treatments (even though it is discouraged by NICE in that it is not cost-effective). The medical Cannabis therapy cannot be obtained from a general practitioner but must be prescribed by a hospital specialist registered with the General Medical Council. The medical doctor may collect data on adverse reactions, which can also be signalled directly by the patient through a yellow card system. (Department of Health and Social Care, 2018; Medicines and healthcare products Regulatory Agency, 2020; MS Society, 2021; National Health Service, 2021; General Medical Council, 2022; National Health Service, 2022; UK Government, 2022)

European Union:

- *Denmark*

All medical doctors are authorized to prescribe Cannabis-based products as part of a 4 years pilot project launched in January 2018. As part of this project, a medical doctor may prescribe medicines that are not approved for distribution or sale in Denmark. However, the medical doctor must take full responsibility for the products they prescribe and must determine the proper dosage for each patient. Medical doctors may refer to the guidelines laid out by the Danish Medicines Agency. The imported plant products available for prescription may vary in content, but they must comply with strict standards and regulations governing the cultivation of the plant species, and the production and standardization of the Cannabis-based product. Herbal Cannabis is available by prescription only in pharmacies, which may also prepare magistral preparations. Regarding industrial products, neurologists may prescribe Sativex® to treat spasticity from multiple sclerosis. In general, medical doctors may prescribe imported Cannabis-derived medicines that have not been approved for sale in Denmark, such as Marinol® and Cesamet® on compassionate grounds, but only if the request is approved by the Danish Medicines Agency. In general, the Danish Medicines Agency indicates that medical Cannabis be considered as a therapy only for the following conditions: painful spasticity in multiple sclerosis, painful spasticity caused by spinal cord damage, chemotherapy-induced nausea, and neuropathic pain. As part of the pilot project, Cannabis may, however, be prescribed to any patient even outside of the guidelines. The use of Cannabis is not recommended for patients under 18 years of age. The prices of the prescribed products within the pilot project are set freely by the manufacturers. It is possible to obtain a reimbursement as of 01/01/2019 (retroactive for 2018). Patients in the terminal stages of a disease are fully reimbursed, while patients with other illnesses receive a 50% reimbursement, up to annual maximum of 10,000 Danish Krone. The reimbursement is automatically deducted at the time of the purchase in a pharmacy. For prescriptions that are not part of the pilot project, the medical doctor may request a reimbursement for an individual patient from the Danish Medicines Agency. It will consider the request for those patients with pathologies where Cannabis-based treatment appears to be effective, and for those whom all other treatments with approved medicines have

been used without effect (The Health Products Regulatory Authority, 2017; ABUHASIRA, et al., 2018; KRCEVSKI-SKVARC, et al., 2018; Danish Medicines Agency, 2020; GUSTAVSEN, et al., 2021).

- *Ireland*

The Medical Cannabis Access Program in Ireland currently provides access to cannabis to patients with one of three conditions when other treatments have been unsuccessful. The three conditions are spasticity (stiff and/ or rigid muscles) associated with multiple sclerosis, nausea and vomiting associated with chemotherapy, and severe epilepsy. An evidence review was conducted by the Health Research Board (HRB) to inform a Department of Health review of the current Medicinal Cannabis Access Program on the suitability of cannabis-based products for medical conditions. Findings The HRB found evidence to support the use of prescribed medicinal cannabis for certain conditions for which it is currently approved in Ireland. These are nausea and vomiting in cancer and spasticity in multiple sclerosis. There was also evidence of a significant benefit for neuropathic or nerve pain, which can occur with conditions such as multiple sclerosis, diabetes, or spinal cord injury. For most other conditions, including anxiety and pain in conditions such as cancer, rheumatic diseases, and fibromyalgia, there was no conclusive evidence to confirm the efficacy of prescribed medicinal cannabis. Regarding the safety of prescribed medicinal cannabis, the review found that although serious adverse events do not appear to be common, there is some evidence that some side-effects such as dizziness, dry mouth, sedation, and headache can occur. Mixed evidence was found, however, on the likelihood of other adverse events such as drowsiness, nausea, and any psychiatric disorder adverse events. The HRB findings are like those reported by other overviews (Drugnet Ireland, Issue 87 – Health Research Board).

- *Germany*

Medical doctors may prescribe medical Cannabis using a specific "narcotics" prescription form. The prescription may be for any condition that has no standard treatment, or the standard treatment cannot be used owing to reactions or based on the patient's specific condition. Among the industrial products available is Sativex®, which is indicated for spasticity in refractory multiple sclerosis. In addition, it is possible to prescribe dronabinol without particular restrictions regarding its indicated use. Nabilone is approved for nausea and vomiting associated with chemotherapy and unresponsive to conventional therapies. Finally, Epidiolex® and many types of Cannabis inflorescences may also be prescribed. Magisterial preparations may be prescribed, and pharmacies may dispense extracts of Cannabis and inflorescences. The patients may request a reimbursement from health insurance companies. For this purpose, the prescribing medical doctor has the task of certifying the seriousness of the disease, that the standard therapies have been ineffective, or cannot be used due to the patient's specific condition, or that there is a reasonable likelihood that medical Cannabis will be effective for that subject.

On final March of 2024, Germany's cannabis reforms were approved overcoming the final legislative hurdle when the Bundesrat, Germany's upper house, voted through the bill that passed with a huge majority in the Bundestag (lower house). Germany's new law came into force on 1st April of 2024, and decriminalizes possession of up to 25g of cannabis for personal use (and up to 50g in the home), allow requests to remove criminal records for past possession offences, legalize home growing of up to three cannabis plants for personal use, and establish a regulatory framework for not-for-profit associations within which cannabis can be grown and supplied to members. (GROTENHERMEN AND MULLER-VAHL, 2012; ABLIN, et al., 2016; The Health Products Regulatory Authority, 2017; ABUHASIRA, et al., 2018; Conseil fédéral, 2018; Federal Institute for Drugs and Medical Devices, 2018; KRCEVSKI-SKVARC, et al., 2018; RASCHE, et al., 2019; Federal Institute for Drugs and Medical Devices, 2022a; Federal Institute for Drugs and Medical Devices, 2022b; Federal Institute for Drugs and Medical Devices, 2022c; Federal Institute for Drugs and Medical Devices, 2022d; German Institute for Medical Cannabis, 2022; The Guardian, 29th March 2024)

- *Netherlands*

In Netherlands, all medical doctors may prescribe medical Cannabis. The pharmacies may also produce extracts using the plant material produced by the Office of Medical Cannabis. These are usually oil extracts to be taken orally or deposited under the tongue. Some types of inflorescences are available for this purpose: the concentration of the active molecules and granulation properties may vary. The inflorescences may also be taken in the decoction form or inhaled through vaporizers. Sativex® is approved for the treatment of spasticity from multiple sclerosis refractory to conventional therapies. Cannabis is indicated for the treatment of pain (multiple sclerosis, or spinal cord injuries), chronic pain, nausea and vomiting (in chemotherapy or radiotherapy, HIV therapies, adverse reactions to hepatitis C medication), palliative care for cancer or AIDS (to increase appetite and alleviate pain, nausea and weight loss), Tourette's syndrome, and refractory glaucoma, epilepsy and epileptic syndromes (even in children). In addition, its use is indicated in the reduction in symptomology of the following pathologies: Crohn's disease, ulcerative colitis, itching, migraine, rheumatic conditions, ADHD, post-traumatic stress disorders, agitation in Alzheimer's disease and cerebral trauma. Medical doctors are in any case authorized to prescribe these therapies for other conditions if they consider it fit. Cannabis-based products must, however, be considered only in cases where authorized medicines have inefficacious or provoked unacceptable adverse reactions.

As concerns the available herbal Cannabis species, Bediol® (THC 6.3%; CBD 8%) is usually recommended as the first-choice therapy to alleviate pain or as an anti-inflammatory therapy. Bedrocan ® (THC 22%; CBD <1.0 %), Bedica® (THC 14%; CBD <1.0%) and Bedrobinol® (THC 13.5%; CBD <1.0%) are considered more effective for the treatment of symptoms such as appetite loss, weight loss, nausea, vomiting, anorexia, cachexia, emesis, Tourette's syndrome, and glaucoma. Bedrolite® (THC<1%; CBD 7.5%) is employed for certain forms of epilepsy. The healthcare system does not reimburse the cost of Cannabis-based medicines. In some cases, the patient may be able to claim from private insurance schemes. (The Health Products Regulatory Authority, 2017; ABUHASIRA, et al., 2018; Conseil Fédéral, 2018; KRCEVSKI-SKVARC, et al., 2018; Bedrocan, 2021; Office of Medicinal Cannabis, 2022)

- *Portugal*: The Portuguese legislation is extensively explained on the next pages (Point 9 – The Portuguese Reality – Regulation and INFARMED perspective.)

9. The Portuguese Reality – Regulation and INFARMED Perspective

In February 2018, the Portuguese Pharmaceutical Association "Ordem dos Farmacêuticos" had elaborated an Opinion Report on the Use of Cannabis for Therapeutic Purposes, before the medicinal use law approval on July 2018.

This report focused on the mandatory topics that must be considered on the Marketing Authorization (MA) process of any medicine and, in particular, considering the cannabis use for medicinal applications. For the discussion on the Portuguese Parliament on this matter, they considered that above all "In order to be granted an MA, the medicine must demonstrate a positive benefit/risk relationship for the proposed therapeutic indication."

Although the European context does not converge towards a uniform legal response regarding medicinal cannabis-based products, in the case of Portugal, its regulatory approach, both in the context of production and marketing authorization, has been pioneering and is being noticed by various countries, whose interest in this field has been increasing. Proof of this, is the entry of numerous foreign investment entities into Portugal, in recent years, in the context of the cultivation, import and export of medicinal cannabis.

The evolution of the activity related to medicinal cannabis in Portugal is under the responsibility of INFARMED, IP. which, as a regulatory authority for medicines, preparations and substances based on the cannabis plant, has followed the development of this area, having played a central role in the development and implementation of the regulatory framework, as well as in licensing and inspection of the various entities operating in the medicinal cannabis market.

The Portuguese legislation applicable to activities related to the use for medicinal products and investigation of controlled substances, arising from the United Nations Conventions of 1961 and 1971, referring, respectively, to narcotic substances and psychotropic drugs, has always enabled the use of controlled substances, as is the case with cannabis, for medicinal purposes.

Based on this legislative framework, the specific regulatory process began in medicinal cannabis, as a result of some international companies having demonstrated, in 2016 and 2017, a clear interest in installing activities related to the cultivation and manufacture of medicinal cannabis in Portugal.

The economic and health value proposition and the novelty that these new activities presented to the national productive fabric in the scope of health products, led to INFARMED, I.P. carry out a survey of international experiences in this area, through the study and knowledge of established regulatory regimes, with a high degree of consolidation, as is the case of Canada and Israel, particularly in areas related to licensing and inspection of cultivation, manufacturing and research activities for preparations and substances based on the cannabis plant.

Likewise, close monitoring of companies that intended to start their activities in medicinal cannabis in Portugal, provided INFARMED, I.P. one opportunity for learning and accumulation of experiences, with direct impacts on the design and improvement of the existing regulatory regime, adapting it to the characteristics, typologies, security and predictability needs in projects and licensing processes.

Access to a controlled regulatory environment for international companies that, despite their own national specificities, they see similarities in regulatory requirements applicable in countries with mature regulations. Associated with the fact that in most European countries there is no specific regulation for the area of medicinal cannabis, has contributed to the growing interest on the part of those companies and investors in launch of operations in Portuguese territory, even though its main market is destinated to Europe.

The regulatory initiative within the scope of licensing and supervision of activities carried out by INFARMED, I.P., was essentially based on 5 vectors, namely:

(1) product quality, through carrying out activities in compliance with Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP);

(2) compliance with the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1961 and 1971);

(3) the implementation of security measures at facilities, records and traceability of the products;

(4) the feasibility of health and economic value proposition of the project;

(5) a multidisciplinary assessment with the involvement in the process, in addition to Health, of several areas such as Agriculture, Internal Administration, Economy and Justice, as well as Local Municipal Councils.

In 2018, the Assembly of the Republic approved the Law (DL n.º 33/2018, July 18th) that regulates the use of medicines, preparations and substances based on the cannabis plant, for medicinal purposes, namely the authorization to place it on the market, its prescription and its dispensation in pharmacy, which was subsequently regulated, based on detailed analysis of various programs within the scope of the use of cannabis substances and preparations for medicinal products already existing in other Member States, namely in Denmark and Netherlands, as well as the assessment of their feasibility in the national reality.

The deliberation taken by INFARMED on January 31, 2019, contains the list of therapeutic indications considered appropriate for preparations and substances based on the cannabis plant:

1. Spasticity associated with multiple sclerosis or spinal cord injuries;

2. Nausea, vomiting (resulting from chemotherapy, radiotherapy and combination drug therapy for HIV and hepatitis

3. Appetite stimulation in palliative care for patients undergoing cancer treatment or with AIDS;

4. Chronic pain (associated with oncological or nervous system diseases, such as neuropathic pain caused by nerve injury, phantom limb pain, trigeminal neuralgia or after herpes zoster);

5. Gilles de la Tourette syndrome;

6. Epilepsy and treatment of severe convulsive disorders in childhood, such as Dravet and Lennox-Gastaut syndromes;

7. Therapy-resistant glaucoma.

In 2021, the Joint Ordinance (Ordinance n. 83/2021, April 15th) was published, which defines the requirements and procedures relating to the granting of authorizations to carry out activities related to the cultivation, manufacture, wholesale trade, transport, circulation, import and export of medicines, preparations and substances based on the cannabis plant, which expressly provided for the already established licensing procedure, and consolidated the synergies already existing between the various authorities involved, in particular with regard to verifying the implementation of security measures by the National Directorate of Security Police Public and evaluation of the investment project, its regional and national relevance and the impact on the country's economy and exports, by IAPMEI - Agency for Competitiveness and Innovation, I.P. (www.INFARMED.pt)

In March 2024, new medicines emerged within the scope of approval of cannabis-based products by the national regulatory entity (Table 3 summarizes the available medicines in Portugal), which well reflects the evolution of this new type of medicine.

The approval of these medicinal products by INFARMED not only expands treatment options but also signifies a pivotal moment in healthcare accessibility for patients across Portugal. The table below shows in detail the medicine approved name, Active Pharmaceutical Ingredient(s) (API), pharmaceutical form, dosage, MA holder and marketing status.

None of these approved medicines are, however, indicated for topical use for dermatological treatment purposes. It is up to the INFARMED, as the Portuguese National Regulatory entity, to adapt the list of approved diseases for treatment with cannabis derived products, and at the same time adopt measures that, within its scope, facilitate and speed up the approval of this type of therapeutic responses, at the level of national procedure application, for herbal medicines and not only herbal substances and/or preparations.

Table 3– Adapted table of cannabis-based medicines authorized in Portugal by INFARMED https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml, accessed on 7th April 2024.

Medicine name	API	Pharmaceutical form	Dose	MA Holder
Epidyolex	CBD	Oral solution	100mg/ml	Jazz Pharmaceuticals Ireland Ltd.
Satalliv	CBD	Oral solution	100mg/ml	Ferraz Lynce, Especialidades Farmaceuticas SA
Sativex	Δ9-THC + CBD extract	Mouth spray solution	27mg/ml + 25mg/ml	Jazz Pharmaceuticals Ireland Ltd.
Tilray Oral Solution THC 5 CBD 20	Δ9-THC + CBD extract	Oral solution	5mg/ml + 20mg/ml	Tilray Portugal Unipessoal, Lda.
Hexacan / Hexa 01 High THC 20%	Δ9-THC + CBD dry flower	Herbal medicine for inhalation by vaporization	20% + ≤ 1.0%	Portocanna SA
Tilray Dry Flower THC 18	Δ9-THC + CBD dry flower	Herbal medicine for inhalation by vaporization	18% + ≤ 1.0%	Tilray Portugal Unipessoal, Lda.

10. Other CBD-based Products Classification

CBD is a non-psychoactive component of cannabis and therefore is not regulated as a controlled drug in many EU member states.

The future of CBD products across the EU is an area in which member states would welcome legislative clarity. CBD is being sold in numerous products, including food, oils, cosmetics, and vaping products, but its legality varies considerably between the EU member states.

Some countries such as Germany have classified CBD food products as not being marketable in Germany due to the European Commission Novel Food Catalogue entry, which was updated in 2019.

In February 2020, the Irish Food Safety Authority recalled more than 16 CBD products including CBD oils and CBD food supplements from the Irish market following a review of CBD products for compliance with Irish food law. Of the products tested, 37% had a THC content that could exceed the European Food Safety Authority safety limits, and the implicated batches of those products were recalled from the market.

In April 11th 2024, INFARMED has suspended the commercialization and withdrawal from the Portuguese market of two creams containing cannabidiol, the use of which is banned in cosmetic products, the medicines authority has announced. INFARMED explains that the decision stemmed from a complaint it received, and suggests also that the creams in question contain cannabidiol, which is obtained from extracts or tinctures of cannabis or its resin and is not permitted in cosmetic products.

The sale and supply of CBD products on the EU market is a grey area that has not yet been fully addressed in legislation at an EU level. Further, some EU member states do not have specific legislation in place covering the sale of CBD products. One challenge for CBD manufacturers is that EU regulators appear to be taking different approaches in relation to permitted THC levels.

In the absence of uniform EU rules relating to CBD products, it is left to the EU member states to legislate to bring clarity and certainty to the industry. This has still not occurred in some EU member states. The result is that cannabis companies currently marketing CBD products across the EU must ensure they comply with a patchwork of laws and regulatory frameworks (or lack thereof in some EU member states), under which they run the risk of having their products recalled from the market in individual EU member states.

In the U.S., at the state level, they are considered legal if either in states that allow for medical and recreational marijuana or in all states if extracted from hemp. Recently, cannabidiol has garnered considerable attention in the public and media as a trendy and popular ingredient in skincare products.

Many products containing CBD are readily available at dispensaries and via the Internet for patients and consumers to purchase; nonetheless, their regulation and legality largely remain controversial

Statement on CBD as novel Food – European Commission, Feb 2023

At the request of one Member State and in collaboration with the other Member States the Commission presented the following statement on cannabidiol as novel food, which was endorsed by the Committee: The hemp plant (*Cannabis sativa* L.) contains more than 100 different cannabinoids, the most common ones being cannabidiol (CBD) and its precursor acidic form cannabidiolic acid (CBD and CBDa respectively), cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), and delta-9-tetrahydrocannabinol and its precursor acid form (Δ9-THC and Δ9-THCa respectively). In its judgment in case C-663/18, the Court of Justice of the European Union concluded that cannabidiol (CBD) should not be considered as a drug within the meaning of the United Nations Single Convention on Narcotic Drugs of 1961 insofar as it does not have a psychotropic effect. The Commission therefore, considers that cannabidiol can be considered as 'food', provided that the other conditions of Article 2 of the General Food Law are met. In accordance with Regulation (EU) 2015/2283 (the 'Novel Food Regulation'), foods for which a history of human consumption to a significant degree within the Union before 15 May 1997 cannot

be demonstrated, are novel and may not be placed on the market within the Union as such or used in foods until they have been authorized and included in the Union list of authorized novel foods. A history of consumption to a significant degree within the EU prior to 15 May 1997 has not been demonstrated for CBD or any other cannabinoids, or products containing either CBD and/or other cannabinoids derived from the *Cannabis sativa* L. plant. Therefore, except for the THC cannabinoids, they are considered novel foods until acceptable and verifiable evidence to the contrary is provided.

The Commission has received over 190 applications for the authorization of CBD and extracts of *Cannabis sativa* L. and derived products containing cannabinoids under the Novel Food Regulation. Of these applications, so far 20 have been considered by the Commission to be valid and are currently being evaluated by EFSA (European Food Safety Authority). In a statement of June 2022, EFSA identified several potential hazards and determined that many data gaps relating to possible health effects need to be filled before the evaluations of the safety of CBD and hemp extracts can progress. At present, there has been no authorization of CBD, or any other cannabinoids, nor of products containing either CBD and/or other cannabinoids derived from the *Cannabis sativa* L. plant under Regulation (EU) 2015/2283 on novel foods.

Member States have the primary responsibility for the correct application, implementation and enforcement of EU legislation. (Judgment of the Court in Case C-663/18 of 19 of November 2020, B S and C A (Commercialization du cannabidiol - CBD), ECLI:EU:C:2020:938; United Nations Treaty Series, vol. 978, No 14152; Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1; Regulation (EU) 2015/2283 of 25 November 2015 on novel foods. OJ L327, 11.12.2015, p. 1; EFSA Journal 2022;20(6):7322)

11. Suggestion of a national (Portuguese) law adaptation – Regulatory proposal

In recent years, the field of dermatology has witnessed a groundbreaking evolution with the advent of CBD-based medicine. This revolutionary approach offers promising solutions for various skin afflictions, ushering in a new era of skincare treatment. With the development of this work, I intend to offer a Proposal for reasoned decision, to suggest the introduction of medicines based on CBD obtained from the cannabis plant for the treatment of dermatological diseases, focusing on its advantage compared to the therapeutic solutions available to date.

As a future direction, CBD-based options hold immense promise, but several challenges must be addressed to fully realize its potential in dermatology. These firstly include the integration by the regulators on the considered therapeutic indications list, always with the premise that all preparations are developed under strict rules of standardization of CBD formulations, elucidation of optimal regimens, and rigorous evaluation of short and long-term safety profiles.

In this sense, develop a decision-making scheme regarding the introduction of substances and/or preparations based on CBD in the treatment of dermatological conditions, namely acne, psoriasis and melanoma, proves to be important as it facilitates and enables the emergence of therapeutic alternatives in this area.

What is proposed as part of the development of this thesis, is that the therapeutic potential of CBD-based medicines to be recognized by the Regulator – INFARMED, and other regulatory authorities, in the treatment of dermatological conditions like Acne, Psoriasis and Melanoma with a view to its better acceptance by clinicians and consequently consideration in the therapeutic alternative for the respective diseases. To obtain marketing authorization, the medicines have to demonstrate their quality, safety and efficacy based on non-clinical trials and clinical trials, and it is concluded that they present, for the approved therapeutic indication, a positive benefit/risk profile.

CBD-based Substances/ Preparations/ Medicines for dermatological medicinal purposes, must follow a specific procedure based on established regulatory guidelines.

HERBAL MEDICINAL PRODUCTS

The Committee on Herbal Medicinal Products (HMPC) issues scientific opinions on herbal substances and preparations, along with information on recommended uses and safe conditions, on behalf of the European Medicines Agency (EMA).

This gives companies and national competent authorities a clear reference point when preparing or assessing an application for marketing authorization or registration of herbal medicinal products in European Union (EU) Member States (www.ema.europa.eu).

Companies seeking to bring herbal medicinal products to the market in EU Member States should follow the national procedures overseen by national competent authorities.

There are three main regulatory pathways, and respective specifications for bringing an herbal medicinal product to market in EU Member States, that are listed on the Table below (Table 4):

Table 4 – Main requirements on safety and efficacy, their Regulatory pathway and Application entities. (Adapted from EMA – "Herbal medicinal products" guideline).

Regulatory Pathway	Main Requirements on Safety and efficacy	Where to apply
Traditional use registration *Article 16a (1) of Directive 2001/83/EC*	• No clinical tests and trials on safety and efficacy are required as long as sufficient safety data and plausible efficacy are demonstrated; • Involves assessment of mostly bibliographic safety and efficacy data; • Must have been used for at least 30 years, including at least 15 years within the EU; • Are intended to be used without the supervision of a medical practitioner and are not administered by injection.	National competent authority of a Member State for national, mutual recognition and decentralized procedures.
Well-established use marketing authorization *Article 10a of Directive 2001/83/EC*	• Scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognized efficacy and an acceptable level of safety; • Involves assessment of mostly bibliographic safety and efficacy data.	National competent authority of a Member State for national, mutual recognition and decentralized procedures EMA if centralized procedure applies.
Stand-alone or mixed application *Article 8(3) of Directive 2001/83/EC*	• Safety and efficacy data from the company's own development or a combination of own studies and bibliographic data.	National competent authority of a Member State for national, mutual recognition and decentralized procedures EMA if centralized procedure applies.

According to the Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use, an Herbal medicinal product is "Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations."

Still, in the same directive, the distinction between "Herbal substances and preparations" refers that:

- ***Herbal substances****: All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).*

  And,

- ***Herbal preparations****: Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.*

Regardless of partially simplified requirements on safety and efficacy data, a **full quality dossier** is required for all herbal medicinal products as well as other fundamental principles that are applicable to all medicinal products including good manufacturing practice, pharmacovigilance and requirements on packaging and labelling.

The Quality Dossier

For any type of application, a full quality dossier is required for all herbal medicinal products. Hence, for the submission of a MA for CBD-based products, the quality dossier must have full information regarding General quality requirements for herbal drugs in Europe.

The herbal drug batch in question must be suitable for the intended use. This intended use is their further processing into preparations or their use as starting material for the extraction of ingredients. The pharmaceutical quality of a drug batch is ensured if it complies with the requirements of the European Pharmacopoeia or the national pharmacopoeias of a member state of the Council of Europe or other EU national pharmacopoeias. If no corresponding requirements exist in a specific case, the pharmaceutical manufacturer or distributor must draw up their own quality specifications.

Relevant specifications for this can be found in the Ph. Eur. monograph "Herbal drugs" and in the guideline "Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products" (Committee on Herbal Medicinal Products (HMPC) 2024).

Cannabis/CBD-based substances and/or preparations in Portugal

With regards to preparations and substances based on the cannabis plant, it is worth highlighting that both substances and preparations, although they are considered medicines as they are intended to be used for therapeutic purposes, have not formally demonstrated their safety and efficacy do not have their own non-clinical trials and clinical trials, which is why it is not possible for regulatory authorities to formally assess their benefit/risk profile.

However, they must comply with all other requirements applicable to medicines, demonstrating their quality from cultivation in accordance with Good Agricultural and Collection Practices (GACP), to obtaining the preparation in accordance with Good Manufacturing Practices (GMP) for Active Substances, guaranteeing constant and reproducible levels between the various batches and also guaranteeing the absence of dangerous contaminants.

Therefore, preparations and substances based on the cannabis plant apply, in addition to the general regime applied to medicines and psychotropic substances, a specific and simplified authorization regime (ACM – "Autorização de colocação no Mercado") for placing on the market provided for in DL n.º 8/2019 of January 15th, with the prescription of these products being limited to cases in which conventional treatments did not produce the expected effects or cause relevant adverse effects and to therapeutic indications approved by INFARMED.

Furthermore, the physician must provide the patient all the instructions necessary for the correct use of the product. In this way, DL n.º 8/2019 constitutes a derogation from the general regime applied to the application for placing medicines on the market and, being a derogation, it must be interpreted strictly which means it must only be used in cases where that it is not possible to effectively demonstrate all aspects of the safety and effectiveness of preparations and substances based on the cannabis plant.

Cannabis/CBD-based medicines in PORTUGAL

For medicines based on the cannabis plant, they should apply trough the normal paths for a MA procedure for medicines, and in Portugal, the MA (AIM – "Autorização de introdução no Mercado") is regulated on the DL n.º 176/2006, of August 30th.

The use of CBD-based products in dermatologic pathologies such as Acne, Psoriasis and Melanoma, with no clinical studies that prove the efficacy in the treatment of the diseases mentioned, doesn't compromise the submission of a simplified dossiers (ACM) for a MA request, in the case of preparations and substances.

Regarding the submission of a MA for a CBD-based medicine, the submission must be complete (AIM) with all the necessary studies, including pre-clinical and clinical studies.

Even so, there are certain topics that must be considered mandatory so that these CBD-based Preparations/Substances/Medicines are placed on the market.

Before submitting the ACM/AIM, the following aspects must be considered:

A. TYPE OF CBD

The choice between CBD derived from cannabis (Natural) or synthetic CBD depends on various factors, including regulatory considerations, quality issues, costs, and ethical considerations. Here are some key points to consider for each option, regarding their advantages and possible limitations:

CBD from Cannabis plant (NATURAL)

Advantages:

- **Natural source**: This means that may appeal to the organic benefits of natural plant-based products. Furthermore, users who suffer from certain illnesses may prefer cannabis-derived CBD due to its natural origins and perceived authenticity when compared to synthetic alternatives;

- **Entourage Effect**: Cannabis-derived CBD may contain other cannabinoids, terpenes, flavonoids and compounds present in the plant, that create an entourage effect, where these compounds work synergistically to enhance therapeutic effects. This is based in studies described by WAGNER H.
  et al., 2009, that consider 4 types of synergies: multi-target effects (each component affects

multiple targets), pharmacokinetic effects (components can increase the solubility or the resorption rate of an active), agent interactions affecting bacterial resistance, and modulation of adverse effects and toxicity. (WAGNER H. et al., 2009)

Limitations:

- **Regulatory patterns:** On regards of Natural CBD, the Regulatory environment could be a limitation, because Natural CBD products may be subject to legal restrictions and regulatory challenges depending on the jurisdiction leading to uncertainty about legally and access.

- **Quality Control**: This topic can be challenging with natural sources like cannabis due to variability in plant genetics, growing conditions and cultivation methods, and extraction methods, and lack of standardized regulations.

  However, reputable producers can implement rigorous quality control measures to ensure consistency and purity, by the implementation of the GACP and GMP practices.

- **Limited Spectrum**: The Limited Spectrum of Natural CBD products is possible due to cannabis plants may contain a limited spectrum of cannabinoids, terpenes and phytonutrients compared to whole-plant extracts, potentially limiting the entourage effect and therapeutic benefits.

- **Potential Contaminants**: Depending on the cultivation and extraction methods, there could be some Contaminants on Natural CBD products, such as pesticides, heavy metals, or residual solvents, posing potential health risks.

- **Psychoactive effects**: While natural CBD is non-intoxicating, some products may still contain trace amounts of THC, which could produce unwanted psychoactive effects, by contamination.

Synthetic CBD:

Advantages:

- **Purity and Consistency**: Synthetic CBD is produced in a controlled laboratory environment, allowing for precise control over purity, potency and consistency. This can be particularly advantageous for pharmaceutical applications where exact dosing is critical.
- **Regulatory Compliance**: Synthetic CBD have clearer regulatory pathways in certain jurisdictions, especially in regions where cannabis is heavily regulated or prohibited. This can facilitate easier market access and regulatory compliance for manufacturers.
- **Cost-efficiency**: Synthetic CBD production can potentially be more cost-effective than extracting CBD from cannabis plants, especially at scale. This cost efficiency can translate to lower-priced products for consumers or higher profit margins for businesses.
- **Eliminations of Contaminants:** Synthetic CBD can be produced without the risk of contamination from pesticides, heavy metals, or other impurities that may be present in cannabis plants. This ensures a high level of purity and safety.

Limitations:

- **Lack of Entourage Effect**: Synthetic CBD may lack the additional cannabinoids, terpenes and phytonutrients found in natural CBD products, potentially limiting its therapeutic effects and the entourage effect.
- **Lack of Research:** Compared to natural CBD, there is Limited research available on synthetic CBD and its effects, leading to gaps in knowledge about its long-term safety, efficacy and potential interactions with other medications
- **Ethical Considerations:** Some consumers and businesses may have ethical concerns about the environmental impact or sustainability of Synthetic CBD production. Some individuals could have some ethical concerns about using synthetic products, preferring natural products instead or have reservations about synthetic pharmaceuticals and industrial production methods, preferring a more environmentally friendly alternative.

In summary, both natural and synthetic CBD have their own set of advantages and limitations, and considerations related to regulatory, quality, safety, efficacy, and ethical concerns. When choosing a CBD product, it should be carefully evaluated, considering these factors.

Ultimately, the choice between cannabis-derived and synthetic CBD depends on the specific needs and priorities of businesses, consumers and regulatory entities.

B. RESEARCH AND EVIDENCE

Friedman A., 2019, highlighted that for topical therapies, investigations into the best delivery method are underway. Topical delivery of cannabinoids in particular, is problematic due to its high molecular weight and relative instability.

One possible solution is having nanoparticles, which slowly delivers cannabinoids into the skin for maximum penetration and benefit to patients.

In vivo models (mouse) of CLE showed the efficacy of using nanoparticles fer delivering cannabinoids into the skin (CHALMERS S. et al. 2018). In addition, the same publication mentioned that two studies found evidence suggesting that cannabinoids could be used to treat acne. Oláh et al showed that CBD inhibited sebocytes and inflammation in immune cells. (OLÁH A. Et al. 2014).

Similarly, Ali et al. found that cannabis 3% extract improved acne symptoms among participants. (ALI A. et al. 2015) However, it is considered important that more trials should be developed to determine the correct dosages for this type of treatment.

These studies and further explorations into the ECS role in skin care and homeostasis show the limitless potential for harnessing cannabinoids for the treatment of various skin conditions, including ones with few other therapeutic options.

In the case of Psoriasis disease, Friedman A. found out that a topical cream with 3% CBD/ 3% THC was used to suppress keratinocyte proliferation through CB1 receptor activation (THC is an agonist) and the activation of CB2 receptors decreases inflammation associated with Th1 (CBD is an agonist of CB2 receptors), and this trial was under recruiting for phase 1 at that time.

On the other hand, for Melanoma, although no studies in humans weren't yet available, Friedman emphasized that the activation of CB1 and CB2 receptors appeared to reduce tumor growth in preclinical models – *in vivo* and *in vitro* animal models.

As it has been demonstrated throughout this thesis, the CBD molecule beneficial effects in the treatment or modulation of diseases such as acne, psoriasis or melanoma. However, the type of administration of the cannabinoid molecule is of special importance with a view to its better absorption by the body and with consequent proven effectiveness.

Because of its wide range of effects, formulation technologies are being developed to ensure better topical delivery of CBD for medical and cosmetic use. The topical use of CBD has been considered in the form of creams, ointments, lotions or oils for the purposes mentioned above, on the direct affected areas of the skin. It is always essential to start with a low dose and monitor the response.

C. THE DERMATOLOGICAL APPLICATION

Absorption VS Safety of the topical CBD products

Regarding the degree of absorption of CBD products for dermatological diseases, its absorption is largely related to the area of topical application and its extent of systemic absorption may be a parameter of little relevance.

In a Research Article for Medical Cannabis and Cannabinoids, Riley D. Kirk et al, explores the Skin Permeability of Cannabidiol and Its Topical Formulations by Skin Membrane Based on Parallel Artificial Membrane Permeability Assay and Franz Cell Diffusion Assay.

It was found that CBD had higher solubility (378.4 μg/mL) in surfactant Tween 20 as compared to its solubility in poly-isobutene. In an acidic environment (pH 5 and 6), Tween 20

maintained the CBD content at 81% and 70% over 30 days, respectively. CBD in the formulations of cream and gel also had considerable skin permeability in the Franz cell diffusion assay.

CBD isolate showed favorable skin permeability in the SwissADME and DERMWIN™ predictions (−Log Kp of 3.6 and 5.7 cm/s, respectively) and PAMPA (−LogPe value of 5.0 at pH of 6.5 and 7.4).

In addition, CBD had higher solubility (378.4 μg/mL) in surfactant Tween 20 as compared to its solubility in poly-isobutene. In an acidic environment (pH 5 and 6), Tween 20 maintained the CBD content at 81% and 70% over 30 days, respectively. CBD in the formulations of cream and gel also had moderate skin permeability in the Franz cell diffusion assay.

This data from artificial membrane-based assays support that CBD is a skin permeable cannabinoid and the permeability and stability of its formulations may be influenced by several factors such as surfactant and pH environment. This study suggest that CBD may have suitable skin permeability for the development of dermatological and/or cosmeceutical applications but further studies using in vivo models are warranted to confirm this.

The fact that CBD can penetrate the skin, is a positive outcome when it comes to speak about the dermatological treatments, because the possibility of penetration of this molecule to the deeper layers of the skin, shows therapeutic potential, since it can achieve therapeutic targets, without, however, compromising its safety, as it acts only locally, without the possibility of systemic absorption.

D. SAFETY OF CBD – LOCAL TOXICOLOGY

The literature in the public domain on dermal application of CBD is predominantly on clinical trial reports secondary findings from animal proof of concept and mechanistic studies.

The following two yellow card reports (MHRA) were the reported incidents of adverse reactions following topical CBD application between the years 2005-2020 (Yellow Card, 2020).

Case 1. Year of receipt 2019 - Female patient taking cannabidiol, both topically and orally, for osteoarthritis experienced indigestion, extreme daytime sleepiness, difficulty sleeping, itchy skin. The onset time from first dose was one day. The outcome given at the time of the report was “not recovered/not resolved”.

Case 2. Year of receipt 2020 – Male patient taking topical cannabidiol for eczema and dihydrocodeine (route unknown) for analgesia. Reported reactions were dizziness aggravated, hyperkinetic reaction, nausea aggravated, pharmacokinetic interaction, pyrexia, serum serotonin increased and vomiting. The onset time from first dose was one day. Outcome at time of report was “recovering”.

Even though cutaneous administration may induce local adverse effects (SCHEFFER et al. 2021) it has also been proven that other three topical formulations (gel, balm and cream) have not induced skin irritation, sensitization and phototoxicity (MAGHFOUR et al. 2021), demonstrating that transdermal and topical route might be a great alternative for a safe, effective and well tolerated CBD administration.

E. ECONOMIC ASPECTS

CBD has gained significant attention in the field of dermatology due to its potential therapeutic benefits for various skin conditions. Some of the economic advantages with CBD in dermatology include:

- **Increased Product Demand:** The growing popularity of CBD-infused skincare products has led to increased demand in the market. This surge in demand creates opportunities for businesses to capitalize on this trend, leading to potential revenue growth.

- **Diversification of Product Lines:** CBD allows skincare companies to diversify their product lines by introducing new CBD-infused formulations. This diversification can attract new customers who are interested in the potential and benefits of CBD for their skin.

- **Premium Pricing:** CBD-infused skincare products often command premium pricing due to the perceived added value of CBD. This premium pricing strategy can lead to higher profit margins for businesses compared to traditional skincare products.

- **Potential Cost Savings**: CBD has been explored for its anti-inflammatory, antioxidant, and antimicrobial properties, which may reduce the need for additional ingredients in skincare formulations. By incorporating CBD, companies may be able to streamline their product formulations, potentially reducing manufacturing costs.

- **Brand Differentiation:** CBD offers a unique selling point that can help brands differentiate themselves from competitors. This differentiation can lead to increased brand loyalty and market share.
- **Expanding Market reach:** CBD-infused products appeal to a wide range of consumers, including those seeking natural and alternative skincare remedies. By offering CBD-infused products, companies can tap into new consumer segments and expand their market reach.

- **Research and Development Opportunities:** The growing interest in CBD within dermatology creates opportunities for research and development. Companies investing in CBD research may benefit from breakthrough discoveries, leading to the development of innovative skincare solutions and patentable formulations.

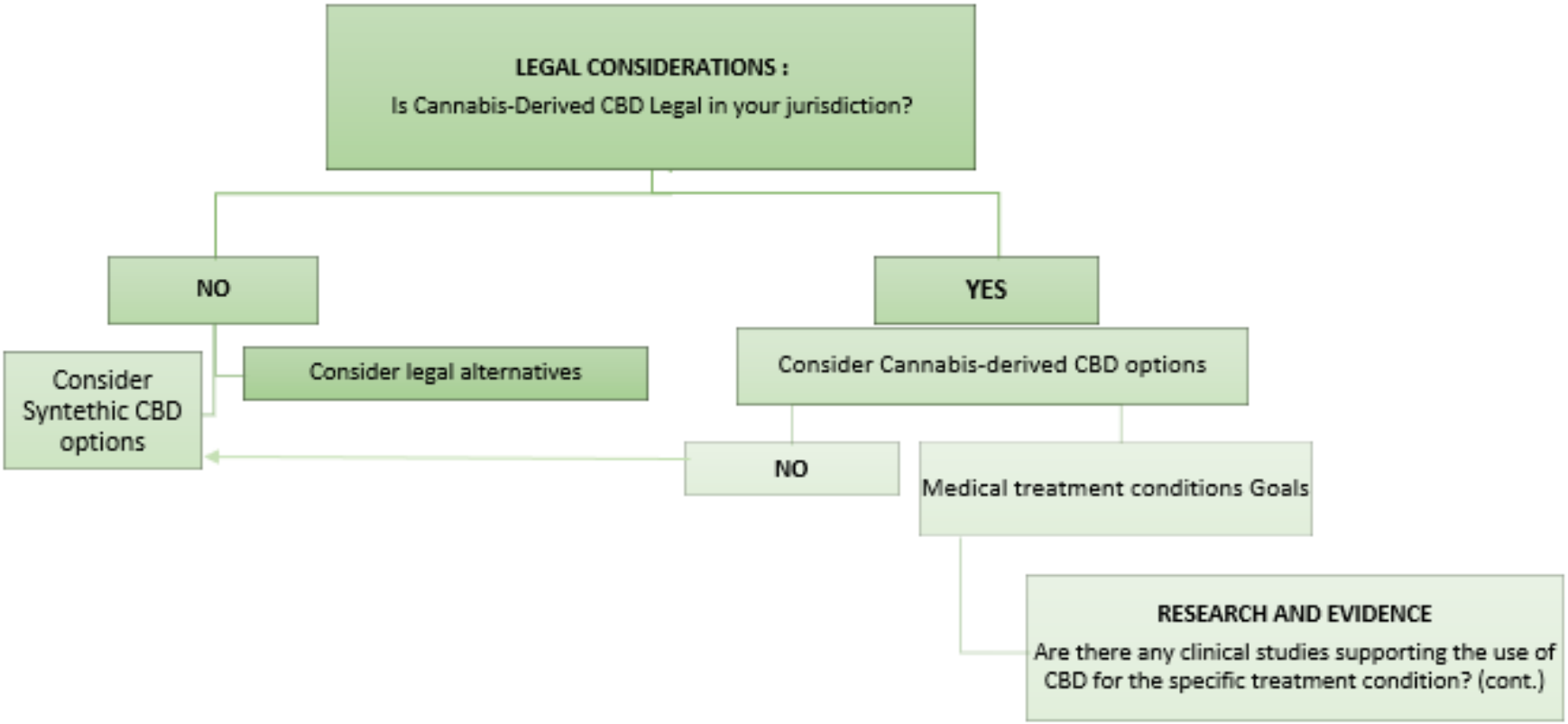
- **Medical Applications:** Beyond cosmetic skincare, CBD has shown promise in the treatment of certain dermatological conditions, such as acne, eczema, and psoriasis. Developing medical-grade CBD formulations for these conditions can open up additional revenue streams and opportunities for collaboration with healthcare providers.

- **Global Market Potential:** As regulatory barriers around CBD continue to evolve, there is potential for companies to expand into international markets where CBD regulations are favorable. This global market expansion can further drive economic growth and opportunity in the CBD dermatology sector.

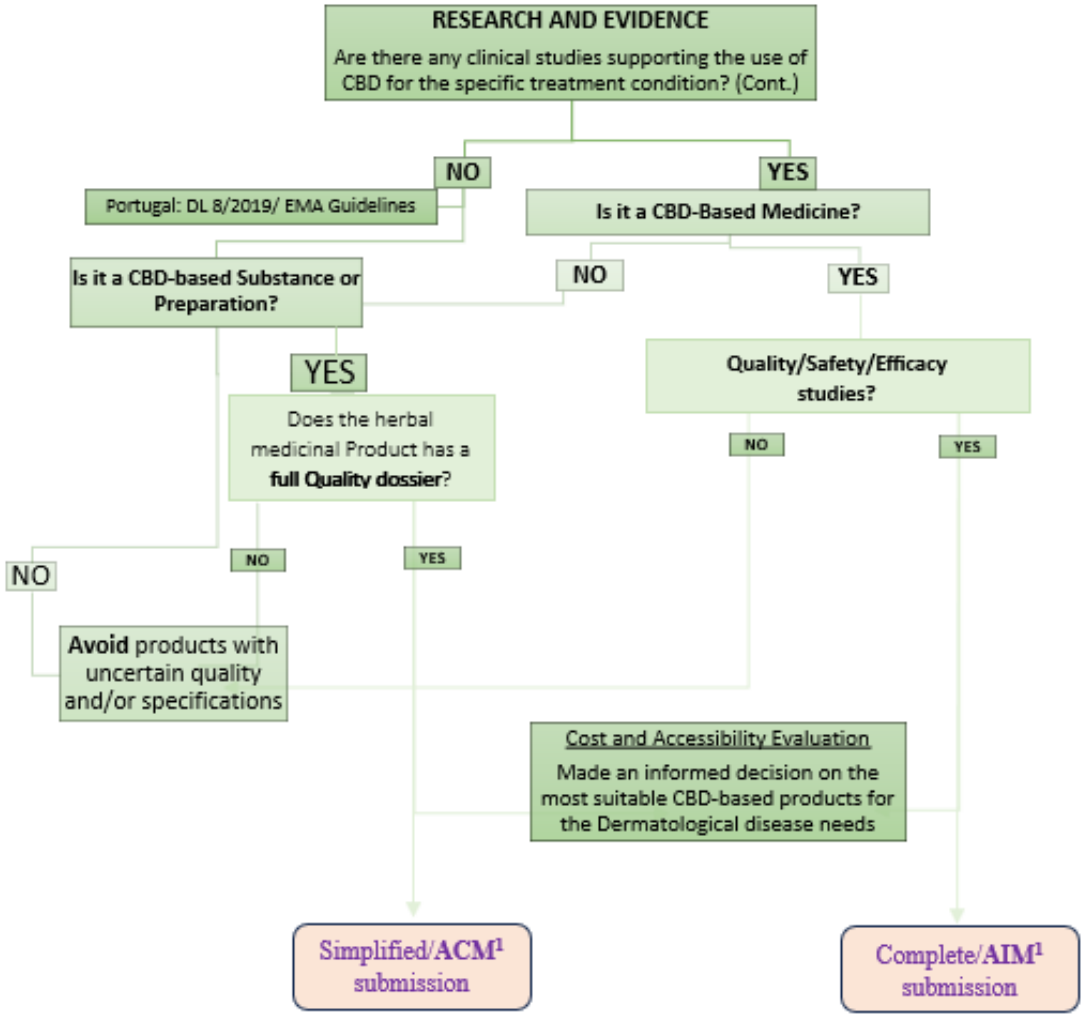
Overall, the economic advantages of CBD in Dermatology stem from its ability to drive product innovation, meet consumer demand, differentiate brands, and potentially reduce costs through streamlined formulations. However, it's essential for businesses to navigate regulatory considerations and invest in research to unlock the full potential of CBD in dermatology field (Silviu-Iulian F. et al 2023).

It is proposed, to simplify the submission process of CBD-based products, to follow the decision chart below, in that it contemplates the essential parameters to be considered during the marketing authorization submission.

Decision Chart 1 – Decision chart of a CBD-based product submission procedure (Part I).



Decision Chart 1 – Decision chart of a CBD-based product submission procedure (Part II).



[1] ACM and AIM are referred to two different types Marketing Authorization submissions in the Portuguese Regulatory context.

12.Regulatory authority adaptation

With this work, it is suggested a regulatory adaptation for the introduction of CBD medicines on the dermatological field by INFARMED, that at the same time should adapt itself on the procedural mechanism treatment, in order to improve access to this type of submission procedure.

In this way, it is necessary to consider:

1. **Speeding up the approval process**:

   Implementation of measures to speed up the approval process for new innovative drugs based on Cannabidiol for dermatological therapeutic proposes, namely to treat acne, psoriasis and melanoma, due to the comproved potential of the CBD to treat these medical conditions, that could be more satisfactory as an alternative treatment.

2. **Flexible evidence assessment**:

   INFARMED must adopt a more flexible approach to assessing clinical evidence, allowing for the inclusion of CBD data from early-phase clinical trials, real-world data, and non-traditional evidence such as Artificial Intelligence (AI) data.

3. **Collaboration with international agencies:**

   It is extremely important to strengthen collaboration with regulatory agencies of other countries and economic blocs to promote faster and more efficient review and approval of innovative medicines on the Cannabis area, while ensuring their safety and efficacy.

   Regarding the European scenario, there should be an attempt to converge laws especially at the EMA level, for greater legal uniformity in European terms on this kind of new therapeutic answers.

4. **Incentives for research and development**:

   The Regulatory Authority of INFARMED should introduce incentives for pharmaceutical companies to invest in research and development of this type of innovative medicines based

on CBD for dermatological application, such as tax credits, grants, and awards for significant discoveries and research.

5. **Transparency and public participation**:

It is important to promote transparency in the drug approval process by disclosing information about the evaluation criteria, decisions, and evidence considered. In addition, involve the public and stakeholders in the decision-making process to ensure adequate representation of society's interests is crucial and necessary.

The CBD therapeutic options are arising and their value on treatments of acne, psoriasis and melanoma should be considered and published.

6. **Continuous post-market evaluation**:

Implement a robust post-market monitoring system to continuously assess the safety and efficacy of drugs after they are introduced into the market, with agile mechanisms to take corrective action if necessary, such as Real-World Evidence (RWE) which can incorporate post-market information and its insights into decisions regarding safety and effectiveness.

7. **Access facilitation**:

Implement policies that facilitate patients access to CBD dermatological treatments and innovative medicines, including early access programs, risk-sharing schemes, and dynamic pricing mechanisms.

8. **Stimulating innovation in digital health:**

Recognize and support the development of medicines that incorporate digital technologies, such as mobile apps, remote monitoring devices, and artificial intelligence, to improve efficacy, safety, and adherence to treatment, as well as its follow-up.

9. **Overview of reviews:**

While traditional systematic reviews gather evidence from existing original research studies (primary studies), an overview of reviews gathers evidence from existing systematic reviews. At this point, INFARMED should focus on systematic reviews of studies of adults who received prescribed medicinal cannabis containing natural or synthetic cannabidiol (CBD)

and excluded evidence on cannabis for recreational use or for medicinal use without prescription/medical supervision. The systematic reviews must cover research from the last decades on a wide range of medical conditions on dermatological area, mainly related to acne, psoriasis and melanoma.

These proposals aim to balance the need to ensure the safety and efficacy of possible CBD medicines for the dermatological treatment's domain, with the need to make innovative treatments available quickly and affordably to patients who need them.

It is INFARMED that has the responsibility to create strategies for the implementation of processes aimed at better access to CBD-based medicines. Thus, regarding CBD-based products for the treatment of dermatological diseases, namely acne, psoriasis and melanoma, INFARMED should consider the possibility of implementing measures for facilitating access to the drug and innovative therapies in this field, aiming at a robust and uniform national law that will eventually be taken as an example in adjacent countries that, like Portugal, currently follow a pattern of legalization of cannabis-based therapies.

13. Highlight the Real-World Evidence in Medicinal Cannabis Research

Still nowadays, there are significant barriers to the integration of Cannabis-based medicinal products (CBMP) within treatment pathways including ongoing stigma, cost, education, complex pharmacology and a paucity of evidence to inform international and national guidelines (Alexander SPH., 2020; Barriers to accessing cannabis-based products for medicinal use on NHS prescription Findings and Recommendations; 8 August 2019).

Randomized controlled trials (RCTs) are necessary and should continue to be the standard against which medical evidence is upheld. However, they are expensive, time consuming and subject to their own limitations (McPartland J, et al.,2001). Whilst these are awaited, there is a requirement to generate evidence of potential benefits and harms to inform policy and clinical practice.

Real World Evidence (RWE) is defined as evidence derived from health data sourced from non-interventional studies, registries, electronic health records and insurance data as opposed to the highly controlled setting of RCTs (Baumfeld AE., et al., 2019).

There is an abundance of this unstructured data, however, the necessary frameworks and governance are needed for the application of this data (Framework for FDA's Real-World Evidence Program. 2018. www.fda.gov.). It is currently used extensively to monitor post-approval pharmacovigilance (Ehrenstein V., et al., 2000–2010; BMJ Open. 2013). There is clear evidence of benefit in using population-based data to detect safety events associated with specific medications to implement restrictions to reduce harm (Baumfeld AE., et al., 2019).

Consistent use of RWE to aid regulatory decision making is yet to be normalized, but the promise is apparent (Baumfeld AE., et al., 2019).

Recently, regulator-supported initiatives have highlighted the desire to incorporate RWE into licensing and guidelines, developing a framework which can incorporate its insights into decisions regarding safety and effectiveness. It is important that studies standardize their methodology according to those set out by regulatory authorities to ensure research has the greatest

impact. Moreover, they should seek to directly address questions set out by governing bodies as areas where there is insufficient research (England NH. Barriers to accessing cannabis-based products for medicinal use on NHS prescription. August 2019).

14. Conclusions

Cannabis has been used since ancient times to the modern times for recreational and medicinal purposes. In most countries, cannabis is considered an illicit drug, although there are several drugs based on phytocannabinoids, chemical compounds synthetized by the plant. These entities have a variety of physiological and often psychoactive effects; they exert their effects mainly by binding to endogenous cannabinoid receptors, CB1 and CB2. The most prevalent phytocannabinoids are THC, which is the main constituent responsible for the psychotropic and toxic effects related to cannabis, and the non-intoxicating compound with numerous medicinal properties, CBD.

Many studies have begun to show that CBD may have potential in treating various skin conditions, but clinicians should exercise caution. Several preclinical studies have demonstrated the potential of CBD in dermatology, namely in pathologies such as acne, psoriasis and melanoma, thus providing an important basis for clinical research in humans. However, are the clinical studies that prove to be essential in determining the safety, efficacy and proper dose of CBD in different dermatological conditions.

With research into CBD-based products for dermatological diseases, it is important to conduct well-designed clinical trials, including randomized, placebo-controlled, and long-term studies, to obtain robust and conclusive results. These studies can help provide solid scientific evidence to support the use of CBD as a treatment option for a variety of dermatological conditions.

Raising awareness among physicians' community to the potential of CBD-derived products, is also a critical point, to ensure that patients have access to effective and safe treatment options. Policies should be adopted around the potential of CBD-derived products, as well as implement strategies to facilitate their proper integration into clinical practice.

In the meantime, the use of prescribed medicinal cannabis along with input from patient groups, clinicians, and service planners should be considered to create greater robustness of knowledge, safety and efficacy of CBD-based products.

The CBD market is growing and is aligned with European sustainability policies, notably in terms of types of renewable cultivation and production, with regulated agricultural practices, which promote controlled and integrated production in a circular economy, where cannabis plant can represent the solution for various purposes, other than just the production of medicinal products.

Although products that include CBD are being marketed to consumers for several purported benefits, lack of harmonization and regulatory certainty continue to pose challenges for the EU cannabis market. However, calls for harmonization of medicinal cannabis and CBD rules, coupled with the potential reclassification of cannabis under international treaties, suggest that the cannabis regulatory landscape in the EU is set for a seismic shift in the not-too-distant future. International businesses will no doubt welcome more certainty when launching their cannabis products in the EU market in the years ahead.

The increasing regulation of the CBD market can encourage businesses to adopt correct practices and provide clear information to consumers about the origin and production methods of their products and, regulatory authorities, both at the level of each country and at the international level, should also adopt strategic measures to standardize the law that regulates this type of medicines.

Regarding Portuguese environment, the authority and industries must adopt joint strategies to encourage research and development of the cannabis-based topical medicines from its cultivation, processing, distribution, and patient appropriate use as well physician education required for their transparent and rational use.

Achieving legal uniformity within the scope of CBD-based products can be challenging, given the current fragmented regulatory landscape and the cultural, political, and legal differences between countries. It would take a coordinated effort between governments, international organizations, and industry stakeholders to develop and implement common regulatory standards

for CBD products on a global scale, but this will be the main solution, to achieve the legal uniformity necessary for a safe and fluent regulatory context.

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