Tarun Belwal
Naveen Chandra Belwal *Editors*

Revolutionizing the Potential of Hemp and Its Products in Changing the Global Economy

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Contents

Chapter 1
Hemp (*Cannabis sativa* L.)-Taxonomy, Distribution and Uses

Hari Prasad Devkota

Abstract *Cannabis sativa* L. (Family: Cannabaceae) is reported as one of the oldest cultivated crops for various purposes such as food, medicine and fiber. It is believed to be originated in central Asia around northwest Himalayas and has spread around the world. It is documented to be used as medicine in India and China for almost six thousand years. However, due to the presence of psychoactive tetrahydrocannabinol (THC) compounds such as (-)-*trans*-$\triangle^9$-tetrahydrocannabinol ($\triangle^9$-THC) and (-)-*trans*-$\triangle^8$-tetrahydrocannabinol ($\triangle^8$-THC), its cultivation and use is restricted/regulated in many countries. On the other hand, cannabidiol (CBD) oil is gaining a lot of attention in recent years for various medicinal purposes such as the treatment of chronic pain and opioid dependence. Apart from the highly disputed medicinal purposes, hemp seeds are used as food and nutritional products in various cultures around the world. Similarly, the oil obtained from the seeds is used as edible oil and other purposes. One of the main industrial use is the production of high-quality fiber from the stem bark used in textiles, clothing, papers, building materials and biofuel. This chapter covers the history, taxonomy, distribution and current uses and future potentials of hemp as sustainable agricultural crop.

Keywords *Cannabis sativa* · Hemp · Tetrahydrocannabinol · Cannabidiol · Fiber · CBD oil

1.1 Introduction

Cannabis sativa L. (Family: Cannabaceae) (Fig. 1.1) is reported as one of the oldest cultivated crops for various purposes such as food, medicine and fiber (Hillig 2005; Żuk-Gołaszewska and Gołaszewski 2018). It is an annual herb of about 2 m in height and propagated by seeds (Fig. 1.2). It is believed to be originated in central Asia around northwest Himalayas and has spread around the world. It has been reported

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Fig. 1.1 Photographs of *Cannabis sativa* plant (Photos by Basu Dev Neupane, Nepal)

Fig. 1.2 Photographs of fruits and seeds of *Cannabis sativa* (Photos by Basu Dev Neupane and Prakash Poudel, Nepal)

to be used in India and China for almost six thousand years as medicine (Hillig 2005; Liu et al. 2017). It was later introduced to Europe around 3500 years ago and to Africa around 2000 years ago by nomadic tribes and traders from Central Asia (Hillig 2005). It is highly regarded as an important medicinal plant in many countries (Watanabe et al. 2005).

Due to wide spread use of various parts of the plant, it had become one of the significant crops in the ancient times. Leaves are used as traditional medicines in many Asian countries for the treatment of diarrhea, dysentery, wounds, etc. However, due to the presence of psychoactive tetrahydrocannabinol (THC) compounds such as (-)-*trans*-$\triangle^9$-tetrahydrocannabinol ($\triangle^9$-THC) and (-)-*trans*-$\triangle^8$-tetrahydrocannabinol ($\triangle^8$-THC) (Fig. 1.3), its cultivation and use are restricted/regulated in many countries. Some varieties of *C. sativa* having low content of THC are cultivated to obtain cannabidiol (CBD) oil from leaves and flowers rich in (-)-*trans*-cannabidiol, hemp seed oil from the seeds and fiber from the stem bark. Such low THC-content and high

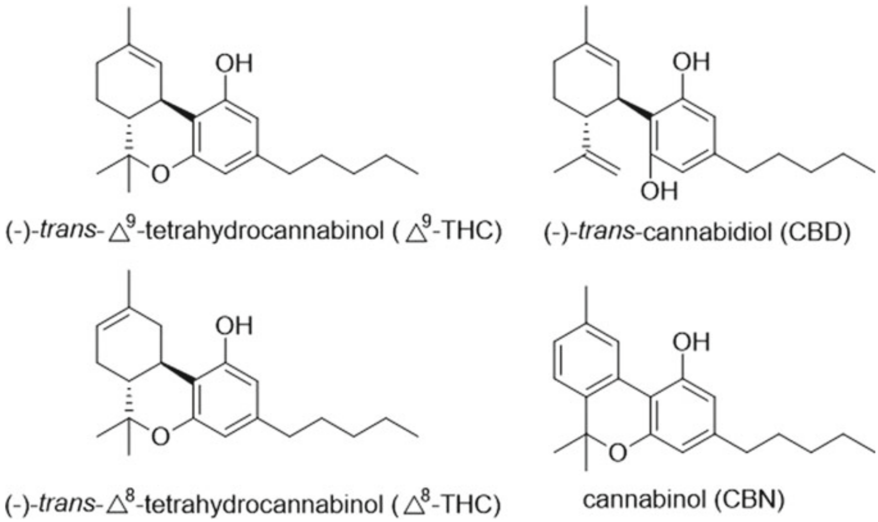

Fig. 1.3 Chemical structures of main compounds of *Cannabis sativa*

CBD content varieties usually cultivated for production of fiber are commonly known as hemp and those with high THC contents are known as marijuana (Hazekamp 2018). CBD oil is gaining a lot of attention in recent years for various medicinal purposes chronic pain and opioid dependence, however researchers have been cautious about their standardization and regulation as the contents in marketed products vary from one product to another (Hazekamp 2018; VanDolah et al. 2019). The Controlled Substances Act (CSA) of 1971 had restricted the cultivation and sell of *C. sativa* in USA. However, the Agricultural Act of 2014 allowed higher education institutions and State Department of Agriculture for the growing or cultivation of industrial hemp, i.e. *C. sativa* plants parts with no more than 0.3% of Δ^9-THC content on dry weight basis, for the research purposes (VanDolah et al. 2019). Cultivation of hemp is restricted by law in many other countries and few regions/countries have their own regulation for the content of THC. For example, in Canada, it is allowed to contain up to 3% of THC. The European Union allows up to 0.2% and Switzerland allows up to 1% of THC content (Hazekamp 2018).

Small (2015) has reported an interesting summary of *C. sativa* use, domestication and cultivation by humans. Along with human utilization, it has been evolved as one of the most useful and controversial plant species (Small 2015; Cerino et al. 2021). Hundreds of vernacular names have been used for *C. sativa* such as weed, hemp, marijuana, *Ganja*, *Bhang*, etc. As explained earlier, hemp is the name commonly used for the cultivar grown for obtaining the fiber having low contents of THC and marijuana is the common name for the cultivar used for euphoric and therapeutic properties having high contents of THC (Small 2015; Cerino et al. 2021). Hempseed is the common name for the seeds used to obtain oil for various purposes.

Apart from the highly disputed medicinal purposes, hemp seeds are used as food and nutritional products in various cultures around the world (Manandhar 2002; Cerino et al. 2021). Similarly, the oil obtained from the seeds is used as edible oil and for other purposes. One of the main industrial use is the production of high-quality fiber from the stem bark used in textiles, clothing, papers, building materials and biofuel (Adesina et al. 2020).

1.2 Taxonomy

The taxonomy of *C. sativa* is disputed as some authors consider it as a monotypic and others as polytypic one. Carl Linnaeus first named *Cannabis sativa* L. as monotypic genus. Later, other species were assigned such as *C. indica* was assigned for a specimen collected from India and *C. ruderalis* was assigned for a specimen from Russia (Pollio 2016). After 1970s, there have been many publications which assign *Cannabis* as monospecific or polyspecific genus (Pollio 2016; Cerino et al. 2021). While some authors argued that *C. indica* to be a variety of *C. sativa*, Schultes et al. described it as a separate species (Schultes et al. 1974). Later in 1976, based on the fruit morphology analysis and contents of THC, Small and Cronquist proposed that *Cannabis* is actually a monospecific genus with two subspecies i.e. (i) *C. sativa* subsp. *indica* and (ii) *C. sativa* subsp. *sativa* and four varieties i.e. (i) *C. sativa* L. subsp. *sativa* var. *sativa*, (ii) *C. sativa* L. subsp. *sativa* var. *spontanea* Vavilov; (iii) *C. sativa* L. subsp. *indica* Small and Cronquist var. *indica* (Lam) Wehmer and (iv) *C. sativa* L. subsp. *indica* Small and Cronquist var. *kafiristanica* (Vavilov) Small and Cronquist (Small and Cronquist 1976). Later in 2005, Hillig proposed that *Cannabis* is a polytypic genus with three species *C. sativa*, *C. indica* and *C. ruderalis* and seven putative taxa based on genetic analysis of the 157 samples collected from various geographical regions around the world (Hillig 2005).

However, many authors have also commonly mentioned two varieties of *C. sativa* i.e. *C. sativa* var. *sativa* commonly known as industrial cannabis/industrial hemp and *C. sativa* var. *indica* commonly known as medicinal cannabis or medicinal marijuana (Żuk-Gołaszewska and Gołaszewski 2018). Some other publications also refer them as subspecies not varieties i.e. *C. sativa* subsp. *sativa* (hemp) and *C. sativa* subsp. *indica* (marijuana) (Lim et al. 2021). Thus, the taxonomy of *C. sativa* has been always a topic of discussion among researchers due to its high market value and regulatory factors.

1.3 Global Dispersal, Distribution and Cultivation

Although the indigenous range is believed to be Central Asia, the northwest Himalayas and possibly China (Hillig 2005), *C. sativa* is widespread all around the world specially in temperate zones. It is cultivated and naturalized in most temperate and tropical areas of the world between 200 and 2700 m (Watanabe et al. 2005). Worldwide distribution map of *C. sativa* is presented in Fig. 1.4. (GBIF 2021).

For at least 6000 years, *C. sativa* has been transported and cultivated in various parts of the world by humans and thus is widespread out of its original range (Small 2015; Liu et al. 2017) which is also supported by many archaeological discoveries. In historic times, it was cultivated mainly as the source of fiber, oil, paper and clothing. It was cultivated widely in Europe in between sixteenth and eighteenth century (Żuk-Gołaszewska and Gołaszewski 2018). Both wild and cultivated varieties grow in open and sunny areas however few wild ones were also found to be growing in shaded places (Small and Cronquist 1976; Small 2015). Several factors such as phenotypic plasticity and resistance to insect damage may have resulted into widespread distribution of *C. sativa* (Small 2015). However at current times, due to strict regulation on the cultivation and use, the permitted verieties for cultivation, their cultivation condition and utilization depend upon these countries' legal frameworks.

According to Adesina et al. (2020), it is now legal to cultivate hemp in 46 states in USA and it is cultivated for scientific or commercial purposes in at least 46 states. Various researchers are now focusing their studies to understand the optimal cultivation conditions for cultivation of hemp to obtain high quality fiber and products for food, nutritional and other purposes.

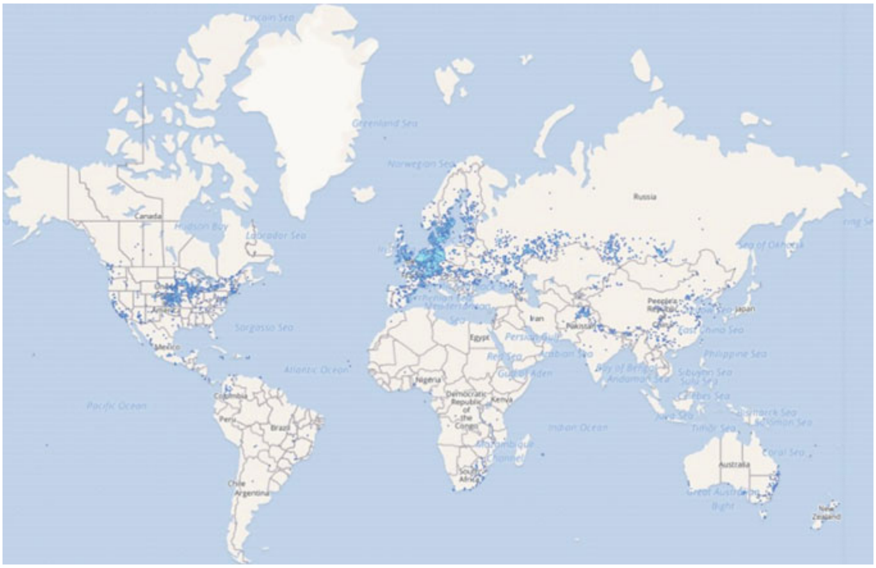

Fig. 1.4 Global distribution of *Cannabis sativa* (GBIF 2021)

1.4 Uses

Hemp has been reported to be used in China and India for almost six thousand years as medicine (Hillig 2005; Liu et al. 2017) and its various uses has made it one of the significant crops in the ancient times. Various plant parts of hemp are used for diverse purposes from food and medicine to fibers which are discussed in detail in following subsections.

1.4.1 Use as Traditional Medicine, Food, Cosmetics and Others

Cannabis sativa has long history of being used as traditional medicine in various countries. Mainly seeds were used in traditional medicines in China by mixing with other herbs to treat constipation (Liu et al. 2017). In Ayurveda, the dried leaves, known as *Vijaya*, are used in many traditional formulations. It is locally known as *Ganja* or *Bhang* in Nepal and the seeds are roasted and used to make pickle. People also chew roasted seeds. Paste of leaves is applied in cuts and wounds. Juice of the leaves is reported to be used in the treatment of diarrhea and dysentery. Leaves are mixed with animal feed to treat diarrhea and dysentery in animals. Leaves are also used as anthelmintic (Manandhar 2002). Leaf juice is used to stop bleeding from cuts and the paste of inflorescence is used to get relief from stomach pain and diarrhea. Resinous exudations of the stem, young leaves and flower buds is used to treat headache, cough, asthma and pain (Watanabe et al. 2005). In Japan, leaves were traditionally used for their pain-relieving properties, however, its use is prohibited now under the law. The seeds known as *Masinin* are used in the treatment of constipation and cough. Seeds are also one of the important ingredients included in a traditional Kampo formulation *Mashiningan* and a famous spice known as *Sichi-mi-togarashi* (Mitsuhasi et al. 1988). Hemp seeds are also used widely in China as food where roasted ones are still sold in markets. They are used as snack and by making porridge along with the edible seed oil (Liu et al. 2017).

Hemp seeds contain about 28–35% oil depending upon various factors such as plant variety, environmental factors, cultivation conditions, etc. (Rezvankhah et al. 2019). Hempseed oil is rich in polyunsaturated fatty acids (70–80%) and have unique ratio of 3:1 of omega-6 and omega 3-fatty acids (Smeriglio et al. 2016; Rezvankhah et al. 2019). Due to being rich in α-linolenic acid and γ-linolenic acid, hempseed oil has received great attention for various applications from foods to cosmetics (Cerino et al. 2021). The oil is also rich in tocopherols having the total tocopherol contents of 832.61 and 927.67 mg/kg for oils obtained by Soxhlet extraction and microwave assisted extraction (MAE), respectively (Rezvankhah et al. 2019). Hempseed oil is also rich in various antioxidant polyphenolic compounds. The methanol extract of the cold-pressed oil obtained from the Finola cultivar of *C. sativa* contained various antioxidant compounds such as phenolic acids (gallic acid, protocatechuic acid, vanillic acid, chlorogenic acid, etc.) and flavonoids belonging to different subgroups including flavonols (e.g. quercetin and kaempferol glycosides), flavanones (eriodictoyl, naringenin, naringin, etc.), isoflavones (diazein, genistein), flavone (apigenin) and flavanols (catechin, epicatechin) (Smeriglio et al. 2016).

Hempseed oil is used for various purposes from as cooking oil to an ingredient in cosmetic formulations, detergents, soaps, lighting, lubricants, etc. Recent studies are also focused to explore its potential as a source of biofuel (CAB International 2021; GBIF Secretariat 2021; Cerino et al. 2021).

1.4.2 As Therapeutic Agent in Modern Medicine

Cannabis sativa has multipurpose application in medical and pharmaceutical field. Hundreds of compounds have been reported from this plant including cannabinoids, phenolic compounds and terpenes (Andre et al. 2016). Psychoactive tetrahydrocannabinol (THC) compounds such as (-)-*trans*-$\triangle^9$-tetrahydrocannabinol ($\triangle^9$-THC) and (-)-*trans*-$\triangle^8$-tetrahydrocannabinol ($\triangle^8$-THC) have received widespread attention due to their both therapeutic potential and narcotic properties. More than 100 cannabinoids are reported which include both psychoactive ones and non-psychoactive such as cannabidiol (CBD) derivatives. The content of THC and CBD derivatives is reported to be inversely proportional (Small 2015). Small and Cronquist (1976) had proposed 0.3% content of THC as a differentiating factor for *C. sativa* subsp. *sativa* (<0.3% THC) and *C. sativa* subsp. *indica* (>0.3% THC) for dry inflorescence or young infructescence. However, other than genetic factors, their contents also vary depending upon the plant part, flowering stage of the plant, cultivation conditions, etc.

Hundreds of preclinical and clinical studies have been published regarding the therapeutic benefits of *C. sativa*-based products for pain management, multiple sclerosis, injury, cancer, diabetes, mental health condition, etc. various systematic reviews have also been published. Pratt et al. (2019) analyzed the published systematic reviews on medical benefits of *Cannabis* products and concluded that the outcomes of these reviews were not sufficient to draw a conclusion on their therapeutic benefit. Similarly, Lim et al. (2021) systematic review of clinical and preclinical research articles about the potential therapeutic benefits of hemp products in various conditions such as dependence, anxiety and constipation and reported that the finding in these studies were not sufficient to provide clinical evidence. Based on the analysis of systematic reviews of randomized trials, Riera et al. (2022) reported that cannabinoids were not therapeutically effective in pain management, but had some benefits in chemotherapy induced nausea and vomiting.

Non-psychotic compounds such as cannabidiol are receiving increasing attention in recent years for their medicinal purposes in management of opioid dependence, pain, cancer, anxiety, etc. The most commonly available formulation is CBD oil (also known as hemp oil) in which the extracts of flowers or leaves of industrial hemp are dissolved in edible oils (Hazekamp 2018; VanDolah et al. 2019). In general, the content of THC in CBD oils should be below 0.3% and the content of CBD about 12–18% (VanDolah et al. 2019). But, the analysis of various marketed CBD oils samples has shown very high content of THC and researchers have been recommending strong guidelines for the standardization and regulation of these products (Hazekamp 2018; VanDolah et al. 2019). Various natural and synthetic derivatives of CBD are being investigated in pre-clinical and clinical studies to understand their mechanism of action, therapeutic potentials, adverse effects and safety profiles (Morales et al. 2017; Nelson et al. 2020).

1.4.3 As Source for Fiber for Various Purposes

Use as fiber is considered to be one of the oldest uses of hemp plant and many archaeological discoveries from China support its use in textile even before the introduction of cotton (Liu et al. 2017). The long and strong fiber in hemp was traditionally used for rope, sails, tarpaulin, canvas bags, clothes and sacs (Watanabe et al. 2005). In recent years, the growing interest in renewable biomass has resulted into the great emphasis on industrial hemp, a fast-growing herbaceous plant, as a potential source of biomass. Fibers obtained from hemp are also used as substitute of glass fibers and to produce bioplastics (Andre et al. 2016). Hemp fiber was also used traditionally to make paper (Liu et al. 2017). Petit et al. (2020) reported that the quality of hemp fiber was affected by environmental factors such as temperature, cultivation conditions and water availability along with genetic factors. Proper understanding of these factors may help in optimal cultivation condition of hemp for obtaining high quality multi-purpose fiber.

1.5 Conclusion

Hemp (*C. sativa*) is one of the oldest cultivated plants and has been used by humans for various purposes from medicinal to food and fiber. Long history of utilization and cultivation by humans has resulted in various verieties of this plant with varying contents of THC and CBD. Strict regulation on the cultivation and use of the products obtained from the plant specially the cultivars with high THC content has resulted in extensive research on the cultivars with low THC content to be used as a source of fiber, CBD oil and hempseed oil along with other non-therapeutic purposes. Further research is necessary to understand the therapeutic benefits of hemp-base products in human health. However, it has high market demand for food and nutraceutical properties of hempseed oil and the wide application of fibers from stems in textiles, fabrics, composites and biofuels. Evidence based regulatory practices, innovations in plant cultivation and product formulations, standardization of the products and commercialization can contribute to global economy and sustainable development.

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Chapter 2
Hemp Varieties: Genetic and Chemical Diversity

Varsha Mishra, Khashti Dasila, Mithilesh Singh, and Deepika Tripathi

Abstract *Cannabis sativa* (hemp) as multifunctional crop have traditional application as fiber, food, paper, textile and pharmaceutical potential as inflorescences and seed as sources of exciting bioactive secondary metabolites. The Genus *Cannabis* is the only producer of phytocannabinoids. Extensive studied have been made to describe the origin history, geographical ranges and genetic identity of the *Cannabis* species but it remains obscured to date. Various high through put genetic marker have been studied to assess the genetic diversity in hemp varieties. Studies also indicated that domestication origin affects the genetic groups of hemp which further consequences on the chemical diversity of the cannabis. Chemotaxonomy using chemical markers also played a crucial role in differencing and allocating the *Cannabis* taxa. Cannabinoids ratio and terpene composition are the major marker to play an important role in studying chemical diversity of *Cannabis* sp. *Cannabis* genus is the only source of phytocannabinoids the dominant chemical class. Other than cannabinoids terpene and non-cannabinoid phenolic compounds also contribute in the chemical diversity of the species. The vast array of phytochemicals presents in the genus have potential application in pharmaceutical industries. However, due to its legalization status very limited study on its chemical and genetic diversity have been done. Therefore, the species needs attention to explore its commercial value.

Keywords *Cannabis sativa* · Hemp · Phytocannabinoids · Genetic diversity · Chemotaxonomy

2.1 Introduction

Cannabis is an erect, annual, dioecious and economically important aromatic medicinal herb belonging to the cannabaceae family (Pellati et al. 2018). The origination of *cannabis* was believed to be from Central Asia about ~500 BC (Farag and Kayser

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2017). Plants belongs to this genus are well grown in wet land sites and near water bodies, where the concentration of nitrogen are found high (Small 2015). *Cannabis* is highly used and described genus in Ayurveda to provide various pharmacological bioactive compounds and benefits. Now a days, people take interest in this multi-purpose plant due to the presence of high content of various nutrients along with bioactive therapeutic compounds having analgesic, anti-spasmodic, anti-tumour, anti-inflammatory, anti-oxidant, antineoplastic**,** neuro-protective, immunosuppressive, anti-nociceptive, antiepileptic, and anti-depressant properties (Carchman et al. 1976; Ameri et al. 1999; Callaway 2004; Gomes et al. 2008; Appendino et al. 2011) Cannabinoids, the major fundamental phytoconstituent of this genus which are chemically a unique class of terpenophenolic compounds having pharmaceutical potential such as anti0inflammatory, anti-cancer, antimicrobial, anti-arthritic, neuro antioxidative, etc. (De Petrocellis et al., 2011). Apart from this, hemp is also used by the mankind as natural fibres in the textile industry and as seed oil in the cosmetic production (Gautam et al. 2013; Clarke and Merlin 2013; Russo et al. 2008; Farag and Kayser 2017). Hemp use as a suitable eco-friendly option for phyto-remediation and bio fuel production has also been reported (Kumar et al. 2017).

Hemp is a highly variable species in plant system and it has been a matter of debate that whether the genus *Cannabis* having one species or more than one species (Chandra et al. 2017). According to Hazekamp and Fischedick (2012), *Cannabis* is a monotypic genus and consists a single species namely *Cannabis sativa* (described by Leonard Fuchs in the sixteenth century). Approximately 700 different varieties/cultivars of *Cannabis* have been identified and distinguished by the plant breeders and recreational users due to the results of centuries of breeding and selection. However, it is unclear whether or not these cultivars reflect any relevant differences in chemical composition.

2.2 Varieties of Hemp

With the course of time, different varieties of hemp have been evolved as the result of plant breeding and selection programme. Till so far, no in-dept study on the monospecific or/and polyspecific character of genus *Cannabis* has been made. According to the (United Nations Office on Drugs and Crime (UNODC) hemp is divided into three different categories like (a) fiber hemp (b) oil seed hemp and (c) drug hemp (Farag and Kayser 2017). Similarly, Schultes et al. (1974) also differentiated this genus into three species such as *C. sativa* L.*,* *C. indica* L.*,* and *C. ruderalis.* However, many reports are available on *Cannabis* is monotypic genus that consist only a single species *C. sativa* (Beutler and Dermarderosian 1978; Hoffmann 1961). Small and Cronquist (1976) divided the monotypic species *C. sativa* into the subspecies 'sativa' and 'indica' each with two different variants i.e., domesticated (*C. sativa* subsp. *sativa* var. *sativa* and *C. sativa* subsp. *indica* var. *indica*) and wild varieties (*C. sativa* subsp. *sativa* var. *spontama* and *C. sativa* subsp. *indica* var. *kafiristanica*). In last

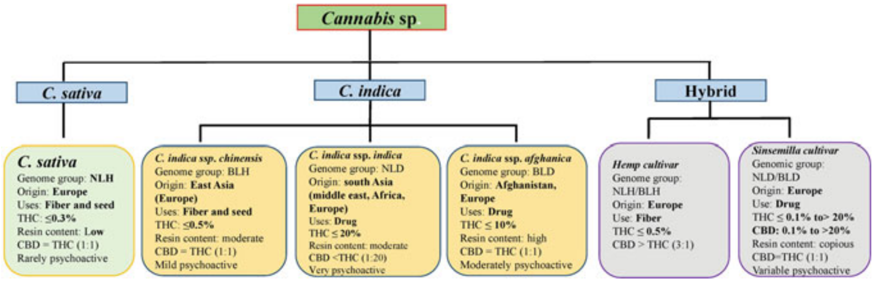

Fig. 2.1 Modern *Cannabis* taxonomy given by Clarke and Merlin (2016). Abbreviation: NLH = narrow leaflet hemp; BLH = broad leaflet hemp; NLD = narrow leaflet drug; BLD = broad leaflet drug; CBD = cannabidiol, and THC = delta-9-tetrahydrocannabinol

two decades, various new hybrid varieties have been also developed like 'Super-sativa', 'Bedrocan', 'Bedrobinol', and 'Bediol' etc. (Clarke and Watson 2002; de Meijer 2004; Flemming et al. 2007). Many *Cannabis* hybrid varieties and some pure strains have been now commercialized by many private farms and ~20 strains are well defined for the cultivation of Hemp. A large number of plant breeders cultivate fiber hemp variety with the target to reduce THC concentration (de Meijer 1995). During the origination process of plant, particularly Hemp opened the path to hybridization and leads the development of thousands of cultivars. Small (2015) stated that there is a serious taxonomic issue to classify the different strains of *Cannabis* and divide the *C. sativa* L. species into 3 subspecies or variants such as '*sativa*' (industrial cannabis/hemp having a limited amount of tetrahydrocannabinol or THC), '*indica*' (medicinal cannabis/marijuana producing principally THC), and '*ruderalis*' (known for wild hemp strains). Clarke and Merlin (2016) referred *C. ruderalis* as ancestor of two modern *Cannabis* sp. (*C. sativa* and *C. indica*), originated from central Asia. The recent taxonomy of *Cannabis* was given by Clarke and Merlin (2016) as presented in Fig. 2.1.

2.3 Geographical Distribution

Cannabis has usually a wide range of geographical and ecological distribution. It is grown worldwide except Antarctica, in a broad range of environment from sub-arctic to temperate and tropical from sea level to over 3000 m elevation (Clarke and Merlin 2013; Glanzman 2015). This genus is believed to have originated in the Northwest Himalayas and widely distributed in the range of Africa. Small and Cronquist (1976) reported that genus *Cannabis*, geographically distributed towards latitude 30°N (North) and 60°N (South) (Hillig 2005).

Clarke and Merlin (2013), reported that *Cannabis* is distributed worldwide by humans for multiple purposes. According to the authors, the putative ancestor of *Cannabis* is originated in Central Asia. It is hypothesized that *Cannabis* distributed

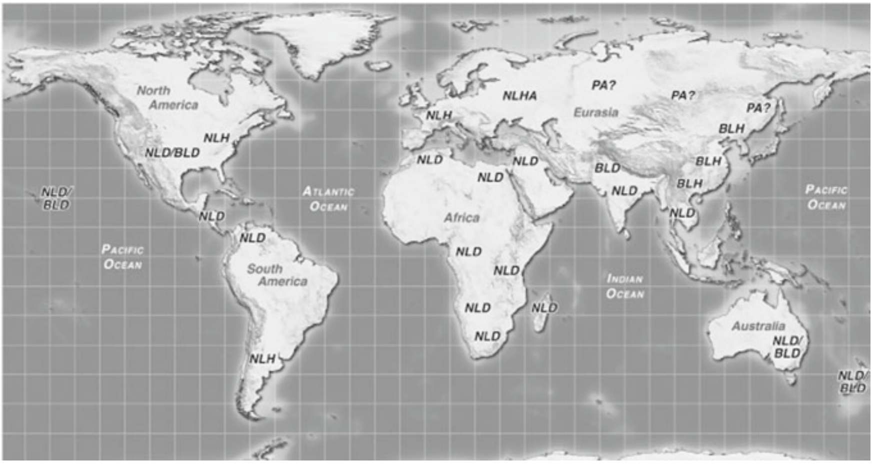

Fig. 2.2 Graphical distribution of *Cannabis* subspecies (Clarke and Merlin 2016)

into new geographical areas and evolved into 4 taxonomic groups along with gene pools as *Cannabis sativa* narrow leaflet hemp (NLH), *C. indica* broad leaflet hemp (BLH), *C. indica* narrow leaflet drug (NLD), *Cannabis indica* spp. *afghanica* broad leaflet drug (BLD). Based on the broad taxonomic groups the worldwide distribution of *Cannabis* is given in Fig. 2.2.

2.4 Genetic Diversity

Identification of functional gene variation and trait mapping is important step for understanding toward the evolutionary and functional aspects of *Cannabis.* Hemp possesses diploid genome (2n = 20) with difference in sizes as 818 Mb for female and 843 Mb for males (Sakamoto et al. 1998). Inspite of being restricted due to legalization stautus various authors attempted to study the hemp genetic for various traits like fiber quality, sex determination, sex expression, assessment of population diversity, and genetic relatedness between strains using various genetic tools etc. The genomic markers used for various trait mapping in hemp species are described in Table 2.1.

Various issues regarding naming, breeding and quality control arises in hemp varieties cultivation. According to Lynch et al. (2016) and Schwabe et al. (2019) traditional classification did not determine the genetic relationship in drug-type and fibre-type *Cannabis* species i.e., '*indica*' and '*sativa*'. Both drug-type and fiber-type *C. sativa* plants are genetically different and have been used for breeding practices for various purposes (van Bakel et al. 2011; Sawler et al. 2015; Lynch et al. 2016; Vergara et al. 2021). Previous studies usually focused on *Cannabis* species having high CBD/low THC but sometime these are closely related to marijuana

Table 2.1 Genetic markers/tools used for the study genetic diversity studies in *Cannabis sativa* (Hamp)

S. no	*Cannabis* sp.	Genetic markers/tool used	Application	Reference
1	*Cannabis sativa*	Random amplified polymorphic DNA (RAPD)	Genetic variation between cultivars/accession	Faeti et al. 1996
2	*Cannabis sativa*	Amplified fragment length polymorphism (AFLP)	Genetic variation hemp and marijuana	Datwyler and Weiblen 2006
3	*Cannabis sativa*	Inter simple sequence repeat (ISSR)	genetic relatedness in drug- type and hemp- type	Hakki et al. 2007
4	*Cannabis sativa*	Organelle DNA (chloroplast and mitochondria)	Differentiation between hemp and marijuana population	Gilmore et al. 2007
5	*Cannabis sativa*	Genomic libraries	Fiber quality	Van den Broeck et al. 2008
6	*Cannabis sativa*	Genomic libraries	Transcriptomes analyse	van Bakel et al. 2011; Laverty et al. 2019
7	*Cannabis sativa*	Amplified fragment length polymorphism (AFLP)	Population genetic diversity	Hu et al. 2012
8	*Cannabis sativa*	Single-nucleotide polymorphisms (SNPs)	Genetic diversity and population structure among hemp and marijuana	Sawler et al. 2015
9	*Cannabis sativa*	amplified fragment length polymorphism (AFLP)	Effect of Gene duplication and divergence on cannabinoid production	Weiblen et al. 2015
10	*Cannabis sativa*	amplified fragment length polymorphism (AFLP)	sex expression in monoecious and dioecious hemp	Faux et al. 2016
11	*Cannabis sativa*	Inter simple sequence repeat (ISSR)	Genetic relationship between strains	Punja et al. 2017
12	*Cannabis* sp. (Hemp and marijuana)	Short tandem repeats (STR)	Characterization of drug vs. non-drug *Cannabis*	Dufresnes et al. 2017

(continued)

Table 2.1 (continued)

S. no	*Cannabis* sp.	Genetic markers/tool used	Application	Reference
13	*Cannabis sativa*	Genotyping-By-Sequencing (GBS)	Genetic diversity and population structure in Iranian cannabis germplasm	Soorni et al. 2017
14	*Cannabis sativa*	Inter simple sequence repeat (ISSR)	Genetic relationship among strains	Punja et al. 2017
15	*Cannabis* sp.	Simple sequence repeat (SSR)	Genetic and population structure	Zhang et al. 2020
16	*Cannabis* sp.	Single-nucleotide polymorphisms (SNP)	Population structure, phylogenetic relationship, population genetics	Henry et al. 2020
17	*Cannabis sativa*	next generation sequencing and nanoHPLC mass spectrometry	Proteomic and metabolomic analysis	Jenkins and Orsburn 2020; Conneely et al. 2021

species (Grassa et al. 2021). However, both types have been practicing to bred for specific compound production like cannabinoids and terpenoids. *Cannabis* genetics evolving with focus on *C. sativa* marijuana-type as compared to CBD-type hemp (Lynch et al. 2016; Vergara et al. 2021, Johnson and Wallace 2021).

2.5 Chemical Diversity in *Cannabis Sativa*

Apart from being controversial crop for various issues related to taxonomic status, origin, morphological and ecological diversity, *Cannabis* exhibited extensive phytochemical diversity in particular reference to cannabinoid and terpenoid (Hillig and Mahlberg 2004). Phytocannabinoids are the dominant chemical class of genus *Cannabis*. Cannabinoids are terpenophenolic compounds which are chemically associated terpenes with its ring structure derived from C10 monoterpene subunit i.e., geranyl pyrophosphate. Geranyl pyrophosphate are the biogenetic origin of cannabinoids (Hanus et al. 2016). Two independent pathways namely cytosolic mevalonate and plastidial methylerythritol phosphate (MEP) are responsible for phytoterpene biosynthesis. MEP pathway is reported for the biosynthesis of the cannabinoid terpenoid moiety biosynthesis (Sirikantaramas et al. 2007; ElSohly et al. 2017). The cannabinoids accumulated in cannabis plant as cannabinoid acids and non-enzymatically decarboxylated into their neutral forms during storage (Small 2015).

Radwan et al. (2021) reviewed the phytochemistry, isolation, identification and structural elucidation of more than 500 constituents including cannabinoids and non-cannabinoids class of C. *sativa*. To date different secondary metabolites class of *C. sativa* were presented in Table 2.2. The chemical structures of cannabinoids and terpenoids compounds are presented in Figs. 2.3 and 2.4.

Table 2.2 Chemical diversity of *Cannabis sativa* (Radwan et al. 2021)

Chemical class	No. of compound reported	Analytical techniques used for identification
Total cannabinoids	*125*	Column chromatography, Thin Layer Chromatography (TLC), Vaccum Liquid Chromatography (VLC), Solid Phase extraction (SPE), Ultraviolet–visible infrared spectroscopy (UV IR), Nuclear Magnetic Resonance (NMR) spectroscopy (1D&2D), UV spectroscopy, Mass spectrometry (MS), semi preparative (Riverse phase- High performance Liquid Chromatography (RP-HPLC), Gas Chromatography Mass spectrometry (GCMS), X-ray analysis and High Resolution mass spectrometry (HRMS)
Δ9-THC type	25	
Δ8-THC type	5	
CBG type	16	
CBC type	9	
CBD type	10	
CBND type	2	
CBE type	5	
CBL type	3	
CBN type	11	
CBT type	9	
Miscellaneous types	30	
Total non-cannabinoids	*400*	
Non cannabinoid phenol	*76*	Silica gel column chromatography, TLC, VLC, 1H and 13C NMR and MS, X-ray crystallography, EIMS, flash chromatograph, HPLC, High resolution electrospray ionisation mass spectrometry (HR-ESIMS), and ESI–MS spectroscopy, GC–MS and RP-HPLC, HPLC–DAD-MS
Spiro-Indans	16	
Dihydrostilbenes	12	
Dihydrophenanthrenes	7	
Simple phenol	*7*	
Flavonoids	34	
Total Terpenes	*120*	Capillary gas chromatography, GC–MS analysis, GC-FID, Spectral data comparison
Monoterpenes	61	
Sesquiterpenes	51	
Diterpenes	2	
Triterpenes	2	
Miscellaneous terpenes	4	
Alkaloids	*2*	Silica gel chromatography, TLC and X-ray crystallography,

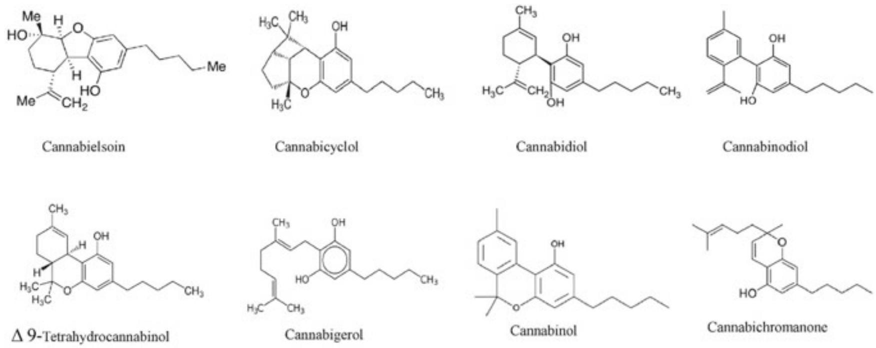

Fig. 2.3 Cannabinoids compounds in hemp

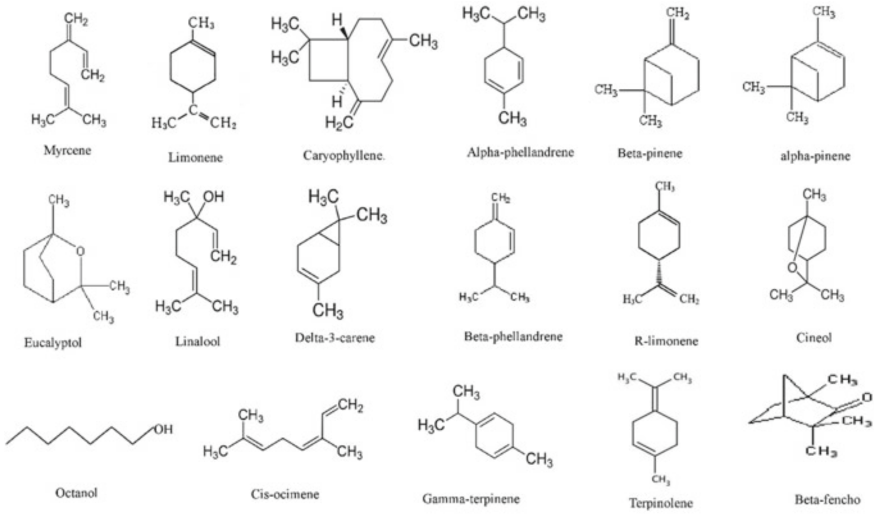

Fig. 2.4 Terpenoids compounds of hemp

2.6 Chemotaxonomic Classification of Hemp

Chemotaxonomy/chemosystematics is used to classify according to confirmable differences and similarities in their biochemical compositions. According to Small (1979a) amount of THC in *Cannabis* is essential for taxonomic characterization. Gas chromatography-flame ionization detection (GC-FID) is commonly used techniques to differentiate *indica* strains from *sativa* strains on the basis of THC content (Small and Beckstead 1973a, Small et al. 1975; Small and Cronquist 1976). Numerous phytochemical markers used for chemotaxonomic classification of *Cannabis* species/varieties are presented in Table 2.3. Based on the quantitative difference in the cannabinoids ratio of tetrahydrocannabinol acid (THC), cannabinol

Table 2.3 Analytical methods used for chemotaxonomic classification and phytochemical quantification of *Cannabis* sp.

S. no	*Cannabis* sp.	Chemotaxonomic markers	Analytical methods applied	Inferences	Reference
1	*C. sativa and C. ruderalis*	Cannabidiol (CBD) and Cannabichromene (CBC)	Gas chromatograph with flame ionization detection (GC/FID)	Cannabinoid content in *Cannabis* species is genetically control and monotypic evidences of *Cannabis* genus	Beutler and Marderosian 1978
2	157 *Cannabis* germplasm	Cannabinoids ratio	GC/FID	Based on THC/CBD ratio authors supported two-species concept of *Cannabis* as if < 25% (*C. sativa*) and > 25% (*C. indica*)	Hillig and Mahlberg 2004
3	*C. sativa* (11 varieties)	Monoterpenoids, sesquiterpenoids	GC/FID, Gas Chromatograph –Mass Spectroscopy (GC–MS)	This methodology is useful for both chemotaxonomic discrimination of *Cannabis* varieties and quality control of plant material	Fischedick et al. 2010
4	*Cannabis* sp. (40 samples)	Gamma terpinene (terpenoids) THC (cannabinoids)	GC, GC–MS	The cannabinoids and terpenoids, present in high concentrations in Cannabis flowers, are the main candidates	Hazekampa and Fischedick 2012
5	*C. indica* and *C. sativa*	Cannabinoids and terpenoids	UFLC (Cannabinoid), GC-FID (Terpenoids)	Studied *Cannabis* cultivars are not distinctly different chemotypes	Elzinga et al. 2015

(continued)

Table 2.3 (continued)

S. no	*Cannabis* sp.	Chemotaxonomic markers	Analytical methods applied	Inferences	Reference
6	*Cannabis* OG strain and Kush strain	Cannabinoids and terpenoids	UFLC (Cannabinoid), GC-FID (Terpenoids	OG strain have relatively high levels of terpenoids than kush strain	Elzinga et al. 2015
7	*Cannabis* (460 accessions)	beta-pinene (Monoterpenes) alpha-humulene (sesquiterpene) CBD (cannabinoids)	GC	Chemical constituents of *Cannabis* may act as markers for differentiation between '*indica*' and '*sativa*'	Hazekamp et al. 2016
8	*C. sativa* (2 varieties)	Cannabinoids profile, terpene composition, polyunsaturated fatty acids content, and favourable protein profile	HPLC–MS, SDS-PAGE LC–MS/MS, HS-SPME GC–MS, and GC-FID	Phytochemical and Ecological Analysis	Pavlovic et al. 2019
9	*Cannabis* (21 varieties) Leaf, inflorescence, stem, bark, and roots	Cannabinoid ratio, terpenoid, flavonoids, sterols, and triterpenoids	GC–MS (mono and sesquiterpenoids, flavonoid) HPLC	Predominant number of identified chemotype markers (with or without THC and CBD) can use in chemical fingerprints for quality standardization or strain identification	Jin et al. 2021

(CBN) and cannabidiol (CBD), in the ratio of (THC) + (CBD)/(CBN) *C. sativa* classified in three different chemical phenotypes. If THC/CBD > 1 phenotype I (drug-type), THC/CBD = 1 phenotype II (intermediate type) THC/CBD < 1 phenotype III (fibre- type or hemp) (de Meijer et al. 2003; De Backer et al. 2009; Galal et al. 2009).

Health benefits associated to cannabinoids and non-cannabinoids have been presented in Table 2.4. The biological properties related to cannabinoids mainly associated with human endocannabinoid system. The system consists of two G-protein coupled receptors i.e., CB1 and CB2 along with two ligands. The system

Table 2.4 Pharmaceutical potential of cannabinoids and non-cannabinoids compounds of *Cannabis sativa*

Secondary metabolite class	Pharmaceutical application	References
Cannabinoids type		
Δ-9 tetrahydrocannabinol	Anti-inflammatory, anti-cancer, analgesic, muscle relaxant, neuro-antioxidative and anti-spasmodic activities	De Petrocellis et al. 2011
Cannabidiol (CBD)	anti-inflammatory, antischizophrenic, antiepileptic, anti-bacterial, anti-anxiety, anti-nausea, anti-arthritic, anti-psychotic, and immunomodulatory properties	Mechoulam 2005, ElSohly and Slade 2005, Burstein 2015, Appendino et al. 2008
Cannabigerol (CBG)	Antimicrobial, analgesic, antileishmanial, and inflammatory bowel disease	Mechoulam and Gaoni 1965; Radwan et al. 2008; Borrelli et al. 2013
Cannabichromene (CBC)	Anti-inflammatory, sedative, analgesic, anti-bacterial and antifungal properties	Shoyama et al. 1972, Delong et al. 2010; Davis and Hatoum 1983, Eisohly et al. 1982
Terpenes		
Monoterpenes	Anti-cancer, anxiolytic, immunostimulant, anti-inflammatory, analgesic and anticonvulsant	Komori et al. 1995; Cleemput et al. 2009; Russo 2011
Sesquiterpenes	Anti-inflammatory and gastric cytoprotector activities	Singh and Sharma 2015
Triterpenes	Anti-bacterial, anti-fungal, anti-inflammatory and anti-cancer properties	Vázquez et al. 2012; Moses et al. 2013
Phenolic Compounds	Antioxidants, antidiabetic, antitumorigenic and anti-obesity activities, anti-inflammatory, anti-cancer and neuro-protective properties, oestrogenic properties, cytotoxic activities	Andre et al. 2010; Wang and Kurzer 1998; Werz et al. 2014; Sun et al. 2014; Cui-Ying et al. 2002

mainly thought to regulatory role in various physiological processes including pain-sensation, mood, apatite, memory, inflammation and metabolic pathways. CB1 receptors also present on cells of gastrointestinal, adrenal, lung, heart and immune systems however, CB2 receptors exerted immunomodulary effect (Andre et al. 2016). Similarly, terpenes and phenolic compounds linked to *Cannabis* sp. possesses various biological activities (Table 2.4).

2.7 Conclusion and Future Prospects

Despite of being controversial status of genus *Cannabis,* it is cultivated worldwide for its high pharmaceutical and industrial potential. Although, chemotaxonomy plays an important role to differentiate various varieties of hemp, but, the origination history and genetic diversity of *Cannabis* species still remain largely unexplored. As identification of elite chemotype is essential for production of cannabinoid for industrial use, it is paramount to first study genetic and chemical diversity of the plant in details. Considering high medicinal value of Indian varieties, it is essential for the scientific community to start working on this important medicinal agriculture crop. This will not only facilitate in drug discovery programme but can be proved as a boon for the marginal communities of the Himalayan region where this plant is growing as a weed.

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Chapter 3
Legality of Worldwide Cannabis Use and Associated Economic Benefits

Vaibhav Rathi, Gurvirender Singh, Praveen Kumar, Meenu Chaudhary, Pooja Singh, and Mudita Mishra

Abstract Hemp is a member of the Cannabaceae plant family, which includes cannabis. It is grown particularly for industrial and therapeutic reasons and has less chemical ingredients than Cannabis. Hemp, is one of the world's fastest growing plants and is used to make a number of goods such as fibres, clothing, paper, rope, paint, insulating material, food, and biofuel. Because hemp and cannabis are profoundly established in diverse countries' civilizations and traditions, they have long been a moral and social issue of laws across the world. With the passage of time, more and more nations are permitting the therapeutic and recreational use of cannabis and hemp. We've covered the laws and economic benefits of hemp all across the world in this chapter. The information is intended to provide readers with a quick overview of the legal status and economic values of those nations.

Keywords Hemp · Cannabis · THC · Cannabinoids · Economy · Export · Medical use · Cultivation

3.1 Introduction

Hemp is a member of the Cannabaceae family, which also includes Cannabis. Hemp's scientific name is *Cannabis sativa* cultivar, which is a botanical variant of Cannabis. Hemp is the world's second fastest growing plant after bamboo, making it a viable contender for a variety of industrial applications while also being economically beneficial (Deitch 2003; Erickson 2019). It may be processed and used to make textiles, biodegradable plastic, rope, paper, animal feed, food, biofuel, insulating material, and other commercial items (Johnson 2019). Hemp has the same chemical elements as cannabis, but in less amounts. THC (tetrahydrocannabinol) and CBD (cannabidiol) are psychoactive substances found in hemp. Hemp has a greater concentration of CBD than cannabis varieties, whereas cannabis has a higher concentration of THC. THC is also more psychotropic. Most of the countries that legalized the hemp and

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cannabis in any form control the concentration of THC and permits only the varieties that has lower concentration of THC, whereas some countries do not permit the hemp in any form (Dunford 2015). Table 3.1 summarizes the various applications of hemp.

Difference Between Hemp and Cannabis

This chapter focuses on the Cannabis genus as a whole, which comprises of Hemp and Cannabis both. According to author both belongs to the same biological source *Cannabis sativa*. Only difference is that Hemp contains THC less than 0.3% dry weight in leaves and buds whereas cannabis contains about 6% of THC, THC is the compound that is responsible for the psychoactive activity of the plants. The chapter distinctly defines the legalities and economic value of both plants' hemp and cannabis, wherever applicable (Hilderbrand 2018).

3.2 Hemp Illegal Countries

Table 3.2 shows the list of countries where hemp and cannabis are completely illegal to use in any form and cultivation, import and exports are banned as well.

Figure 3.1 shows the countries around the globe, the colours represent legal status of the countries and Fig. 3.2 shows the legality of hemp for medical and recreational purposes.

3.3 Countries Using Hemp: Current Legal Status and Applications

3.3.1 Antigua and Barbuda

The cannabis Act, passed on 28 November 2018, regulates the possession, manufacturing and sale of marijuana especially for medicinal uses. This act permits individuals to possess up to 15 g of marijuana along with four marijuana plants in their possession. Also, licensed dealers may distribute marijuana to patients for medical purpose. Though the recreational use of marijuana is legal, but there are still restrictions and marijuana smoking in public is illegal (Lamers 2019; Cannabis Bill 2018).

The cultivation of hemp has provided country to gain the profit in farming and export. Also, the marijuana tourism has increased the tourists' interest from all over the world, especially from the countries where cannabis is illegal (Borgen 2021).

Table 3.1 Various applications of hemp

Entire plant	Boiler fuel		
	Pyrolysis feed stock		
Cell fluid	Abrasive chemicals		
Stalk	Bast fibers	Consumer textiles	• Apparel
			• Diapers
			• Fabrics
			• Hand bags
			• Shoes
			• Fine fabric
		Industrial textiles	• Twine
			• Rope
			• Nets
			• Canvas
			• Traps
			• Caulk
			• Carpets
			• Brake/Clutch linings
			• Argo-fiber molds
			• Geotextiles
		Paper	• Printing paper
			• Fine paper
			• Filter paper
			• Newsprint
			• Cardboards
Leaves	Pulp	Building materials	• Fiber boards
			• Insulation
			• Fiberglass substitute
			• Cement
			• Stucco and mortar
		Animal materials	• Animals bedding
			• Mulch and compost
Flower	Extracts		• Oil
			• Distillate
			• Isolates
Seeds	Hempseed oil	Foods	• Salad oil
			• Margarine
			• Food supplements

(continued)

Table 3.1 (continued)

			• Cooking oils
		Industrial products	• Car parts
			• Bio-plastics
			• Scooters
			• Semiconductors
			• Animal bedding
			• Oil paints
			• Varnish
			• Printing ink
			• Fuel
			• Solvents
			• Lubricants
			• Putty
			• Coatings
		Personal hygiene	• Soap
			• Shampoo
			• Bath gels
			• Cosmetics
			• Lotions
			• Balms
	Seed cake		• Animal feed
			• Protein rich fibers
	Foods		• Granola
			• Birdseed
			• Cereal
			• Bars
			• Protein powder

3.3.2 Argentina

The country has made hemp decimalized for private and small amounts consumption according to a law passed in 2009, and medical cannabis is legal since September 2021 (Bricker 2009; Infobae 2017).

Argentina has kickstarted its economic cultivation of hemp, it could be used for the production of medicinal components and exports (Gomes 2021).

Table 3.2 List of hemp illegal countries (World Population Review 2021)

S. No.	Name of the country	Recreational use	Medical use
1.	Afghanistan	Illegal	Illegal
2.	Albania	Illegal	Illegal
3.	Algeria	Illegal	Illegal
4.	Andorra	Illegal	Illegal
5.	Angola	Illegal	Illegal
6.	Armenia	Illegal	Illegal
7.	Azerbaijan	Illegal	Illegal
8.	Bahamas	Illegal	Illegal
9.	Bahrain	Illegal	Illegal
10.	Belarus	Illegal	Illegal
11.	Benin	Illegal	Illegal
12.	Bhutan	Illegal	Illegal
13.	Bosnia and Herzegovina	Illegal	Illegal
14.	Botswana	Illegal	Illegal
15.	Brunei	Illegal	Illegal
16.	Burkina Faso	Illegal	Illegal
17.	Burundi	Illegal	Illegal
18.	Cameroon	Illegal	Illegal
19.	Cape Verde	Illegal	Illegal
20.	Central African Republic	Illegal	Illegal
21.	Chad	Illegal	Illegal
22.	People's republic of China	Illegal	Illegal
23.	Comoros	Illegal	Illegal
24.	Democratic republic of Congo	Illegal	Illegal
25.	Cuba	Illegal	Illegal
26.	Djibouti	Illegal	Illegal
27.	Dominical Republic	Illegal	Illegal
28.	East Timor	Illegal	Illegal
29.	El Salvador	Illegal	Illegal
30.	Equatorial Guinea	Illegal	Illegal
31.	Eritrea	Illegal	Illegal
32.	Eswatini	Illegal	Illegal
33.	Ethiopia	Illegal	Illegal
34.	Fiji	Illegal	Illegal

(continued)

Table 3.2 (continued)

S. No.	Name of the country	Recreational use	Medical use
35.	Gabon	Illegal	Illegal
36.	Gambia	Illegal	Illegal
37.	Greenland	Illegal	Illegal
38.	Grenada	Illegal	Illegal
39.	Guatemala	Illegal	Illegal
40.	Guinea	Illegal	Illegal
41.	Guinea-Bissau	Illegal	Illegal
42.	Guyana	Illegal	Illegal
43.	Haiti	Illegal	Illegal
44.	Honduras	Illegal	Illegal
45.	Hong-Kong	Illegal	Illegal
46.	Hungary	Illegal	Illegal
47.	Iceland	Illegal	Illegal
48.	Indonesia	Illegal	Illegal
49.	Iraq	Illegal	Illegal
50.	Ivory Coast	Illegal	Illegal
51.	Jordan	Illegal	Illegal
52.	Kazakhstan	Illegal	Illegal
53.	Kenya	Illegal	Illegal
54.	Kiribati	Illegal	Illegal
55.	Kosovo	Illegal	Illegal
56.	Kuwait	Illegal	Illegal
57.	Kyrgyzstan	Illegal	Illegal
58.	Latvia	Illegal	Illegal
59.	Liberia	Illegal	Illegal
60.	Libya	Illegal	Illegal
61.	Liechtenstein	Illegal	Illegal
62.	Macau	Illegal	Illegal
63.	Madagascar	Illegal	Illegal
64.	Malaysia	Illegal	Illegal
65.	Maldives	Illegal	Illegal
66.	Mali	Illegal	Illegal
67.	Marshall Island	Illegal	Illegal
68.	Mauritania	Illegal	Illegal
69.	Mauritius	Illegal	Illegal
70.	Micronesia	Illegal	Illegal
71.	Monaco	Illegal	Illegal

(continued)

Table 3.2 (continued)

S. No.	Name of the country	Recreational use	Medical use
72.	Mongolia	Illegal	Illegal
73.	Montenegro	Illegal	Illegal
74.	Mozambique	Illegal	Illegal
75.	Myanmar	Illegal	Illegal
76.	Namibia	Illegal	Illegal
77.	Nicaragua	Illegal	Illegal
78.	Niger	Illegal	Illegal
79.	Nigeria	Illegal	Illegal
80.	Oman	Illegal	Illegal
81.	Palau	Illegal	Illegal
82.	Qatar	Illegal	Illegal
83.	Romania	Illegal	Illegal
84.	Russia	Illegal	Illegal
85.	Saint Lucia	Illegal	Illegal
86.	Samoa	Illegal	Illegal
87.	Sao Tome and Principe	Illegal	Illegal
88.	Saudi Arabia	Illegal	Illegal
89.	Senegal	Illegal	Illegal
90.	Serbia	Illegal	Illegal
91.	Seychelles	Illegal	Illegal
92.	Sierra Leone	Illegal	Illegal
93.	Slovakia	Illegal	Illegal
94.	Solomon Island	Illegal	Illegal
95.	Somalia	Illegal	Illegal
96.	South Sudan	Illegal	Illegal
97.	Sudan	Illegal	Illegal
98.	Surinam	Illegal	Illegal
99.	Syria	Illegal	Illegal
100.	Taiwan	Illegal	Illegal
101.	Tajikistan	Illegal	Illegal
102.	Tanzania	Illegal	Illegal
103.	Togo	Illegal	Illegal
104.	Tonga	Illegal	Illegal
105.	Tunisia	Illegal	Illegal
106.	Turkmenistan	Illegal	Illegal
107.	Tuvalu	Illegal	Illegal

(continued)

Table 3.2 (continued)

S. No.	Name of the country	Recreational use	Medical use
108.	Uganda	Illegal	Illegal
109.	Ukraine	Illegal	Illegal
110.	UAE	Illegal	Illegal
111.	United Kingdom	Illegal	Illegal
112.	Uzbekistan	Illegal	Illegal
113.	Vatican City	Illegal	Illegal
114.	Venezuela	Illegal	Illegal
115.	Vietnam	Illegal	Illegal
116.	Yemen	Illegal	Illegal

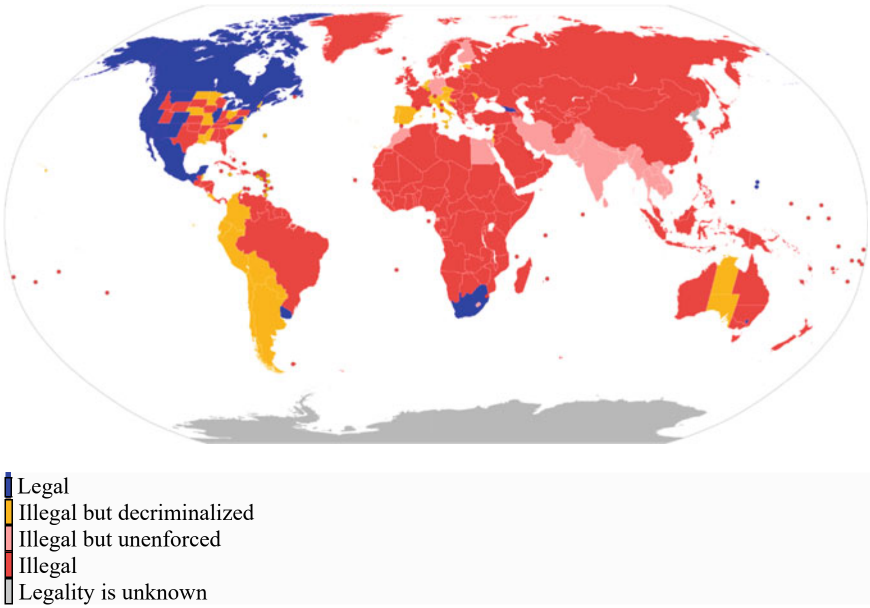

Fig. 3.1 Map showing legal status of hemp and cannabis around the globe (updated 2019)

3.3.3 Australia

Hemp is decriminalized in northern and southern Australia and fully legal is Australian capital territory for personal use but it is not allowed for sale. The residents could grow two plants and possess up to 50 g of cannabis. Medical use is legal and qualifications and conditions vary from state to state (Cannabis Support 2016).

The cultivation of hemp plays a vital role in the country's economy, which is used for medical and exports. Low THC content seeds are also used for the consumption as food in Australia and New Zealand (AIHA 2019).

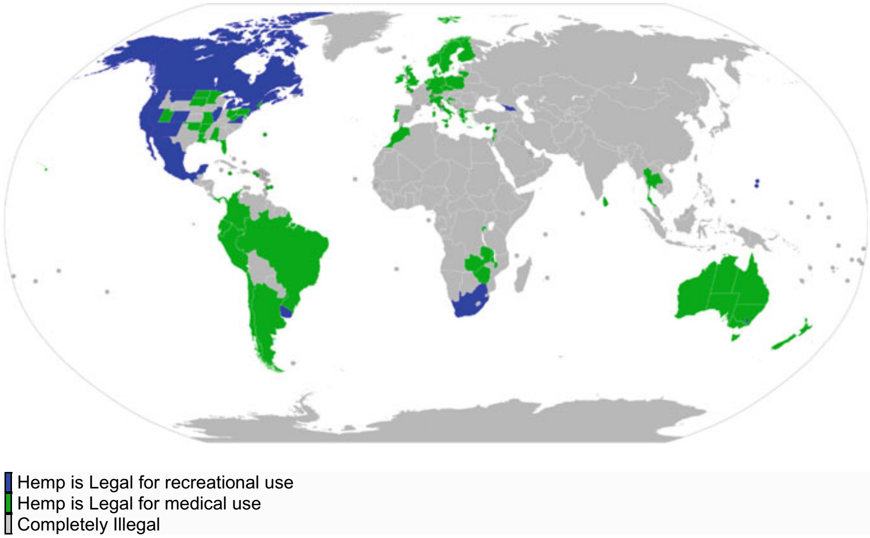

Fig. 3.2 Map showing legality for recreational and medical purposes

3.3.4 Austria

Cannabis is allowed in Austria for research and medicinal purposes, but recreational use is prohibited. Small quantities of cannabis for personal were decriminalised in 2016. Dronabinol, Sativex, Nabilone are the official cannabis medicines that are allowed to use for medical purposes under the supervision (Veldman 2021a, b, c).

Hemp is officially cultivated in Austria but it should not contain not more than 0.3% THC. Around 70-ha hemp is grown in hanftal valley. Austria produces hemp for textile, building materials and oilseed crops. Hempstone which is a combination of plastic is used for the production of furniture, musical instruments (Deniz and Staber 2021).

3.3.5 Bangladesh

Since the late 1980s, all kinds of cannabis production, transit, sale, purchase, and possession have been banned in Bangladesh, but enforcement has been slack, and the substance remains popular. Since 2017, marijuana regulations have been strictly enforced, and the government has been cracking down on the drug. The Narcotics Control Act of 1990 governs cannabis in Bangladesh. The Act allows judges the option to inflict the death penalty for possession of cannabis in excess of two kilos (Bok 2010).

In the northwestern districts of Naogaon, Rajshahi, Jamalpur, and Netrokona, as well as the mountainous regions surrounding Cox's Bazaar, Bandarban, Khagrachhari, and Rangamati in the southeast, cannabis is still grown (bordering Myanmar). Although there are no reliable estimates for the overall area of cannabis growing in Bangladesh, cultivation in the Chittagong Hill Tract region is purportedly on the rise (Hood and Hoyle 2008).

3.3.6 Barbados

Cannabis is prohibited for recreational use in Barbados, although it is nevertheless in great demand. Local dealers combine resources to acquire cannabis consignments, which are brought by go-fast boats, from St. Vincent and Jamaica (Brownfield 2011).

The Medicinal Cannabis Industry Bill, which was signed into law in November 2019, made it legal to consume cannabis for medical purposes. The Sacramental Cannabis Bill, which was also enacted, permits for the spiritual use of cannabis through registration (McDonald et al. 2020).

3.3.7 Belgium

Cannabis is one of the most widely used restricted narcotics in Belgium, both for cultivation and use. Despite substantial legal changes to cannabis-related regulations since 2010, many aspects of cannabis usage and cultivation are still regarded to be in a "legal grey area" under Belgian law. Although cannabis is officially prohibited in Belgium, it has been decriminalised since 2003. Adults over the age of 18 may possess up to 3 g of cannabis. The legal attempt to prohibit cannabis production and growth has steadily waned, resulting in a rise in cannabis cultivation and consumption (Letizi et al. 2015).

Cannabis for therapeutic reasons is permitted in Belgium under certain conditions, and its usage is on the rise. In Belgium, pharmacists and general practitioners have been able to legally supply "pre-packaged" cannabis-based medications such Sativex, as well as cannabidiol powder, since 2015. Dispensing items or medications containing one or more tetrahydrocannabinols is still illegal. While cannabis growing remains a legal grey area under Belgian law, persons who require medicinal cannabis can legally produce their own self-improvement as long as they adhere to the constraints set down in the July 1st 2019 legislation (Tom 2019).

3.3.8 Bermuda

Cannabis is permitted in Bermuda for medicinal use and has been decriminalised for recreational use. In November 2016, Bermuda's Supreme Court voted in favour of permitting medicinal cannabis usage. Patients were forced to acquire medicinal cannabis products on the illegal market due to a yearly importation restriction of only 1 g. The limit was eventually raised, but individual patients must still apply to bring their own cannabis products into the country. Bermuda's Decriminalization of Cannabis Amendment Act, which decriminalised simple possession of up to 7 g of cannabis, was introduced in 2017 (Martin 2020).

The Supreme Court of Bermuda decided in favour of permitting the medicinal use of cannabis in November 2016. Some doctors have been licensed to recommend the medicine as of July 2018 (Jonathan 2018).

3.3.9 Bolivia

Cannabis production, sale, or possession for medicinal purposes is still prohibited in Bolivia. Although the attitude toward cannabis is softened, and many individuals in the nation use it, possession of the drug is technically prohibited and punishable. Bolivia's government has chosen to legalise cannabis for medical use and has been working on the legislation for some time. The 2018 Farm Bill made hemp and hemp-derived products lawful in the United States under federal law. Hemp's removal from Schedule I of the Controlled Substances Act has helped to dispel the long-held stigma surrounding cannabis and hemp (Brownfield 2011).

3.3.10 Brazil

Although cannabis is banned and criminalised in Brazil, possession and production of small quantities for personal use were decriminalised in 2006 (Crumpton 2015). Patients who are terminally sick or have exhausted all other therapeutic options are authorised to use cannabis drugs. In the early 1800s, Portuguese colonists brought cannabis to Brazil. Although the Portuguese intended to produce hemp fibre, the slaves they brought from Africa were familiar with cannabis and used it psychoactively, prompting the Municipal Council of Rio de Janeiro to outlaw the importation of cannabis into the city and punish any slave who used it. Selling, transporting, and trafficking narcotics are all regarded criminal offences that carry sentences ranging from 5 to 15 years in jail and fine (Clarke and Merlin 2013).

3.3.11 Bulgaria

Bulgaria became the first EU member to authorize the free sale of cannabidiol produced from hemp. As long as the CBD oil does not include more than 0.2% THC, it is legal and easy to obtain in Bulgaria.

Furthermore, the parliament has authorized measures to increase the THC restrictions in CBD products from 0.2 to 0.3% (Hasse 2019).

3.3.12 Canada

Industrial hemp cultivation became permitted in Canada in 1998. Producers still encounter several difficulties eighteen years later. Farmers must first get a government permission to produce hemp. They may only sow seeds of a certain variety of hemp after that. The Canadian government has allowed these specific cultivars because they contain very little THC (Louis 2021).

In Canada, the Cannabis Act and associated Regulations establish a legal framework for cannabis possession, manufacturing, distribution, and sale. The Industrial Hemp Regulations, which are classified as a cannabis plant under the Cannabis Act, provide out the regulatory framework for managing and approving specific operations with industrial hemp, which is recognised as a cannabis plant under the Cannabis Act (Government of Canada 2018).

Bloomberg News published a report in October 2019 that portrayed a dire image of the legal cannabis market. The illicit market accounted for 86% of cannabis sales, according to an independent cannabis research organisation. Legal cannabis was selling for roughly $10.23 per gram on a national level in Canada (David 2019).

3.3.13 Cambodia

Cannabis was most likely brought to Southeast Asia in the sixteenth century, when it was utilised both medicinally and in food. Cannabis has long been produced in Cambodia and is used in a variety of foods. It was theoretically rendered illegal in 1961, in accordance with the Single Convention on Narcotics Treaty, but the legislation was not implemented, and marijuana was openly marketed. The substance was expressly proclaimed illegal during a United Nations intervention in 1992, but the legislation was never implemented (Law on Drug Management 2012).

Despite the fact that cannabis usage is prohibited, authorities do not harass users, and companies freely sell cannabis products to the general population. According to the UNODC, cannabis growing had “ceased to be a serious problem” in Cambodia as of 2009 (Cohen 2012).

3.3.14 Chile

Cannabis is banned for both manufacturing and public use in Chile, while private at-home usage is permitted. Despite this, cannabis is extensively used in Chile, having the greatest per-capita consumption in Latin America. Chile initiated clinical trials on medical cannabis in 2014, and a legalisation law passed Chile's lower house of Congress in 2015. Chile has the highest cannabis use of any Latin American country. Cannabis is imported in significant quantities from the country's neighbours (Olivia 2012).

With official approval, producers began cultivating cannabis in Chile in 2014, including a facility in Santiago to manufacture oil for cancer patients (Long 2014).

3.3.15 Colombia

The Colombian Legislative Court declared in 1994 that it was allowed to regulate cannabis and other narcotics in small amounts for personal use. Colombia's government authorised the possession of up to 20 g of cannabis in 2012. The Colombian Supreme Court declared in 2015 that growing up to 20 cannabis plants was legal (Henderson 2015; Adriaan 2015).

3.3.16 Costa Rica

Although it appears that publicly possessing Cannabis is banned in Costa Rica, personal usage is not. Marijuana sales, on the other hand, might result in criminal charges. Costa Rican laws are ambiguous when it comes to cannabis and hemp legalisation. Costa Rica doesn't have any specific law for the possession of specified "Small Amount" also the economic valuation is not clear (Emily 2016).

3.3.17 Croatia

Cannabis is decriminalised for personal use and authorised for certain medicinal purposes in Croatia. Since 2013, the Croatian penal law has made a distinction between numerous prohibited substances; they are now divided into heavy drugs and light drugs, such as cannabis. Growing or selling cannabis is a criminal punishable by a mandatory jail sentence, according to the legislation (three years minimum). Drug use in public is punished by a fine of up to €100. Art. 20 of the Disturbance of the Public Peace Act (CDDU 2017).

3.3.18 Cyprus

The hemp is illegal for personal use but it is medical use as per law passed in January 2017 for advanced cancer patients, in 2019 a more expansive law was passed and some more medical conditions were included for the use of hemp (Tharoor 2017; Healtheuropa 2019).

3.3.19 Czech Republic

Although recreational use of cannabis is banned in the Czech Republic, personal possession has been decriminalised since January 1, 2010, and medicinal cannabis has been allowed since April 1, 2013. CBD oil is lawful if the THC content is less than 0.3%. Possession of up to 10 g of dried cannabis for personal use or production of up to five plants is also legal. Cannabis remains illegal, and possession of bigger amounts might result in a one-year prison term. Trafficking is a criminal offence that has a minimum sentence of two years in jail and a maximum sentence of 18 years in prison (Tourism LLC 2017).

The law went into effect on April 1, 2013, and medicinal cannabis usage has been legal and regulated in the Czech Republic since then. The law provides for 180 g of dry matter per month if recommended by a specialist and received using an electronic prescription form (Nerses 2016).

3.3.20 Denmark

Medical use is allowed via a four-year pilot program initiated in January 2018. CBD oil is legal to buy if it contains less than 0.2% of THC (Frank 2016; Laegemiddelstyrelsen 2019).

Small quantities (up to 9.9 g) for personal use are naturally punished with a fine. A warning can be issued instead of a fine in certain circumstances, such as when a person is socially vulnerable. Larger amounts (more than 100 g or 3.5 oz) usually result in incarceration.

The Danish Medicines Agency authorised three forms of cannabis by-products for medicinal use (Sativex, Marinol, and Nabilone) in 2011, however they all require a prescription. These are typically used to relieve pain and nausea in cancer patients, as well as to relieve muscular stiffness in people with multiple sclerosis (Danmark 2014).

3.3.21 Dominica

Cannabis is classified as a Class B substance in Dominica, making it illegal to grow, sell, or possess it. This implies that possession is punished by 12 months in prison and $12,000 in fines, or two years in prison and $20,000 in fines. Supplying, producing, or importing is punished by 3 years in prison and $100,000 in fines, or 14 years in prison and $200,000 in fines. The Commonwealth of Dominica government passed an amendment to a law on October 26th, 2020, to legalise the possession of 28 g or 1 oz or less of Cannabis. The amendment also permits them to grow up to three cannabis plants in their home (LD Act 1998; Law of Dominica 2021).

Dominica was identified by the US government in 1995 as a modest cannabis producer with a “increasingly exploited transit route”, with some cannabis being grown on the island but most being consumed locally. Authorities in the Dominican Republic confiscated 741 kg of cannabis and destroyed 48,855 plants in 1994 (Brownfield 2011).

3.3.22 Ecuador

In Ecuador, cannabis is allowed for personal consumption in amounts up to 10 g. The selling of marijuana is banned throughout Latin America (Reformas 2020).

3.3.23 Egypt

Although cannabis is banned in Egypt, many Egyptians consume it as part of their everyday lifestyle. Smuggling cannabis on a large scale is punished by death, and even little amounts can result in harsh punishments. Despite this, the legislation is not strictly enforced in many places of Egypt, where cannabis is freely used in local cafés. World News, Gibson (Charles 2010).

In the Sinai Peninsula and Upper Egypt, cannabis is produced all year round. The expertise is mostly employed in Sinai, which has been the focus of eradication operations since 1994, when 7 million cannabis plants (together with 10.3 million opium plants) were eliminated (Brownfield 2011).

3.3.24 Estonia

Cannabis is prohibited in Estonia, however possession of up to 7.5 g is deemed personal use and is subject to a fine. Large quantities and distribution are criminal offences that can result in a 5-year prison term (Andres 2018).

3.3.25 Finland

In 2001, Finland's criminal process for personal use of illicit substances was overhauled. The move was made to relieve the courts of the burden of personal use cases, speed up enforcement, and standardise enforcement practices—especially, to prevent instances from being unpunished owing to a lack of resources. Possession of up to 10 g of cannabis or 15 g of hemp is considered personal use in practise, and entails a fine of 10–20 days. Hemp is grown in Finland for medicinal and textile purposes (Archive 2014).

3.3.26 France

Cannabis derivatives can now be used to make therapeutic goods in France as of June 8, 2013. Only a prescription is required to access the drugs, and they will only be supplied if all other treatments have failed to adequately relieve discomfort (Törnkvist 2018).

CBD oil is permitted to buy online in France if the TYHC concentration is less than 0.2%, according to general European legislation (Parisien 2020).

3.3.27 Georgia

The constitutional court of Georgia made possession and consumption legal on 30-July-2018 for both recreational and medical purposes, though sales are still illegal and no dispensing system exist for medical purposes. In 2019, another law was passed which allowed the large-scale cultivation of hemp after acquiring a license from the government, and Cannabis is only allowed for local consumption and possession (rftel.org 2018; agenda.ge 2018; Roberts 2018; Niesse 2019).

Georgia currently producing flowers of hemp for export in other countries (Coolong 2020), the law that allowed cultivation of hemp, opened new opportunities for export and raw material supply for active cannabinoids for various medical purposes (Niesse 2019).

3.3.28 Germany

Hemp and its related products are illegal for possession and recreational purposes, it might be refrained in small quantities and only for personal use. In May 2016 German cabinet allowed the use of cannabis in seriously ill patients with the doctor's prescription and also when there are no alternatives remain. On March 10, 2017 the legal draft took effect that allows the procurement of license for growing medicinal cannabis (Grotenhermen 2002; Berlinger 2016).

Germany is one of the last European countries to legalize country to legalize hemp and associated CBD (cannabinol) Germany currently cultivating the hemp for medicinal purposes under state control and imports in other countries (Industrial Hemp Update 2020). Germany has been using natural hemp fiber in automotive industry for a long time, particularly for the application as natural fiber thermoplast and thermostat. The increase demand over the years has caused the hemp production for fibers is going up and Germany exports the fibers to all over the world (Karus 2013).

3.3.29 Ghana

Cannabis is illegal for recreational and personal use in Ghana but it is allowed for medicinal purposes only if the THC (tetrahydrocannabinol) is less than 0.3% and only hemp variety is allowed (Jagielski 2020).

Cannabis is cultivated in Ghana and transported to other countries in Western Africa and European countries (Paul 1996).

3.3.30 Greece

Greece has made cannabis illegal for recreational purposes, but it was legalized for medical uses in 2017, but law was actually implemented in 2018. Hemp derived CBD products that contain less than 0.2% are legal to purchase online and OTC in Greece (Archive.org 2017).

3.3.31 India

Cannabis is illegal for recreational and medical use in India, but bhang (local name for hemp) is excluded from the definition of cannabis variety. Bhang has deep rooted religious and cultural significance. Charas (resin from cannabis), ganja (fruiting top) and any preparations made from former two are illegal (Malhotra 2015).

It is also illegal to grow cannabis in most of the Indian states. Uttarakhand is the first state in northern India that has legalized hemp for cultivation in 2018. Till date no other state of India has allowed the cultivation of hemp or Bhang (Jayan 2018).

3.3.32 Iran

The law regarding the control of hemp in Iran is not clear, though hemp (hashish) is decriminalized for recreational but illegal for medical purposes. Selling cannabis is considered to be much more serious offence than consuming, because consumption is only vaguely mentioned in the law. The cultivation and collection are also illegal in Iran but still a significant number of people consume it (Veldman 2021a, b, c).

3.3.33 Ireland

Hemp and cannabis are illegal for recreational purposes but it has become legal to use medicinally as part of 5-year pilot program which was enacted in 2019 June, also CBD oil is legal in Ireland if that's extracted using only cold press method. Medical uses require case by case approval from minister of health (Debates 2016; Fsai 2021).

3.3.34 Israel

Cannabis is decriminalized in small quantity for the first two instances but according to law third time offence can lead to criminal charges, though possession in privacy in the home is punishable. The medical use of cannabis is allowed by the law in Israel (TOI 2019).

Cannabis and hemp derived THC (Tetrahydrocannabinol) are being used since 2004 for Israeli military for the treatment of PTSD (Archive 2004). As of 2017 data it was reported that Israeli medical industry is worth hundreds of millions of dollars industry, it was reported that in April 2017, Israel gave permission to export medical cannabis and generate around 267 million dollars per year, and as today it might add upto 4 billion shekels to Israeli economy (Bloomberg 2017).

3.3.35 Italy

In Italy, the possession of small amount for personal use can be fined and some documents such as passport or driver's license can be suspended. The sale is criminalized and punishable by law. The licensing for cultivation is also very strictly regulated. According to law passed in 2013. The medical and industrial use of hemp is legal (Affairitaliani 2017; Sensiseeds 2017).

The authorization is not required to grow the hemp with the level below 0.2% THC. Above that the license needs to be obtained from authority. The rule was passed to compensate loss of wheat agriculture due to low prices. Italy also has authorized industrial and ornamental hemp seeds that has no THC content. Hemp seed is also used in the preparation of various edible products (Biscuits, bread, flour, beer, tofu etc.) in Italy due to its nutritional values. The oil derived from hemp is used for cosmetics and fuel. Fabrics is also used for thermal preparations (The Guardian 2018; Coldiretti 2018).

3.3.36 Japan

Hemp is illegal for medical and recreational purposes but the cultivation of industrial hemp is legal and strictly regulated. CBD is also legal only if it is made from the stalks and stems, which practically doesn't contain any THC (Dooley and Hida 2021).

3.3.37 Jamaica

Jamaica has decriminalized the use and possession of hemp/cannabis upto 57 g and an individual can cultivate up to 5 plants for personal use. Jamaica has also legalized the medicinal uses of the hemp and had opened medical cannabis dispensary in 2018.

Rastafari religion of Jamaica has cannabis in their religious practices thus the followers are allowed to use the ganja (local name) (The Guardian 2015b; Kelly 2018).

As of 2021, the JCLA (Jamaica cannabis authority) has 29 cultivators, 73 transports and retailers registered to be legal and the legal ganja is about 5–10 times costlier than the illicitly sold hemp on the street (Hendricks and Coto 2021).

3.3.38 North Korea

The legal status is largely unknown in the country because strict laws and dictatorship, some travelers have reported that cannabis is not considered to be the drug, hence there are no rules around it, other reported that there is strict action against using the cannabis or hemp (The Guardian 2014).

3.3.39 South Korea

In November 2018, the hemp was legalized for medical uses but it remained illegal for recreational uses. South Korea is the first East Asian country to legalized medical cannabis, though medical use is also only allowed after the approval from Ministry of Food and Drug Safety. Only the drug named Epidiolex, Marinol and Sativex are allowed to be used, rest natural derivatives and raw cannabis is not allowed to be used (MFDSRK 2018).

Hemp has been the source of fabric for Korean people since the historical times. Around 9000 ha of hemp is cultivated just for the fibers. South Korea currently imports the cannabis for medical uses (Ju-young 2018).

3.3.40 Lebanon

Cannabis is illegal for personal use, and it's also illegal for trade and cultivation. Cannabis is known as Hashish in Lebanon and many other Middle East countries. In 2020 the parliament of Lebanon legalized cannabis use and cultivation for medical use, it is the first Arab country to do so. Cultivation of non-psychoactive hemp is also legal which is used for fibers (Qibalwi 2018; Lemon 2020).

3.3.41 Luxembourg

Marijuana is used clinically in Luxembourg. The cannabis is legally use in medicinal prescription in the European country Luxembourg. The Luxembourg government's announcement to change the country's approach to the recreational use and cultivation of cannabis in the face of the lack of deterrence bans. Legally, anyone over the age of 18 can legally grow up to four cannabis plants per household for personal use. Provided that content of the main psychoactive ingredient, tetrahydrocannabinol (THC) doesn't exceed more than 0.3% (The Guardian 2021; Lequotidien 2017).

3.3.42 Malta

In Malta Cannabis used as medical purpose only. The trading of Cannabis in Malta remains a criminal offense under the Drug Ordinance Act of in chapter 101. The selling of drugs by law penalties ranges from 4 to 30 years in prison and fines range from €2329.37 to €116,468.67428, but such imprisonment was decided by the court for reasons. For all other drug offenses under the Drug Ordinance 430, the penalties are 12 months to 10 years imprisonment and a fine of €465.87 to €23,293.73. The Cannabis is also known Marijuana in Malta. MA's view of what is happening in Malta's local scene regarding the use of marijuana (or cannabis) in recent years is very confusing and very disturbing. It's clear that the laws and restrictions governing the use of recreational cannabis aren't working. Relief, a local organization that promotes the liberalization of cannabis use in Malta, explains its purpose as a criminal organization that robs people of economic power and puts it in the hands of people and the state (Axcisa 2017; Julian 2019).

3.3.43 Mexico

The use of cannabis in Mexico is legal. Cannabis is legally marketed in Mexico for medicinal and other uses. On March 10, 2021, in the Mexican Legislative Chamber legalized the production of cannabis for industrial, medical and recreational purposes. Under the new law, anyone in Mexico over the age of 18 can buy and own cannabis weighing less than 28 g. If someone exceed 200 g, the individual could be punished as per the law. Adults who grow eight or more cannabis plants at home can also face up to 10 years in prison. Adults are not allowed to smoke in front of children or in public places (Brookings 2021).

3.3.44 Morocco

Morocco is the world's greatest producer of cannabis and hashish, and hashish is also known as vans in Morocco. Selling for medicinal reasons is lawful; however, selling for profit is prohibited but not a crime. Morocco is remains the greatest producer of cannabis resin in the world (hashish). Moroccan cannabis producers have demonstrated incredible perseverance in the face of government attempts to destroy or restrict cannabis growing, as well as incredible adaptability to changing worldwide market conditions, during the last 50 years. Under present law, cannabis production, sale, and use are all prohibited (Blickman 2017; Laura 2017).

3.3.45 Nepal

Nepal has been using Cannabis since long time ago, the cultivation and commercial use of Bhang is illegal in Nepal. It is also banned in medicines in this Country. But only festival of Hindus, it is used in Mahashivratri. Nepal legally bans cannabis with symbolic cultural value and economic and medical benefits. Farmers will probably benefit from legalization. Employment opportunities, tourism and government revenues will increase. Exporting cannabis can reduce a country's trade deficit. Due to growing public support for the legalization of cannabis, a recent bill has been submitted for consideration by the Nepalese parliament. This study provides a comprehensive analysis of cannabis status, including the history of cannabis in Nepal and its potential positive effects if legalized (Khanal 2021).

3.3.46 Netherlands

Use of Cannabis is legal in the medicinal use but up to 5 g drug is illegal in the case of commercial and personal case. The hemp is only used for the coffee shops and continental purpose, but only if it produced from European hemp and contains 0.05% or less THC (CAB 2019).

3.3.47 New Zealand

The use of cannabis is illegal for commercial purposes, but it is legal for medicinal purposes, and hemp is sold on a doctor's prescription. The government has accepted a proposal to authorize cannabis production from seed to sale, limit the size of the total market, and allocate quotas so that producers do not exceed 20% of the total market. This model can be used to get people into legally taxable jobs and bring the long-awaited income to the Province of New Zealand. The first document shared the results of BERL modelling to provide an estimate of New Zealand's illegal market and the current range of harms or benefits associated with cannabis use in New Zealand. Once this is understood, it is possible to identify various proposed policy settings, including the New Zealand statutory market, including structures, production, processing, retail, and related policy recommendations to regulate the legal market for recreational cannabis (Drug Foundation 2020).

3.3.48 Norway

Hemp is used in Norway as medicinal use not for commercial use. It is also known as Cannabis in Norway (Andreas et al. 2021).

3.3.49 Pakistan

Cannabis is illegal for recreational use, but the extracts of cannabis can be used for industrial and medical uses. Cannabis is known as bhang in Pakistan (The Express Tribune 2020).

On September 2020, federal government of Pakistan allowed the hemp production for the different products such as fibers, green plastic, medicines and CBD oil for export (Rana 2020).

3.3.50 Panama

Consumption of cannabis is illegal for recreational use but it's usually unenforced. Panama legalized the medical use of cannabis in October 2021. Panama is also first central American country that legalized medical cannabis (Pensa 2020; Reuters 2021).

It is illegal to cultivate hemp in Panama.

3.3.51 Paraguay

Paraguay is second largest producer of cannabis in Latin America, despite this usage of cannabis was largely illegal and only amount lower than 10 g is allowed for personal usage. Medical use is still illegal (The Guardian 2015a; CNN 2008).

Most of the cannabis that is grown in the country is used for the preparation of pressed marijuana and sold throughout South America. Paraguay has red fertile soil that is appropriate for the hemp cultivation, it yields around 6000 pounds per hectare (CNN 2008).

3.3.52 Peru

In Peru the medical use of hemp oil is allowed for the treatment of Epilepsy in children. Individual can keep it for personal use within eight grams quantity. As per Cannabis Law proposed in 2017 cannabis was legalized in Peru for medical and personal use. But it is fall under the category of illegal if it is used for amusement. Cannabis and its derivative can be produced commercialize, import and investigate for medical use only. In October 2020 two laws had been proposed for the consumption of cannabis is only allowed for specific patients called as 'Registry of Patients'. (Those patients whose supervision is regulated by competent government authority.) The cultivation, collection and sale are punishable for 8–15 years of imprisonment (Fleming 2017).

3.3.53 Philippines

Cannabis and hemp commonly known as marijuana. Both are illegal in Philippines. In June 2018 Government authorities of Philippines removed it from Dangerous Drug act. FDA approved and suggested that it is permissible for 'compassionate use of marijuana'. It is used for terminally ill patients like HIV, AIDs and cancer (Patricia 2018).

3.3.54 Poland

As per the draft bill in April 2021 the concentration of THC (delta-9-THC-2-carboxylic acid) in raisin form should not be exceeded from 0.2% in the species of *Cannabis sativa*. It is permissible for the commercial purpose like plant protection as fertilizer, for beekeeping and for veterinary use. Recently their consumption is allowed in pharmaceutical, paper, food and cosmetic industries (Prawda 2021).

3.3.55 Portugal

Cannabis allowed for medical use in Portugal. CBD only available on the prescription of registered medical Practitioner only. The cultivation of cannabis hemp and marijuana are not allowed for personal use. As per the amendment done in mid-2018 the CBD oil used as medical purpose for the management of the symptoms of multiple sclerosis, Tourette syndrome, Chronic pain and spinal cord injury chemotherapy induced nausea and vomiting, Hepatitis. Special permit is required for import and export of can cannabis in Portugal (Topshoiva 2021).

3.3.56 Romania

As per the guidelines proposed in 2005 the consumption growth and import of cannabis is only allowed for medical use. The concentration of THC should be zero percent in CBD oil. They are cultivated for seed, grain, oil, fiber resin extract and tincture. In 2018 cannabis was decriminalized. According to the latest update of July 2019 the maximum allowable concentration of THC is 20% for medical use on the prescription of RMPs only (Peru 2018).

3.3.57 Saint Vincent

Cannabis is legal in Saint Vincent and it is decriminalized. There will be no criminal offences will be executed on keeping up to fifty-seven grams of cannabis. It is legal for medicinal purpose. As per the cannabis bill in 2018 the approval of cultivation of commercial medical use of cannabis can be obtained. Medicinal Cannabis Authority (MCA) allows the transport sell export and import for conduction of experimental procedure research and development. Cannabis available on prescription of RMPs and it is valid for thirty days only. The dispensing of cannabis is strictly regulated under the supervision of Pharmacist. As per the amendment done in 2018, the possession and consumption of cannabis considered as criminal offence at nearby or in schools, colleges medical educational institutions, cultural and sports venue (Searchlight 2019).

3.3.58 Singapore

Cannabis is strictly prohibited in Singapore. CBD is only allowed for medicinal purpose in patient of epilepsy who are not responded to existing drug therapy. Recently as per the guidelines of TGA (Therapeutic Goods Administration) CBD can be consumed in the dosage form of oral, oral mucosal and sublingual (Koe 2021).

3.3.59 Slovenia

The CBD and hemp oil is legal in Slovenia if the THC content is below 0.2%. But cannabis is Illegal in Slovenia. It is prescribed by doctor only in medical urgency. The small quantity for individual use can be permissible. The cultivation of hemp for industrial purpose in Slovenia is Legal. It is not mandatory to take license from government if cultivation of hemp is less than 0.1 ha (Veldman 2021a, b, c).

3.3.60 Spain

The cultivation and collection of cannabis is illegal for trade and commercial use. The permissible amount of cannabis is hundred grams. It can be consumed for personal amusement and euphoria in private places, but the THC content should not exceed more than 0.2%. In October 2005 the government allows the use of CBD in major illness from cancer to Multiple Sclerosis. In 2017 Catalonia, a city of Spain legalized cannabis consumption, cultivation for the members of Cannabis Club. It is nonprofit organization which provides facility of cannabis to eighteen plus individuals (Alba 2021).

3.3.61 Sri-Lanka

Cannabis is lawfully marketed in Sri Lanka through Ayurveda herbal stores, and it can be utilised for medicinal and scientific reasons provided the Ministry of Health grants a license (Uragoda 2000; News.nidahasa 2009). In Sri Lanka, recreational cannabis usage is prohibited. Its usage was legalized in 1980 as a result of a colonial law modification and the Ayurveda Act (Udan 2014). Nothing "shall impair the authorized import, export, supply, manufacturing, use, or ownership of galenical preparations (extract and tincture) of the hemp plant," according to the revised colonial legislation. It is not banned for medical purpose.

3.3.62 Sweden

Cannabis is prohibited in Sweden in all forms. It is forbidden for any type of recreational use as well as common medicinal uses, and possession of even little amounts is a crime (Bejerot et al. 2021). As a result, only extremely restricted medicinal use of cannabis-based medications for specified diseases is permitted. In Sweden, it is prohibited to be under the influence of any illicit substance. This basically classifies all cannabis usage for recreational purposes as a crime. Cannabis has no official medicinal use in Sweden, and medical use is not considered an extenuating circumstance (Krcevski-Skvarc 2018).

3.3.63 Switzerland

The manufacture, culture, use, and possession of cannabis are all forbidden and deemed criminal infringements under the Federal Law on Drugs until 2020, according to the Federal Law on Drugs (Bag.admin 2021). In September 2020, the Swiss parliament established laws allowing the start of pilot programmes where adult-use cannabis can be legally manufactured, imported, and delivered to registered users (O'Brien 2021). Cannabis should be controlled in Switzerland, according to the Social Security and Health Commission of the Council of States (SGK-S), in order to govern the "cannabis market for greater youth and consumer protection." The legislation stipulates that "possession of up to 10 g of cannabis for personal use is not regarded a criminal offence" as long as it is not consumed or sold to minors (thelocal.ch 2021).

3.3.64 Thailand

Thailand became the first Southeast Asian country to allow medical marijuana in 2019. The country has eased regulations even more, allowing cannabis leaves, stems, stalks, and roots to be used in food and cosmetics. Cannabis is no longer considered "illegal" in Thailand, however there are still some restrictions on its use (Nikkei Inc. 2021).

Medical cannabis will be available for purchase from regulated stores beginning in 2021, and for personal use families will be able to grow up to six plants. Although portions plants having less than 0.2% tetrahydrocannabinol (THC), such as the roots, stalks, stems, and leaves (Nikkei Inc. 2021), can be sold or used for food or cosmetics, recreational use is still illegal, and flowers and seeds must be transferred to state medical facilities (Chuwiruch 2021). Patients' medicinal requirements and the potential health advantages of cannabis appear to be secondary in Thailand to the possible commercial gains from expanding the industry. In August 2019, 10,000 bottles of cannabis oil were delivered to patients with a prescription. By November 2020, 14,236 people had received medical cannabis, indicating a slight improvement in access (Tanguay 2021).

3.3.65 Trinidad and Tobago

Cannabis cultivation, possession, and consumption are all legal in Trinidad and Tobago. The government passed legislation in Parliament in December 2019 decriminalizing the cultivation and possession of small amounts of cannabis. President Paula-Mae Weekes signed the bill into law on December 23, 2019 (Tt.loopnews 2019; Morgan 2018). In Trinidad and Tobago, possession of less than 30 g of cannabis is no longer illegal (Nathu 2019).

3.3.66 Turkey

In Turkey, it is prohibited to use cannabis for recreational purposes. Marijuana production for therapeutic and scientific purposes is authorised in 19 Turkish provinces. However, if given permission, this can be done in other provinces as well (Yurtsever 2020). Legislation was passed in 2016 allowing the use of sublingual cannabis drugs (like Sativex) with a doctor's prescription. The use of whole-plant cannabis is still prohibited (Cumhuriyet 2016).

Manufacturing or trafficking is prosecuted by a minimum of 10 years in jail, whilst sale and supply are punishable by 5–10 years in prison. Turkey, unlike certain EU countries, has a strict drug policy that makes simply possessing illicit narcotics like cannabis/marijuana a crime. While the Turkish Penal Code No. 5237 (TPC) distinguishes between drug trafficking (Art. 188), allowing drug sales (Art. 190), and drug possession for personal use (Art. 191), all three are regarded crimes and punishable acts (Yurtsever 2020).

3.3.67 Ukraine

The medical use of cannabis in Ukraine is forbidden, except for the limited use of certain cannabis-based psychoactive compounds (Nabilone, Nabiximols, and Dronabinol) (the "Allowed Substances") for medical purposes (Danevych 2021). In Ukraine, recreational cannabis use is illegal. Industrial hemp can be grown in

Ukraine using seeds from cannabis plants with a THC level of less than 0.08% in dried straw, as long as they are listed in the State Register of Plant Variety of Ukraine ("Industrial Hemp") (Aliekperova et al. 2020).

3.3.68 United Kingdom

Despite the fact that cannabis is banned in the United Kingdom and is only available for medical purposes, the UK is the world's largest exporter of legal cannabis (INCB 2018).

Despite widespread public support for legalization, cannabis for recreational use by adults remains illegal in the United Kingdom. The legalization of medical cannabis in the United Kingdom was announced in November 2018 and THC content should not exceed more than 0.2% (Liam 2021).

3.3.69 United States

The Controlled Substances Act of 1970 makes it illegal in the United States to use or possess cannabis for any reason (CSA). Cannabis is classed as a Schedule I substance under the Controlled Substances Act (CSA), which implies it has a high potential for misuse and no accepted medicinal usefulness, making even clinical use of the drug unlawful (mpp.org. 2015). State laws on medical and recreational cannabis use, on the other hand, vary greatly, and the majority of them conflict with federal law (mpp.org. 2015).

Medicinal cannabis is permitted in 36 states, four of the five permanently administered US territories, and the District of Columbia with a doctor's recommendation. THC content restrictions were established in 12 more states to make cannabis products high in cannabidiol (CBD), a non-psychoactive component, more accessible (ncsl.org 2021). Cannabis is allowed for recreational use in 18 states, the District of Columbia, the Northern Mariana Islands, and Guam. It is now legal in 13 other states, as well as the US Virgin Islands (Hartman 2021). Although it is still unlawful to consume cannabis on a federal level, the Food and Drug Administration has approved several of its derivative compounds for prescription use. The FDA has authorised cannabinoid drugs such as Marinol (THC), Syndros (THC), Cesamet (nabilone), and Epidiolex (cannabidiol). Cannabidiol produced from industrial hemp is permitted in the United States for non-prescription use, while state laws and enforcement differ (Hudak 2018; Williams 2019).

3.3.70 Uruguay

The drug is completely lawful for both medical and recreational use within its borders. Only two private companies will first contract with and provide Uruguay with marijuana, in addition to the country's 12 governmental pharmacies that sell the drug. Simbiosys and the International Cannabis Corporation are the companies in question (ICC). While the state controls the majority of the marijuana industry and enjoys minimal profit margins, legalisation benefits both the national and international economies.

State-approved pharmacies keep a third of their income and investments from Simbiosys and the ICC. Around 7000 Uruguayans had registered with the authorities for home cultivation as of late 2018. The Uruguayan government wants to expand their cultivation and production abroad in order to increase their annual earnings. Uruguay's exports have more than doubled in a year since it began exporting globally in 2019 (Zoe 2021).

3.3.71 Vanuatu

Cannabis is illegal for recreational use in Vanuatu; however, it is authorized for medical and industrial use (Independent Staff 2018). The government's Council of Ministers adopted Decision 157/2018 on September 20, 2018, allowing for the development of companies to produce medical cannabis and industrial hemp (Vanua 2017).

3.3.72 Zambia

In Zambia, recreational cannabis use is prohibited. It was allowed for export and therapeutic purposes only in December 2019 by unanimous decision (Spears 2019). The Minister of Health refuses to give growing permits, the Narcotics Drugs and Psychotropic Substances Act outlaws the possession, cultivation, and sale of cannabis. Any criminal conduct using marijuana normally carries a sentence of 10–15 years in jail.

Zambia has made cannabis production and export lawful for both economic and therapeutic reasons (Malena 2013). Citizens can apply to the Ministry of Health for a license to cultivate medical marijuana under section 9 of Zambia's Narcotic Drugs and Psychotropic Substances Act. In February 2017, when the Honorable Minister Kampyongo issued a declaration to Parliament declaring that medical marijuana growing permits were permitted, the law was brought to public attention (Spears 2019).

3.3.73 Zimbabwe

Except for recognized medical use, cannabis is banned in Zimbabwe, and possession can result in a sentence of up to 12 years in prison (sundaynews.co.zw 2017). Zimbabweans can now "apply for permits in producing cannabis specifically for medical and research," according to a press release published in Business Report on April 30, 2017. David Parirenyatwa, the country's health minister, announced new procedures for licensing individuals and businesses to cultivate cannabis. If a license poses a risk to public health or security, the health minister has the authority to deny it (Reuters 2018).

In May 2020, farmers were offered full ownership of their land for the growing of medicinal marijuana (Tapfumaneyi 2020). Finance Minister Mthuli Ncube claimed cannabis production for therapeutic purposes has "immense potential" to produce export receipts and tax income in his budget statement on November 26, 2020. Oils, bulk extracts, and dried cannabis flowers will all be subject to up to a 20% tax. Growers can produce $40 million to $46 million worth of cannabis per month, according to Treasury's "extremely cautious" projections (Bloomberg.Com 2020).

3.4 Economic Benefits of Hemp

Hemp is a versatile plant that grows quickly and has a lot of potential as an economic asset for most countries since it can grow in a range of environmental conditions, to mention a few economic advantages. Hemp can be used to make fibres that are 10 times stronger than cotton and consume far less resources. Hemp material may be used in lieu of wood and is just as affordable and durable. Hemp also is a good source of amino acids, so it can be utilized to make protein supplements. Hemp also uses less water than cotton. Hemp takes a lot less water, for example, 1 kg cotton requires roughly 18,000 L of water, but hemp only requires 2650 L for the same amount, so even small farmers may produce it and benefit more than other crops. CBD oil has global demand and can be a great source of income for farmers and the country, the paper produced from hemp are just better almost in every way like they are brighter (doesn't even require bleaching), durable and highly reusable (can be recycled up to 8 times), Hemp may benefit numerous countries both nutritionally and economically (Clarke and Merlin 2016; Mahapatra 2018) The nations that are actively growing hemp and have an economic significance are listed in Table 3.3.

3.5 Conclusion and Future Prospects

Hemp is one of the world's fastest growing plants, which is also one of the most versatile; it requires far less water and time than many of its counterpart plants, such

Table 3.3 List of countries actively growing hemp and have significance in economy

S. No.	Countries	Economic value
3.3.1	Australia	Around 2500 ha of hemp are being grown in Australia, with Tasmania being the biggest state for hemp production. In 2011, 185.5 ha were added to the national total. This compares to 280 ha planted in Western Australia and 200 ha in Victoria. Australia cultivates hemp for seed and fibers but mostly for seeds which are used for food and sale to the cultivators (Industrial Hemp Update 2020) The first commercial crop was planted in South Australia last year, and the sector is estimated to be worth roughly $3 million per year in that state alone within the next five years (Kilvert 2020)
3.3.2	Austria	Austria produces around 4% of total hemp production of Europe. Most of that is used for food items production, automotive and construction materials (European Commission 2021). No specific data on revenue was found
3.3.3	Canada	The hemp and cannabis industry has recorded the revenue growth of almost double from 2019 to 2020 alone, around 2.6 billion dollars revenue was recorded in 2020, which is only supposed to increase in the future and create around 4000 jobs in the process. Canada recorded 318.7 million Canadian dollars alone in June 2021 (Hasse 2021)
3.3.4	Chile	Chile is largest producer of hemp in south America, which is mainly used for CBD and hemp food products (Pascual 2019a, b). By 2028, the market value of medicinal cannabis in Chile is expected to exceed 3.3 billion dollars. Meanwhile, the South American country's recreational cannabis industry is estimated to be worth about 1.7 billion dollars (Statista 2021)
3.3.5	China	Hemp and its related products are illegal for recreational and medical purposes but China is currently growing 6.54×10^4 ha of hemp making it world's largest area for the production of hemp and its related products, most of the hemp is used for the seeds, bast fibers, insulating materials, bioplastic and animal food preparations. China recorded around $1.2 billion revenue alone in 2018 (Zhao et al. 2021; The New Frontier Data 2019). The data for 2021 has not released at the time of writing this chapter
3.3.6	Denmark	In the fourth quarter of 2020, the capital area of Denmark experienced the highest sales value from medicinal cannabis, with over 6.9 million Danish kroner in primary care and roughly 131 thousand Danish kroner in hospitals. Overall medical cannabis product sales (Epidiolex) climbed by more than 20% in the third quarter of 2021, from over 13 million Danish Krones ($2 million) in the second quarter to about 16 million Danish Krones in the third quarter. European hemp is mostly used to make equipment and seeds for oil and medicinal preparations throughout Europe (Statista 2020; Pascual 2021)

(continued)

Table 3.3 (continued)

S. No.	Countries	Economic value
3.3.7	France	France is the largest producer of hemp which accounts for more than 70% of total European hemp production. Industrial hemp is mainly used for the production fibers, shivs and dust (used for incarnation, compost), flower and leaves for medical application, food supplements and bast fiber for automotive insulating material (European Commission 2021; Carus et al 2013)
3.3.8	Italy	The cultivation of hemp is legal since 2017, till 2020 more than 800 farms are cultivating around 4000 ha of hemp, from which around 80% goes into food industry and remaining 20% is used for cosmetics, nutraceuticals and green building. In Italy hemp yields around 600 euros/ha (USDA 2020)
3.3.9	Korea (South)	S. Korea is one of the highest producers of Hemp, according to current estimates the annual production of commercial hemp is approximately 14,000 tons, which is mainly used domestically. South Korea is second only to China in terms of hemp fiber production. According to ITC trade statistics, South Korea trades moderate amounts of raw or processed hemp internationally. From 2001 to 2017, Korea imported 28 tons worth an average of $138,000 a year. Korea export only 3 tons worth about $40,000 a year. The growing demand for imported hemp products can be seen in the booming health and beauty sectors of the country. In 2017, South Korea was the third largest importer of CBD cannabis oil, with a value of US $176 million, accounting for 6.6% of the world market (after the United States and Germany). The top suppliers were China, Vietnam, France, USA and India (APSA 2019)
3.3.10	Netherlands	In the Netherlands, hemp traditionally regulated by Dutch opium law preceded to 1928. According to Dutch law Hemp fiber and Hemp seed cultivation is legal, but CBD production remains banned. Finally, Over the years, the Dutch Hemp seed market has grown rapidly. Netherlands is the largest exporter of raw hemp in world. In 2019, the Netherlands was responsible for 71% of global true hemp exports (10,550 MT valued at $7.3 million). As a large exporter, but the Netherlands imported less hemp. Imports of Raw hemp totaled $285,716 (832 MT) in 2019. Netherlands produces around 10% of total European hemp production (Marjolein 2021; European Commission 2021)
3.3.11	New Zealand	The New Zealand Hemp Industries Association (NZHIA) has left the government to unleash this fast-growing “wellness” industry. New Zealand can grow high quality plants that are suitable not only for the products required by the naturopathic industry, but also for industrial products such as hemp fiber. Since the processing takes place near cannabis cultivation, the promotion of industry also promotes local employment. The global cannabis industry is currently estimated at $4.6 billion and is expected to grow to $65 billion by 2030. New Zealand’s chance is to become an opportunity breeder offering cannabinoid products such as premium seeds, wine, kiwifruit and manuka honey (Scoop 2020)

(continued)

Table 3.3 (continued)

S. No.	Countries	Economic value
3.3.12	Poland	Poland's industrial cannabis market has exploded with a small number of small employees of 4444. Poland is the largest cannabis growing country a subsidiary of Canada's Green Organic Dutchman. Cannabidiol (CBD) is the most processed non-food product from cannabis seeds. The CBD is the most popular product. The CBD market is growing very rapidly, and in the last few years a small Polish company has been established, producing CBD primarily for foreign companies. When you turn on the cannabidiol product, the rate of Polish hemp flowers changes. There is an oversupply of flowers in the EU market. It costs about €4444, €4000, €6000, $7088) per ton of biomass. Polityka perception evaluates that Poland's production of CBD, including oil, cosmetics and food, was about 218 million zloty ($58.7 million) last year. Hemp is occupying an estimated 15–20% in the market of Poland. According to Polityka Insight's analysis, Poland imported about 1200 tons of raw biomass last year to make CBD extract, most of which came from Lithuania, France, Germany and Kazakhstan (Raymunt 2020)
3.3.13	Portugal	Portugal is a medical cannabis manufacturing facility that serves the growing European market. Currently, it is fully operational to grow cannabis in Portugal, and only about companies are licensed. Most are licensed. Due to the warm climate and natural light, Portugal has the advantage of having the lowest production cost of in the world. In August 2019, Canadian licensed producers announced an agreement with German importer medical to supply Germany with cannabis worth €3 million (US $3.3 million) through a Portuguese subsidiary. This is the first commercial export of medical cannabis from Portugal to Germany and was shipped in September. According to the German television station ProSieben, the show is worth 5 million euros and has a total of 500 kg of flowers (Pascual 2019a, b)
3.3.14	Romania	According to a USDA (United States Department of Agriculture) report, 1414 ha of hemp plants were sown in 2018, and hemp seed imports climbed by 50% for the next processing year of 2019. The entire revenue was around $2.6 million Romania is now one of the top five EU member nations growing hemp. Industrial hemp comes in a wide range of kinds that may be used both locally and internationally in Romania. In Romania, hemp is grown solely for seed, fibres, and oil. The maximum amount of THC permitted is 0.2%. Romania will import 1500 metric tonnes of hemp seed in 2019. In Romania, the total value of hemp exports and imports is $4.2 million, with polyphenols and fibres accounting for $3.3 million (Slette 2020)
3.3.15	Slovenia	Slovenia's sector, which employs over 200 people and earns over 50 million euros in revenue. Only pharmaceutically manufactured CBD can be marketed or produced in Slovenia. In Slovenia, there is no established set of health indications for prescription cannabis medicines that is founded on research. The state has yet to set up a clear method for funding cannabis medications through the health insurance fund (Mag 2020)

(continued)

Table 3.3 (continued)

S. No.	Countries	Economic value
3.3.16	Spain	Hemp is currently farmed mostly in northeast Spain (800 ha). Farmers recognise its agronomic and economic benefits, but the crop's future is dependent on the impact of recent EU rules and industry's ability to produce new hemp-based goods. These dangers affect everyone in the sector, not just growers. The extraction of hemp CBD is only permissible from seeds, according to the current legal framework. Furthermore, only hemp seeds and derivatives are allowed in meals. According to statistics provided by the Spanish Agrarian Guarantee Fund (FEGA), the area allocated to hemp growing in Spain went from 61 to 510 ha in 2020, representing an eightfold growth since 2016 (King 2016)
3.3.17	Thailand	Thai government legalized the cultivation, trading and production from hemp in January 2021. The Thai hemp industry is expected to be worth THB 15.77 billion by 2025, with a CAGR of 126% (Sowcharoensuk 2021)
3.3.18	The United Kingdom	Medical cannabis products were allowed in the United Kingdom for the first time in 2018. The country's medicinal cannabis industry is expected to grow dramatically as a result of this legislation. The medical cannabis business in the United Kingdom generated less than $200 thousand dollars in sales in 2019, but this figure is predicted to rise to almost 1.3 billion dollars by 2024 (Mikulic 2020)
3.3.19	The United States	According to a recent research, legal sales in the United States reached a new high of $17.5 billion, up 46% from the previous 2019 (Yakowicz 2021)
3.3.20	Zimbabwe	In Zimbabwe Since September, when the government published guidelines for cultivating cannabis, 44 licenses have been awarded, with revenues expected to reach $1.25 billion in 2021 (Ndlovu R 2020)

as cotton, which is used to make fibres, biopolymers, and insulation materials; it can be used to make a extensive range of products, from medicines to fibres. Many nations have legalized hemp and related plants, and many more are contemplating doing so in the future as they see hemp's potential. As previously noted in the economic evaluation of various nations, it is easy to extrapolate that hemp cultivation and manufacture of various goods may help many countries substantially. The worldwide industrial hemp market was worth USD 3.61 billion in 2020, and it is predicted to increase at a CAGR of 16.2% from 2021 to 2028. The COVID-19 epidemic had a detrimental influence on the business in 2020 and 2021, but the sector will continue to thrive in the next years. Countries such as India, Brazil, Japan, and Switzerland, among others, offer favourable conditions and area for the growth and manufacturing of hemp products.

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Chapter 4
Hemp Usage in Textile Industry

Görkem Gedik and Ozan Avinc

Abstract Though, hemp served to humans as a fiber plant for thousands of years, its importance faded away due to miscellaneous reasons in the beginning of twentieth century. Since the last few decades, hemp plant has been revisited for a fiber source, but not without a reason, as a result of the sustainable raw material seeking. Global concerns such as shortening resources, pollution and global warming push the textile industry to choose environmentally friendly production methods, like all other industry branches. At this point, hemp fiber has shined out with its serious sustainable production potential. This chapter mainly focuses on hemp fiber usage and production methods in textile engineering rather than the sustainable features of hemp fiber. In this context, first, the information regarding hemp plant agriculture for fiber production, fiber extraction from hemp plant and fiber properties were given. Moreover, yarn spinning from hemp fiber was explained, and hemp fabric weaving, knitting and nonwoven production were analyzed. Chemical wet processing (textile finishing processes) such as pre-treatments (such as bleaching etc.), dyeing, and finishing of hemp fibers were also reviewed. Finally, end-use applications and application areas of hemp fibers in textiles, the situation of hemp in the textile industry and the economic contribution of the hemp fiber production were given.

Keywords Hemp fiber · Textile · Sustainable · Hemp fabric · Hemp products · Pre-treatment · Bleaching · Dyeing · Finishing

4.1 Introduction

The most important element of the textile industry is fiber; the production chain and planning begin with fiber selection. Despite all our engineering practices, final

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product properties are heavily dependent on fiber type and properties. Moreover, sustainable raw material, which is fiber for textile industry of course, selection is required in the first place for a sustainable production chain. From this perspective, hemp fiber is a very serious alternative for environmentally friendly and sustainable production. Hemp is a very low input plant; it may grow with no or little intervention such as irrigation, fertilization, or pesticide application and so on. The fiber properties, processing, possible end use applications and economic feasibilities should be well projected to gain the maximum benefit from hemp fiber, otherwise, the eco-friendly properties of hemp fiber will be wasted.

Hemp plant is an annual dioecious plant (monoecious species have also been cultivated) belongs to *Cannabaceae* family (Fike 2016). Though hemp has been cultivated for its fibers since ancient times by humans, the hemp cultivation dramatically decreased in the beginning of twentieth century. The main concern and the biggest obstacle to cannabis farming is drug (marijuana) production from diversified species, especially from female *Cannabis indica* (van der Werf 2004; Salentijn et al. 2015). Thus, very intensive effort has been spent on the development of new hemp varieties which contains low amount of narcotic substance, THC (tetrahydrocannabinol) (Fike 2016). The genetic studies are not only limited with low THC containing varieties, but also are ongoing for creating hemp plant varieties that give high yields according to the planting purpose. Hemp is a multipurpose crop, which means it may be cultivated for seeds, fibers, hurds or even THC for pharmaceutical uses. Naturally, textile industry deals with hemp plant cultivation for fiber production.

The abuse of hemp plant as a drug was one of the most significant factors that caused textile industry turn away from hemp, but it was not the only reason. In the same period, cotton fiber processing technologies were also developing. Cotton fabrics had had many advantages over hemp fabrics; cotton fabrics were more comfortable and cotton processing was easier with new developed techniques. Moreover, the introduction of the synthetic fibers to the market completely pushed the hemp fiber to the background. Cotton farming requires high amount of agricultural chemicals and vast amount of irrigation and synthetic fibers depends on petroleum industry, however, people did not have any concerns about sustainability or climate change back then, and they did not really care about the environment (Gedik and Avinc 2020).

Today, the demand for hemp fibers is in an increasing trend due to the eco-friendly awareness and thanks to the latest research and technologies which have improved hemp product quality and have expanded the usage areas of hemp fibers. In this chapter, hemp textiles production methods and hemp textile products were deeply reviewed rather than hemp fiber's sustainable properties. During the journey of hemp fiber from seed to consumer, there are a lot of steps and process chains which have substantial effects on the final products. Therefore, every stage involving to hemp textiles production should be monitored in detail. The hemp plant variety has a crucial influence on the fiber quality. Fiber length, fiber yield, cellulose amount, fiber tenacity or so on are highly dependent to the hemp plant selection. However, the genetics is not only determinative factor on the fiber properties, the environmental conditions and fertilization also have significant effect on the fiber quality. Some details may seem unimportant in the first place during hemp cultivation, but they may shape the characteristics of the finished products. Hemp is a lignocellulosic bast fiber, therefore, chemical, and physical fiber characteristics of the hemp fiber should be well examined. Cotton yarn spinning lines are widespread throughout the world, however, hemp yarn production differs from cotton spinning in several points. Thus, hemp yarn spinning and cottonization of hemp fiber were discussed and weaving, knitting and nonwoven production from hemp fibers were explained in this chapter. Pre-treatments (such as bleaching etc.), dyeing, and finishing processes of hemp fiber textiles were reviewed in order to underline high end hemp fiber products. In the next part of this book chapter, hemp cultivation for the hemp fiber production, which is essential for hemp fiber textile products, was explained.

4.2 Hemp Cultivation for Fiber Production

Like all culture plants, hemp plant requires some human intervention for high yield fiber production. This intervention starts with seed selection for appropriate breed, fertilization, and irrigation with concerning sustainability for high yield, taking care of suitable harvesting time for better fiber quality and so on.

There is a still ongoing debate on the taxonomic classification of *Cannabis. C. sativa* is proposed as monotypic genus by some research, but in other hand some scientists identify three species including *C. sativa, C. indica and C. ruderalis* (Salentijn et al. 2015). Different classifications of hemp (C. sativa) are possible, however, mainly hemp is divided into two distinct groups according to purpose of production: hemp and marijuana. Marijuana is cultivated for its narcotic properties related with high content of intoxicating compound tetrahydrocannabinol (THC). On the other hand, hemp is produced for fiber, seed, and medicinal compounds. In Europe and North America, 0.2–0.3% TCH containing hemp cultivars can be legally cultivated (Schluttenhofer and Yuan 2017). Therefore, there is an important effort to improve new hemp cultivars for the reason of cultivation (fiber or seed) and decrease THC amounts (Fike 2016). Canada's government published 71 approved industrial cultivars for 2021 growing season (The official website of the Government of Canada 2021). In this point, it is important for the farmers to know and select the best genotypes for end use purpose and the environmental conditions and location of their farms (Campiglia et al. 2017).

Hemp plant is typically dioecious which means the population consists of male and female plants having separate flowers. Male plants are tall and thinner, female plants are short and survive till the end of seed maturity. However, monoecious (male and female flowers are on the same plant) plants have been developed by breeders during the effort for more uniform production (Fike 2016). Male hemp plants supply more quality fibers for textile utilization rather than female plants for dioecious varieties (Gedik et al. 2010).

Hemp fibers are classified as bast fibers due to their position on the outer stem tissues. Primary and secondary fibers are the two hemp bast fibers which the first is sclerenchyma cells from procambium and the latter is formed by vascular cambium. These two fiber types exhibit different characteristics and chemistry in structure which affects their processability and end use properties. Secondary fibers are shorter and thinner also they have more lignin content than primary fibers which make them less desirable for textile industry. With plant age, the secondary fiber presence increases, and primary and secondary fibers generally cannot be separated during processing, therefore, the harvesting time should be chosen wisely depending on the end-use purpose (Fernandez-Tendero et al. 2017; Schumacher et al. 2020; Cherney and Small 2016). According to Mediavilla et al. (2001) the technical maturity of monoecious varieties for fiber production is when most of the bracts are seen that is the peak of flowering. On the other hand, the technical maturity of dioecious varieties for fiber production is come up to the period that most of the flowers on male plants are opened (full flowering) and bract formation of female plants begins. If the harvesting is delayed posting flowering in a seed aimed production, the ratio of lignin in the fibers increases. Also, the fiber yield changes 25% between the harvesting before flowering and full flowering, therefore early harvesting should be avoided (Amaducci and Gusovius 2010).

Harvesting time directly affects the fiber quality in terms of non-cellulosic impurities, crystalline cellulose amount, fiber strength, fiber diameter and so on. For paper production purposes these parameters may not be so important but in the manner of textile and composite applications fiber characteristics are so significant (Mediavilla et al. 2001). Secondary wall formation starts during the vegetative phase of the plant and goes on with flowering (Amaducci et al. 2005). Hemp fibers (both primary and secondary fibers) do not produce secondary cell wall during elongation period (Snegireva et al. 2015). The maximum bark and fiber yield is reached during full male flowering or in the end of male flowering (Salentijn et al. 2019; Liu et al. 2015). As the flowering stage continues, lignin proportion increases followed by a decrease on cellulose concentration. This phenomenon results in lower number of primary fibers and higher proportion of secondary fibers which are more lignified and shorter, formation (Salentijn et al. 2019).

Hemp is a short-day plant and hemp possesses a critical photoperiod and its flowering is triggered around 14 h (Salentijn et al. 2019). In long day regime, plant maturity is delayed (Fike 2016). The selection of the proper cultivar is crucial in this manner. For instance, if northern cultivars are sown in southern latitude, the plants will start flowering earlier due to the earlier critical day length in south, which results in lower yield (Salentijn et al. 2019; Fike 2016).

Amaducci et al. reported that the fiber quality diversifies along the hemp stem, fiber concertation is higher in the bottom half, whereas fibers in the top part is finer with lower secondary fiber count (Amaducci et al. 2008). Li et al. reported that fibers in the middle of the hemp stalk have better mechanical properties (Li et al. 2013a, b). However, in practice, disadvantages occurred when processing hemp stems by dividing them to top and bottom parts. The fiber loss was very high and processing of the top part of the plant was difficult due to the thin diameter (Amaducci et al. 2008).

Plant density and fertilization are also important factors that is determinant on fiber quality. Higher planting density leads self-thinning phenomenon which is a result of the competition for light. Plants become thinner and longer to access more sunlight. In this case, stems have longer and thinner internodes, however, the competition at high planting densities consequently limits the plant growth and stems have shorter thinner and less internodes. The harvesting is easier and consequently the energy consumption decreases during harvesting when the stem diameter is thinner. On the other hand, total biomass and fiber yield are low when the seeding density is higher (Amaducci et al. 2015). Seemingly, optimal density for fiber hemp sowing exhibits variations according to the location and the plant variety. Amaducci et al. (2015) reported that 90–100 plants per m^2 is targeted in Italy, whereas fiber yield maximized with 120–150 plants per m^2 density in China. Though, the stem diameters vary in a wide range in a field, Chen et al. (2004) calculated the mean energy requirement of cutting a hemp stem as 2.1 J. They also stated that higher moisture content of a stem results in higher energy consumption.

Deng et al. (2019) examined the influences of nitrogen, phosphate and potassium fertilizers and planting density on the fiber quality. They reported that nitrogen fertilizer rate was effective in the first order followed by planting density, potassium fertilizer rate and phosphate fertilizer rate, respectively. They suggested 251–273 kg/ha nitrogen, 85–95 kg/ha phosphorus and 212–238 kg/ha potassium application according to their experiments performed in China.

High temperature and water shortage accelerate flowering of hemp, however under these conditions, plant growth and fiber maturation is negatively affected (Amaducci et al. 2015), however, thanks to its developed roots, hemp resists for short droughts. Total rainfall of approximated 700 mm during grooving season. Total temperature is 800–3500 °C according to the location of the field and optimum photosynthesis temperature is 25–30 °C (Zuk-Golaszewska and Golaszewski 2020). In the next section, information regarding the extraction of hemp fiber and hemp yarn production were given.

4.3 Extraction of Hemp Fiber and Hemp Yarn Production

4.3.1 Extraction and Preparation of Fibers for Yarn Production

Extraction of the fibers from the hemp plant stem, in other terms decortication, comes first in the fiber production. In this step, fibers were separated from stem in form of ribbons. Retting operations are applied to make fiber extraction easier, by removing pectin in biological processes. In conventional manner, retting is applied in two main ways: field retting (dew retting) or water retting. For field retting, harvested and cut hemp stems left on the field for a long period of time, during this time pectin gum is degraded by microorganisms living on the plant or in the soil. Opposite to

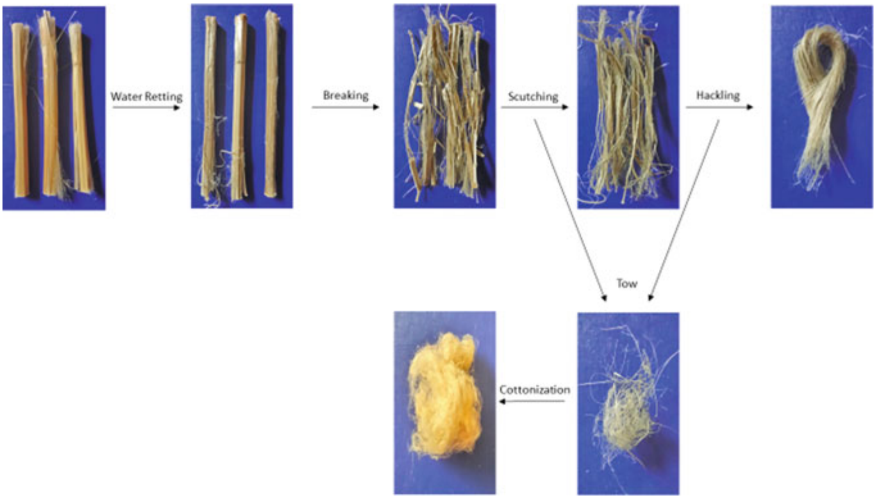

Fig. 4.1 Lab scale processing of hemp fiber from stem to cottonized fibers (personal archive)

field retting, water retting is an anaerobic process. Cut hemp stems are dried and soaked into a water tank. Water retting is shorter in time and supplies more quality fibers than field retting, on the other hand, total costs and environmental impacts are higher, also water retting requires high labour. Further information about retting and the influence on sustainability is given in a former study (Gedik and Avinc 2020).

In the end of retting period, breaking is carried out to the stalks. There are smooth rollers (break the stalk longitudinally) and ribbed rollers (crumble the hurds into smaller pieces) in the breaking machine. The crushed hurds mostly separated from the fibers in this step (Sponner et al. 2005). Un-retted or green stems can also be fed into breaking machine (Riddlestone et al. 2006), but the quality of the fibers is lower. After breaking step, the process goes on with scutching operation. The aim is to remove all remaining impurities from the fibers. Two pairs of bladed turbines are responsible for scutching. As the fibers pass through the turbines, all foreign matter is shed. Scutching also supplies opening and softening function. The next step is hackling, which is actually a combing procedure for long staple fibers. Prior to hackling, fibers are teared to certain length (usually 6–7 cm), in the cutting process. Also, defective tips of the fibers are removed in the cutting which improves the quality. Hemp slivers are obtained after hackling (Gedik and Avinc 2020). Lab scale fiber extraction is shown in Fig. 4.1.

4.3.2 *Spinning of Hemp Fibers*

Cotton is the most cultivated natural cellulosic fiber. Therefore, complicated cotton processing systems are well known and most of the yarn mills are designed for cotton fiber. However, being a bast fiber, hemp fiber requires different processing approaches comparing to cotton (Papadopouloua et al. 2015). First, hemp fibers present on the plant bast tissue as fiber bundles which are consist of elemental fibers glued together with non-cellulosic substances such as lignin and pectin (Gedik and Avinc 2020). Hemp fiber bundle and elemental hemp fibers are seen in Fig. 4.2. The elemental fibers of the primary and secondary fibers are 5 mm and 2 mm, respectively (Salentijn et al. 2015).

Two kinds of fibers are obtained after preparation processes: long fibers and short (tow) fibers and the origin of the short fibers (noils) could be scutching (scutching tow) or hackling (hackling tow) (Moussa et al. 2020; Papadopouloua et al. 2015).

Bast fiber spinning exhibits differences from short staple fiber such as cotton spinning (Papadopoulou et al. 2015). Long and short fibers (tows) are generally used for yarn production in separate lines. Short fibers allow coarser yarn production, however, thanks to the technological developments, short fibers are now utilized for other purposes such as composites reinforcement. The spinning machinery of short and long fibers is similar except drawing zone is shorter for short fibers (Sponner et al. 2005). Hemp can be spun with two methods, either dry spinning or wet spinning (Muzyczek 2012). The slivers reach spinning frame by passing through roving. Roving supplies further lengthened and slightly twisted slivers. Drafting can be applied following roving, for more parallelized and drawn fibers (Dhondt and Muthu 2021). When compared to wet spinning, coarser yarns are produced in dry spinning. Flyer system or ring spinning frame can be employed to obtain final yarn in dry spinning (Lord 2003). The difference in the wet spinning system is that the rove is passed through a trough and immersed into hot water, the spinning goes on wet from this point. The hot water assists to dissolving of non-cellulosic substances and supplies enhanced mobility to fibers. This, results in finer and more even yarn structure. Also breaking stops are reduced with wet spinning which supports yarn count variability (Dhondt and Muthu 2021; Lord 2003). It should also be noted that, wet spinning

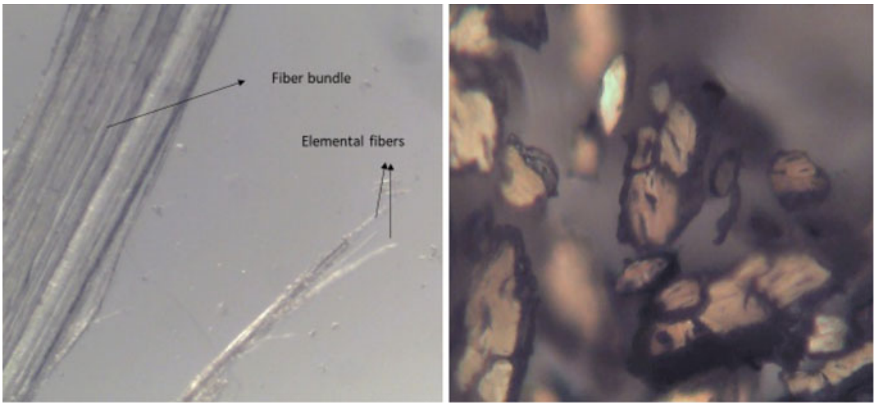

Fig. 4.2 Longitudinal view of hemp fiber bundle and elemental fibers (on the left) and hemp fiber cross-section (on the right) (personal archive)

brings in high costs and environmental problems (Sponner et al. 2005). The influence of spinning type (wet-dry) and roving technique (hot water-bleaching) on water sorption–desorption properties of hemp and flax yarns were explained by Mustata and Mustata (2013). They stated that wet spun hemp yarns absorbed more water.

The pure hemp yarn production has some drawbacks such as high cost and limits on the quality and fineness of the yarn (Cierpucha et al. 2004; Jinqiu and Jianchun 2010). Additionally, though ring spinning system is suitable for a very wide range of fiber types, the production speed is limited (Dhondt and Muthu 2021). These circumstances restrain the designing flexibility and the variability of hemp textile products (Jinqiu and Jianchun 2010; Moussa et al. 2020).

One solution proposal against the challenges towards conventional hemp yarn production is cottonization which yields cotton-like or wool-like fibers, that allows us to work more effectively with flax and hemp fibers (Cierpucha et al. 2004). Noils and short fibers are suitable for cottonization in the manner of pricing (Rieter Catalogue 2011; Papadopoulou et al. 2015; Kozlowski et al. 2013; Mankowsky et al. 2006). Generally, mechanical process is preferred for the cottonization of hemp and flax fibers (Cierpucha et al. 2004), however, it is probable to acquire finer cottonized fibers by chemical or enzymatic methods. But it should be noted that these methods have higher costs and labor needs (Papadopoulou et al. 2015; Kozlowski et al. 2013). Cottonized hemp fiber's length is like traditional fiber types (Papadopoulou et al. 2015). After cottonization, hemp fibers are able to be used in cotton spinning systems, which let us to obtain finer and softer yarns essential for quality woven and knitted fabrics. Cottonized hemp fibers can be employed in the open-end system. It is possible to spin yarns with high elongation, low hairiness low impurity content with rotor spinning. Besides the high-speed production advantage, rotor spinning tenders benefits in the end-product of bast fibers such as better abrasion resistance, high dyeability, better comfort properties and low crease tendency. Blending of cottonized hemp fibres with other natural fibres and synthetic fibres is also possible (Kozlowski et al. 2013; Jinqiu and Jianchun 2010; Ali 2013; Rieter Catalogue 2011). By this way, specialized hemp fiber blends can be produced that will enables us more flexibility to diversify hemp products according to fashion and technological demands (Jinqiu and Jianchun 2010). In the upcoming part, the production of hemp fabrics and the different usage applications of hemp fibers were reviewed.

4.4 Hemp Fabrics and Their Usage

As formerly mentioned, the sustainable and eco-friendly features of hemp fibers are taking the lead on the reasons that cause rising attention of hemp fibers. However, limiting the hemp fiber's demanded properties only with sustainability would be inequity, hemp fiber also provides superior end-use properties with its natural structure. Hemp fiber offers good thermal and anti-static properties, ultraviolet and microbial protection, high water permeability and so on (Novakovic et al. 2020; Tama et al. 2020). Ju et al. (2016) investigated US customers' subjective sensibility perception on bast fibers including hemp and reported that the consumers tend to perceive bast fibers in wearable modern and rich sensibility categories. From this perspective, the negative sides of bast fibers should be recalled. These are low elasticity and flexibility, rough handle, and hardness, which affect subjective comfort sense in negative way (Novakovic et al. 2020; Zhang and Zhang 2010). We must keep in mind that, being a sustainable fiber is not adequate for marketing, the negative properties should be eliminated in the production to an acceptable level. The efforts for this purpose go on. Hwang and Ji (2012) applied liquid ammonia to hemp woven fabrics. They reported that crease recovery, wicking speed, drying ratio, and washing shrinkage properties were improved after treatment. In a parallel line Ji and Lee (2016) reported enhanced softness and flexibility of hemp woven fabric after liquid ammonia treatment. Zhang and Zhang (2010) achieved decreased flexural rigidity of the hemp woven fabric by the application of epoxy modified silicone oil. Stankovic and Bizjak (2014) reported that the comfort properties are enhanced for knitted fabrics with the two-folding of hemp yarn with increased air and water vapor permeability. They also stated that thermal properties were not affected negatively. Stankovic et al. (2019) investigated the comfort characteristics of hemp yarns plied with cotton yarns. They stated that by this way it was possible to combine both fiber characteristics and intrinsic yarn properties. Novakovic et al. (2020) mixed hemp and acrylic yarns in the knitting stage to obtain softer fabrics.

One of the solution proposals to overcome hemp fiber rigidity and utilize this fiber in a wide variety of products is blending this fiber with other natural, regenerated, or synthetic fibers. For this purpose, as explained previous sections, generally cottonization of hemp fibers is necessary. An example study was performed by Ahirwar and Behera (2021) who stated that hemp fiber with cotton blending has a great potential in use of summer clothing. Kim and Kim (2018) produced hemp/tencell (30–70%) yarns in ring, siro spun and air vortex systems. They determined that bending rigidity of knitted fabric developed by air vortex yarn was lower. Also, air vortex system supplied yarns with better unevenness values. Petrulyte et al. (2013) produced terry towels with hemp pile and investigated water vapor absorption. Kocic et al. (2019) produced hemp/cotton and hemp/viscose knitted fabrics where they blend yarns during knitting.

The main criteria for processability in bast fibers weaving and knitting is the yarn characteristics independent from the fiber material. Our personal experiences revealed that Nm 20/1 100% hemp yarn is very rough to process in knitting machinery, it causes stops due to thrusts and needle breaks related with rough yarn structure and low flexibility. The knitted fabric structure constructed with this yarn was also very stiff. However, sizing was eliminated in weaving as the same yarn was utilized in warp, which can be counted in the "benefits" side.

Natural fibers, including hemp find novel application areas in automotive, acoustics, construction, marine and so on. They are not only cheaper than synthetics, also eco-friendly and sustainable. Starting from this point of view, Hysek et al. (2016) investigated the air laid nonwoven production from hemp and flax fibers. They carried out needle punching for ensuring the mechanical bonding and stated that nonwoven production from hemp and flax fibers were successful. Hemp fiber is also very useful raw material for sound isolation in nonwoven or composite form (Liao et al. 2020).

As known, biodegradable natural materials are taking place more and more in composite materials day by day. In addition to its renewable, sustainable, natural, and biodegradable characteristics, hemp fiber is one of the strongest and stiffest natural fibres among natural fibers, and hence has a huge potential and utilization as reinforcement in composite materials (Väisänen et al. 2018; Faruk et al. 2012). Therefore, hemp fiber is utilized as reinforcement in polymer-based composite materials because of its biodegradable, natural, sustainable, renewable, and strength properties, and it is observed that the amount of its use and different areas of its usage are increasing day by day. The new developments in the composite science delivered hemp in a new dimension (Mussig et al. 2020). Indeed, hemp is the second most consumed natural fiber in composite production after sisal (Shahzad 2012). Natural fibers are eco-friendly cheaper, lightweight alternatives for synthetic fibers in composite production. Natural fibers can be utilized in very different items as reinforcement materials in a polymer matrix from aerospace industry to our daily lives (Gedik and Avinc 2020). Ballistic, thermal, and mechanical performance of hemp fibre reinforced epoxy composites were explored by Ribeiro et al. (2021). 30% hemp fiber reinforcement increased Izod absorbed energy 7.5 times and tensile strength more than 60%. Hybrid reinforcement material design is being popular to leap over the water absorption and weak bonding problem of pure cellulosic fibers-hydrophobic polymer matrix (Akash et al. 2018). In another study, glass fiber hybridization of untreated and alkali treated hemp fiber in epoxy matrix was carried out for automotive industry purposes. The results revealed that hemp fiber hybrid composite is suitable for the replacement of conventional materials (Nachippan et al. 2021). Not only the reinforcement material is important for composites, but also polymer matrix strongly determines the mechanical behaviour of the material. In the manner of flexural and tensile tests, 30% hemp fiber reinforcement exhibited better results in epoxy matrix, rather than polyester matrix (Neves et al. 2020).

While the utilization of natural fibres as filler or reinforcement offers many benefits to composite materials, some natural properties of natural fibers can give composites some undesirable properties (Väisänen et al. 2018). The four main challenges which could significantly limit the application of natural fibres in composites are: limited mechanical characteristics, excessive water absorption, poor fire resistance, and problems with processing and homogeneity (Väisänen et al. 2017). Various chemical and physical modification techniques have been developed for polymer matrices and natural fibres to at least partially solve or minimize these difficulties in association with natural fiber-polymer composites (Väisänen et al. 2018; Adekunle 2015). In other words, the fibers used as reinforcement in such composite applications can be subjected to different modification processes from time to time to improve their properties.

In one of these efforts, Väisänen et al. (2018) studied the efficacy of various modification techniques, i.e., alkali, enzymatic, steam, and wood distillate treatments, to boost the properties of hemp fibres (*Cannabis Sativa* L.) for composite applications and the suitability of modified hemp fibres as reinforcements for epoxy resin was investigated by preparing composites at approximately 30 wt% hemp fibre contents. It was reported that the incorporation of modified or unmodified hemp fibers into epoxy resin could efficiently cure the material (Väisänen et al. 2018). Modification of hemp fibres with alkali, enzymes or steam impairs the tensile characteristics of the fibres, which leads to a weakening of the characteristics of the composites (Väisänen et al. 2018). However, all modifications were found to significantly reduce the hygroscopicity of hemp fibers, resulting in lower water absorption. In Spite of the diminished mechanical characteristics, composites containing modified or unmodified hemp fibres possess sufficient strength for multiple application types, comprising decoration, marine applications, and automotive interiors (Väisänen et al. 2018). Modification of hemp fibres with various methods allows composite material manufacturers to adapt the characteristics of fibres or composites to varying directions, which could be viewed as a key benefit of these materials (Väisänen et al. 2018).

Therefore, many different modification techniques were investigated on hemp fibres for composite material production purposes such as combined fungal and alkalization and alkali treatment (Mwaikambo and Ansell 2002; Pickering et al. 2007a), plasma treatment (Brunengo et al. 2019), fungal and alkali interfacial modification (Pickering et al. 2007b), alkaline and silane treatment (Sepe et al. 2018; Sair et al. 2017), silanes and potassium permanganate (Panaitescu et al. 2016), mercerization and maleated polyethylene (MAPE) addition (Désiré et al. 2016), silane modification and interfacial ultraviolet aging (Han et al. 2021), modification utilizing silane coupling agents (Rachini et al. 2012) etc.

4.5 Wet-Processing of Hemp Fibers

In this part, wet processes such as pre-treatments, dyeing and finishing applied to hemp fibers were discussed.

4.5.1 Pre-treatments Applied to Hemp Fibers

In textile wet processing, different pre-treatments could be applied to the fibres prior to dyeing, printing, and finishing. In this section, the types of pre-treatments applied to hemp fibers were discussed. Different kinds of pre-treatments could be applied to fibers for different purposes.

In one of these pre-treatment applications, hemp fibers were modified by plasma treatment at atmospheric pressure and the effect of dielectric barrier discharge on the physico-chemical characteristics of hemp fibers was explored (Skundric et al. 2007). As an outcome of the plasma oxidation process, it was determined that the content of various hydrophilic functional groups on the surface of the hemp fibre enhanced. In addition, the capillarity of plasma-modified hemp fibres is six times higher than the original unmodified hemp fibers, and the wetting rate is about 300 times faster than its unmodified counterpart (Skundric et al. 2007). Skundric et al. (2007) concluded that dielectric barrier discharge at atmospheric pressure might procure the manufacture of fibers of high hydrophilicity, improved chemisorption, and adhesive characteristics, and developed biocompatibility. So overall, plasma-modified hemp fibers displayed highly improved wetting characteristics without altering physico-mechanical characteristics (tensile strength and elongation) (Skundric et al. 2007).

In a study of Radetic et al. (2007), scoured and bleached hemp "honeycomb" woven fabrics were dyed at 60 °C with acid dyestuff (C.I. Acid Blue 113) and direct dyestuff (C.I. Direct Red 81) in order to investigate the effects of low-temperature air plasma and cellulase enzymatic pre-treatment on the dyeing characteristics of hemp fabric. First, it was mentioned that low-temperature plasma treatment possesses a positive influence on dyeability of hemp fabric as the dyeing rate and dyestuff exhaustion of both dyestuffs substantially enhanced in comparison with untreated counterpart (Radetic et al. 2007). On the other hand, Radetic et al. (2007) stated that cellulase enzymatic pre-treatment resulted in a decline in the dyeing rate in the event of acid dyestuff and a minor rise in the event of direct dyestuff, though the dyestuff exhaustion of both dyestuffs diminished. Finally, it was concluded that low-temperature plasma + cellulase enzyme pre-treated hemp fabrics displayed a more decline in dyestuff exhaustion and decrease of dyeing rate in comparison with all other studied hemp fabrics (Radetic et al. 2007). Radetic et al. (2007) mentioned that this can be attributed to more a noticeable digestion of the amorphous areas of the hemp fiber that became substantially more reachable to cellulase enzymes after plasma etching (Radetic et al. 2007). All studied hemp fabrics displayed akin and low colour fastness levels (Radetic et al. 2007).

In another later study, bleached hemp plain weave fabrics were pre-treated with chitosan and epoxy modified silicone oil in various volume ratios to improve the dyeing depth and softness (Zhang and Zhang 2009, 2010). Zhang and Zhang (2010) stated that, in the case of chitosan/silicone oil treated hemp fabric, the handle was improved although the tensile strength characteristics worsened. Color strength increased as the chitosan content of hemp fiber fabric increased. They reported that rubbing, wet scrubbing, and washing durability were also developed when the volume ratio of chitosan to silicone oil was 5:1 (Zhang and Zhang 2010).

Zhang et al. (2011) stated that liquid ammonia application could improve the characteristics of a hemp fibre and expand its application for textile purposes. In their study, treatments with liquid ammonia of hemp fibres were implemented and influences of various approaches of NH_3 removal on the structure and characteristics of hemp fibres were discovered (Zhang et al. 2011). They reported that the liquid ammonia application led to a reduction in the crystallinity of hemp fibres and a lattice transition of partial cellulose I into cellulose III (Zhang et al. 2011). Furthermore, liquid ammonia application could enhance the thermal stability and the dyeing behaviour of the hemp fibres. On the other hand, different ammonia removal methods were found to have discrepant influences on the structure and characteristics of hemp fibres. In this regard, regarding the influence of discrepant ammonia removal methods on the dyeing behaviour of hemp fibres, it was reported that removing ammonia with water led to the highest dyestuff uptake and removal of ammonia by evaporation led to the lowest dyestuff uptake (Zhang et al. 2011).

Later, in other study, the influences of liquid ammonia application on the surface characteristics of hemp fibres were investigated by Zhang et al. (2014a). Zhang et al. (2014a) reported that the quantity of lignin on the hemp fiber surface diminished substantially after liquid ammonia application. What is more, the contact angles of the hemp fibres treated in this manner were decreased corresponding with those of the pristine hemp fibers, implying that the wettability property of the hemp fibres was enhanced by this application (Zhang et al. 2014a). Finally, they concluded that liquid ammonia treatment didn't alter the large dislocation structures in hemp fibres, however the removal of non-cellulosic materials from the hemp fibre surface enhanced the roughness of the hemp fibre surface (Zhang et al. 2014a).

In other research, the influence of alkaline treatment on the quality of hemp fiber (grown in China) was explored by Zhang et al. (2014b). They concluded that the optimum quality of hemp fibre could be obtained under the following conditions: alkaline treatment with 10 g/L alkaline dosage at 1:10 liquor ratio for 5 h (Zhang et al. 2014b).

Moreover, the modification of hemp fabric with cellulase enzyme and acrylamide was carried out by Li et al. (2013a, b) to enrich the dyeability of hemp fabric with natural dyes. This research described an enzymatic process utilizing cellulase for increasing the graft copolymer of hemp-acrylamide on hemp fabric and exhibiting saturation dyeing with various natural dyes in the presence of mordant. It was reported that the enhanced number of reducing ends in the cellulose structure as a result of the cellulase enzyme process improved the graft point (Li et al. 2013a, b). Finally, the modification of hemp fabric with acrylamide pursued by pre-mordanting process with aluminum mordant and dyeing with lawsone and juglone natural dyes displayed quite good saturation with medium to good colour fastness characteristics (Li et al. 2013a, b).

In the following sections, enzymatic treatments and bleaching applications applied to hemp fibers as pre-treatment processes were reviewed.

Enzymatic treatments applied to hemp fibers

In a study of Merdan (2017), untreated greige hemp fibers were pre-treated with laccase enzyme in various concentrations (1, 2 and 3% w/v) for various treatment times utilizing conventional, ultrasonic energy and microwave energy methods. Merdan (2017) concluded that the best outcomes were observed in 20 min via the conventional technique, 5 min via the ultrasonic energy technique, and 1 min via the microwave energy technique and laccase enzyme treated hemp fibres via microwave technique were improved only after 3 min of treatment period. Moreover, it was also reported that the microwave and ultrasonic techniques consumed less energy in shorter time periods than the conventional technique. And finally, when the two eco-friendly techniques were compared, time and energy consumptions of microwave energy technique were less than those of the ultrasonic energy technique (Merdan 2017).

In another study, the cellulase and pectinase enzyme treatments were applied to hemp/organic cotton (55%/45%) blend knitted griege (untreated) fabric (200 g/m^2) and the effects of cellulase and pectinase enzyme additives on the hairiness, strength, whiteness, and dyeing characteristics of the blended greige knitted fabrics were explored (Ya et al. 2019). Ya et al. (2019) reported that the enzyme treated hemp/organic cotton knitted fabric displayed soft handle, smooth surface, good elasticity, and high levelness, along with low strength decrease rate under the optimized conditions of liquor ratio of 1:12, cellulase amount of 0.3%, pectinase amount of 1 g/L at 55 °C and pH 6 for 80 min.

Bleaching of Hemp Fibers

In a study of Wang and Postle (2004), acidic scouring, alkali boiling, and peroxide bleaching treatments were applied to hemp fibers (grown in Australia) for comparison from the colour point of view. They reported that the alkaline boiling application exhibits an efficient technique for improving hemp fibre colour from the standpoint of X, Y, Z, whiteness (WIE), and yellowness (YIE) (Wang and Postle 2004). By augmenting the concentrations of sodium hydroxide and sodium sulphite in the alkaline boiling application, whiteness enhances linearly. The utilization of sodium sulphite in the alkali boiling application could also increase the whiteness property of hemp fibres for a long alkaline boiling treatment period (Wang and Postle 2004). On the other hand, it was reported that acidic scouring application doesn't a substantial impact on hemp fiber colour, therefore acidic scouring was not recommended for hemp fiber preparation for textile purposes. Finally, they concluded that peroxide bleaching could significantly improve hemp fibre colour in terms of whiteness, particularly when a high bleaching temperature was provided (Wang and Postle 2004).

Qu et al. (2005) bleached hemp with one bath alkaline-hydrogen peroxide. They stated that alkaline not only removes most of the hemicelluloses, pectin, and lignin from the hemp but also procures hydrogen peroxide (H_2O_2) an alkaline environment to optimize the action of hydrogen peroxide and to remove lignin more effectively during alkaline-hydrogen peroxide one-bath pre-treatment (Qu et al. 2005). In this application, the additive $MgSO_4$ and a stabilizer of hydrogen peroxide were also added to avoid cellulose from oxidation. Finally, Qu et al. (2005) concluded that 10.5 g/L NaOH, 9.8 g/L H_2O_2, 0.1% $MgSO_4$, and 2.7 g/L stabilizer of H_2O_2 at 100 °C for and 127 min were the optimum parameters; then, a compromise was obtained amongst the lowest lignin content, the residual gum content, and the best strength and whiteness of hemp fibre.

In a study of Gedik and Avinc (2018), 100% hemp fiber woven fabric was bleached with peracetic acid (with various temperature, pH, process time, concentration) with exhaustion and padding methods. In their study, hydrogen peroxide bleaching processes were also carried out in addition to peracetic acid bleaching processes in order to make comparisons. Even though higher whiteness levels obtained with hydrogen peroxide bleaching, COD (chemical oxygen demand) analysis revealed the high waste load on the hydrogen peroxide bleaching effluent (Gedik and Avinc 2018). It was reported that peracetic acid resulted in no remarkable deterioration on physical characteristics of the hemp fibre. Hydrophilicity and crease recovery properties of peracetic acid bleached hemp fabrics were improved in comparison with greige (untreated) hemp fabric (Gedik and Avinc 2018). Higher whiteness levels were acquired with exhaustion bleaching than pad-batch bleaching. Gedik and Avinc (2018) concluded that fairly high whiteness values (up to 68.13 Stensby) accomplished with peracetic acid bleaching process without considerable fiber damage.

In this section, bleaching studies related to hemp fibers were examined. In the light of these studies, it was revealed that hemp fibers can be successfully bleached with hydrogen peroxide or peracetic acid. In the next section, different dyeing applications applied to hemp fibers were reviewed.

4.5.2 Dyeing of Hemp Fibers

When the literature was examined, studies in which reactive dyestuffs and natural dyes were used are generally encountered in studies on dyeing hemp fibers. In this section, firstly the dyeing of hemp fibres with the utilization of reactive dyestuffs and then the dyeing of hemp fibers by using different natural dyes were discussed.

In a study of Kabir et al. (2017) a mixed bi-functional reactive dyestuff (Sunfix Supra Red S3B 150% dyestuff: C.I. Reactive Red 195) was implemented to the 100% cotton and 100% hemp woven fabrics. It was stated that the cotton woven fabric displayed higher exhaustion and better levelness than its hemp counterpart, conceivably because of the lower crystallinity and degree of orientation (Kabir et al. 2017). It was also stated that salt and alkali addition increase the colour yield of hemp fiber owing to lower crystal size which augments the surface area of the hemp fiber. Finally, they concluded that the build-up and color fastness properties of the cotton and hemp woven fabrics appeared to be nearly similar (Kabir et al. 2017).

In some scientific studies, blended fabrics containing hemp and cotton fibers were dyed with reactive dyestuffs. In two of those studies (Koh et al. 2008; Lee et al. 2009), the 100% cotton knitted fabrics and the 20% hemp/80% cotton blend knitted fabrics were dyed with a mixed bi-functional reactive dyestuff (Sunfix Supra Red S3B 150% dyestuff, C.I. Reactive Red 195) in order to compare their dyeing and fastness properties. Lee et al. (2009) reported that color fastness characteristics of reactive dyestuffs on cotton/hemp blend and cotton were found to be virtually identical. It was reported that the cotton/hemp blend fabric displayed higher exhaustion levels and better build-up characteristic than cotton fabric, probably owing to the lower crystallinity (Lee et al. 2009). They concluded that hemp fibers can be utilized in cellulose fabrics as a vital alternative to universal solely usage of cotton fibers in cellulose fabrics (Koh et al. 2008; Lee et al. 2009).

Now it is time to give information about some natural dyeing studies on hemp fibers. Grifoni et al. (2009) explored the laboratory and outdoor evaluation of UV protection displayed by flax and hemp plain woven fabrics dyed with some of the widespread natural dyes [dyer's woad (*Isatis tinctoria* L.), madder (*Rubia tinctoria*

L.), logwood (*Haematoxylon campechianum* L.), lipsticktree (*Bixa orellana* L.), brasilwood (*Caesalpina brasiliensis* L.), weld (*Reseda luteola* L.) and cochineal (Dactylopius coccus L.).]. They stated that studied natural dyes can bestow good UV protection, depending chiefly on their various UV radiation absorbing characteristics (Grifoni et al. 2009). Grifoni et al. (2009) concluded that flax and hemp fabrics dyed with weld (*Reseda luteola* L.) led to the highest protection level in this study.

In another study, dyeing properties of bamboo leaves extract on hemp and ramie fibres were discovered (Min 2011). Min (2011) stated that fabrics dyed with bamboo leaves extract were in yellowish color shades and color strength (K/S) of hemp fiber was higher than that of ramie fiber. Dyeability of both hemp and ramie fibers were enhanced by the mordant usage (Al, Fe, Cu). In the case of copper (Cu) mordant usage, dyeability was highly improved than any other studied mordants and dyeing with copper (Cu) mordant utilization displayed deep color shades (Min 2011). Min (2011) concluded that dyed hemp and ramie fabrics displayed very good wash-fastness performance (4–5 Gy scale ratings for each case) and the light-fastness ratings of dyed hemp and ramie fabrics were in the range of 4–4/5.

What is more, the influence of cationization process and its conditions on dyeing characteristics of hemp woven fabric with natural dye extracted from Arabica coffee ground was studied by Butthongkum et al. (2016). It was reported that hemp fabric cationized with 5% owf of cationic agent at 90 °C for 30 min resulted in the highest color yield (K/S) on hemp fabric dyed with Arabica coffee ground natural dye (Butthongkum et al. 2016).

In another study, dyeability and antibacterial finishing of hemp plain woven fabric utilizing natural bioactive neem extract were investigated by Inprasit et al. (2018). In here, two functional compounds were effectively extracted from neem (*Azadiracta indica*): a tannin-rich natural dye and an antibacterial substance. The utilized natural dye was extracted from the neem bark with the utilization water and antibacterial substances were extracted from the neem leaf with the utilization methanol. Hemp fabrics were dyed with tannin-rich natural dye extracted from neem bark. The optimum dyeing conditions for neem bark natural dye extract on hemp fabric was 5% w/v natural dye usage at 100 °C for 60 min leading to high color yield (K/S), a reddish appearance and good to excellent color fastness properties (the color fastness to washing, water, sea water, and acid and alkaline perspiration) (Inprasit et al. 2018). They reported that this was attributed to the creation of an insoluble complex of tannin on the hemp fabric surface, inhibiting leaching of the natural dye (Inprasit et al. 2018). Antimicrobial substances were effectively extracted from the neem leaf with the utilization of methanol and finished on dyed hemp fabrics utilizing a padder machine (Inprasit et al. 2018). In other words, naturally dyed hemp fabrics were padded with antibacterial substances (dark brown residue was obtained with the extraction from neem leaf) using two dips two nips. The dyed and finished hemp woven fabric displayed powerful antimicrobial activity against *S. aureus* (Inprasit et al. 2018). The antibacterial activity diminished as the rise of washing cycles, but it still maintained efficient up to 15 washing cycles, with a decrease of 36.17% (Inprasit et al. 2018).

Natalie (2019) was studied the natural dyeing using tea, pomegranate, and myrobalan of environmentally friendly hemp textile. Natalie 2019 reported that optimum natural dyeing parameters for hemp using tea, myrobalan, and pomegranate were the usage "alum" as a mordant via pre-mordanting or post-mordanting application methods at 20% natural dye concentration leading to good wash fastness levels.

In another study of Grifoni et al. (2020), the UV protection characteristics were analyzed on plain woven hemp fabric dyed with water extracts from madder, chestnut, onion, inula, and logwood, at three escalating concentrations. Grifoni et al. (2020) reported that according to the results of natural dyeing studies carried out with hemp fabric, the minimum protection level (UPF = 15) at the highest dyebath concentration was achieved by using chestnut and onion natural dyes.

Inprasit et al. (2020) applied the natural pomegranate (*Punica granatum*) peel extracts to plain woven hemp fabrics to develop their dyeability and antibacterial characteristics. In this study, a tannin-rich natural dye was extracted from pomegranate peels with the utilization of water at 100 °C and antibacterial substances were extracted utilizing Soxhlet technique via methanol at 55 °C since the antibacterial agents were sensitive to temperature (Inprasit et al. 2020). It was determined that the optimum dyeing parameters of the hemp fabric were a 60 min dyeing process with 6% w/v extract application at 80 °C. And this process led to yellowish-brown appearance. Finally dyed hemp fabrics displayed good to excellent color fastness to washing, water, sea water and perspiration (Inprasit et al. 2020). The treated hemp fabric was found to be 99.99% effective against *Staphylococcus aureus*, and this antibacterial effect was maintained for 20 wash cycles (Inprasit et al. 2020).

Özomay and Akalın (2020) studied the optimization of colour fastness characteristics with one of the multi-criteria decision-making techniques called as Gray Relational Analysis (GRA) method in dyeing of plain-woven hemp (cultivated in Turkey) fabric using *Sambucus Ebulus* L. in company with natural [gallnut extract (*Quercus Aegilops*)] or classic mordants (potassium aluminum sulfate and citric acid). Özomay and Akalın (2020) concluded that the usage of the *Quercus Aegilops* natural mordant in natural dyeing the woven hemp fabric with *Sambucus Ebulus* L. natural dye resulted in better outcomes from the standpoint of colour difference and colour efficiency as well as higher wash and light fastness properties.

Finally, Yan et al. (2021) studied the suitability of dried extracts from the flowers of *Buddleja officinalis* for natural dyeing plain woven hemp fabric. Optimum dyeing outcomes were accomplished when natural dyeing at 60 °C and pH 5 for 90 min leading to pale to dark yellow colour shades and yellow–green colour shade on hemp fabric according to mordant presence and mordant type (Yan et al. 2021). On the one hand, the wash fastness colour change levels of dyed hemp fabrics were mostly very poor and on the other hand, wash, perspiration and rubbing fastness staining levels were good to excellent (Yan et al. 2021). Yan et al. (2021) concluded that the utilization of aqueous extract from the flower of *B. officinalis* combined with studied natural mordants exemplifies a hopeful method for textile coloration.

Konstantinović et al. (2019) studied the decolorization of model wastewater (prepared by using a reactive dye; C.I. Reactive Blue 109) by adsorbent obtained from waste hemp fibers (acquired during rope manufacturing from 100% hemp fibers). This research paper is not about dyeing hemp fiber. But we have seen before that hemp fiber is successfully dyed with reactive dyestuffs. However, in this study, the decolorization of waste dyebath containing reactive dyestuff was studied by using waste hemp fibers as absorbent. So here, decolorization was achieved on an adsorbent made from physico-chemically modified waste hemp fibers, acquired as a by-product from the rope manufacturing (Konstantinović et al. 2019). They stated that the removal of reactive dyestuff with adsorbent obtained from waste hemp fibers depends on contact time, initial dyestuff concentration, temperature, and pH of the solution (Konstantinović et al. 2019).

The acquired adsorbent made from physico-chemically modified waste hemp fibers was a finely dispersed material with heterogeneous porous particles, whereas the inner structure includes expressed cracks, holes, and canals. Konstantinović et al. (2019) reported that the higher degree of decolorization was attained at lower initial dyestuff concentrations, even though the highest initial dyestuff concentration resulted in higher dyestuff adsorption. Konstantinović et al. (2019) concluded that the adsorbent generated from waste hemp fibers introduces an effective adsorbent for the removal of reactive dyestuffs from the aqueous dye effluent solution through potential application on an industrial scale production.

In this section, dyeing studies related to hemp fibers were examined. In the light of these studies, it was revealed that hemp fibers can be successfully dyed with reactive dyes and many different natural dyes.

4.5.3 Finishing of Hemp Fibers

In this section, different finishing applications applied to hemp fibers were reviewed. Li et al. (2010) studied the modifying influences of solely liquid ammonia treatment and in combination with resin treatment (crosslink finishing with modified DMDHEU) on the appearance qualities, comfort and mechanical characteristics of hemp, ramie, and linen plain woven fabrics. Li et al. (2010) reported that NH_3 treatment and particularly by liquid ammonia pre-treatment in combination with crosslink finishing led to an improvement on the crease recovery, washing shrinkage and other appearance qualities of studied hemp, ramie, and linen plain-woven fabrics. After the solely application of NH_3 treatment, moisture regain properties of the studied cellulosic fabrics enhanced and water retention of those diminished. Crosslink finishing resulted in a decrease on the air permeability, moisture permeability and other comfort properties (Li et al. 2010).

Racu et al. (2012) examined the antimicrobial characteristics (against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans*) of hemp fibers grafted with β-cyclodextrin derivatives (Monochlorotriazinyl-β-Cyclodextrin: MCT-β-CD; containing ferulic acid, caffeic acid, ethyl ferulate and allantoin compounds with inclusion complex). Racu et al. (2012) concluded that hemp fibers finished with cinnamic derivatives and allantoin, utilizing Monochlorotriazinyl-β-Cyclodextrin, displayed adequate antimicrobial activity against four microbial strains (*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans*), particularly against *S. aureus*.

Kostic et al. (2014) studied the preparation and characterization of silver-loaded water-retted hemp fibres with antimicrobial activity [against *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) and *Candida albicans* (ATCC 24433)]. Here, hemp fibers were oxidized utilizing oxidizing agents such as hydrogen peroxide and potassium permanganate to improve their sorption characteristics by boosting their cation exchange functions (Kostic et al. 2014). Kostic et al. (2014) reported that 1.84 mmol of Ag+ ions per gram of fibres was found to be the maximum sorption capacity of modified hemp fibres and Acquired silver-loaded hemp fibers exhibited antimicrobial activity against tested pathogens namely *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Treated hemp fibres displayed discrepant activity against different micro-organisms, usually exhibiting stronger bactericidal influences for gram (+) bacteria *S. aureus* than for gram (−) bacteria *E. coli*. and Kostic et al. (2014) recommended that these treated hemp fibres could be utilized in the production of particular textile materials such as bedding-sheets and shirts for e.g., the patients with atopic dermatitis or footwear lining.

In a study of Arık et al. (2018), crease-resistance improvement of desized and bleached plain woven hemp fabric via crease resistance finishing treatments with utilization of sol–gel technique, crosslinking technique, and commercial crease-resistant finish products (formaldehyde-free commercial crease-resistant finish product and commercial crease-resistant finish product with low formaldehyde content) was investigated. Arık et al. (2018) reported that both sol–gel and crosslinking techniques displayed equivalent close outcomes to the commercial crease-resistant finishing products. On the other hand, sol–gel technique was better than crosslinking technique particularly when tensile and tear strength properties were compared (Arık et al. 2018). The crease recovery angle results of sol–gel and crosslinking techniques were close to those of commercial finishing products. What is more, chitosan biopolymer inclusion was not noted to be effective from the standpoint of crease-resistance and physical performance characteristics (Arık et al. 2018).

In another research, Liu et al. (2017) examined the shrink resistant finishing and mechanism analysis on the silk/hemp/cotton woven fabric (Fiber content: 34% silk, 36% hemp and 30% cotton with the weight of 89 g/m^2). The fabric warp shrinkage decreased considerably, and the weft shrinkage altered a little by way of the shrink resistant finishing process. Liu et al. (2017) stated that the optimum processing parameters for chemical finishing process were 3:1 ratio of citric acid/poly (maleic acid), 40 g/L dosage of poly (maleic acid) and citric acid, and 30 g/L dosage of catalyst sodium hypophosphite. Liu et al. (2017) concluded that after processed by the optimum physical and chemical finishing, the shrinking percentage of silk/hemp/cotton fabrics declined to zero (0%).

4.6 Hemp Economy: Case of Turkey

The investigation of hemp economy is a grifted issue since there are some uncertain points for hemp market, however, some points can be taken into account to understand market dynamics. Hemp has a relatively small market in the world, but it has entered a growing trend in last years. The production of hemp is increasing due to the consumer demand, policy changes, new investments, and improvement in production methods. Additionally, hemp has various application areas that supplies producers and customers intensive alternative products (Mark and Snell 2019).

According to Zhao et al., World's total hemp harvested area for fiber production was 41,587 ha in 2018. The leading country was North Korea with 21,457 ha which was followed by China in 2018 with 4449 ha (Zhao et al. 2018 Regional Comparison and Strategy Recommendations of Industrial Hemp in China Based). The hemp production of the world is met by total 30 countries (Shen et al. 2020). Despite the high cultivation area of China, the fiber production yield gap is notable between China and other European countries. The fiber yield of China was 2837.5 kg/ha in the 2018. On the other hand, the Netherlands, Italy and Austria produced 7642.9 kg/ha, 6911.9 kg/ha and 4742.6 kg/ha, respectively (Zhao et al. 2018). This situation probably arisen due to man-power dependent production methods of China (Zhao et al. 2018; Shen et al. 2020). According to the Preferred Fiber and Materials Market Report 2021 report of Textile Exchange (Textile Exchange 2021), hemp fiber and tow displayed an estimated world production volume of around 174,027 tonnes in 2020 and hemp plant for textile fibers has mainly been grown in China, however there are also emerging initiatives in many different other countries such as America etc. Recently, many different studies have been carried out to expand the utilization of hemp. For instance, research and projects continue about the usage of hemp and jute as feedstock to produce man-made cellulosic fibers and even to produce bio-based leather imitation products (Textile Exchange 2021). It is estimated that hemp production will enhance worldwide in the coming years as a result of the successful outcomes of research and projects leading to an increase in the usage areas and demand of hemp, as well as the enhancing environmental concerns and positive efforts in increasing sustainability.

Hemp plant is also grown in Turkey. It is known that, in Turkey, hemp fibers were utilized for naval applications and daily life textile materials such as clothes, home textiles and so on during Ottoman Empire era in sixteenth and seventeenth centuries (Ceylan 2021). The modern hemp production attempt was begun in Turkey in the beginning of 1950s with the first investment on hemp fiber processing factory at Taskopru Hemp Factory established by government in Kastamonu province in 1946. Regrettably, the factory had to be closed in 1951 due to deficit related with low capacity working. After the closure of fiber processing factories, Turkey's hemp production was slipped to paper production purposes, SEKA paper factory was established in Taskopru in 1984. However, this factory went out of business in 2004 with miscellaneous reasons (Ordu Commodity Exchange, 2021). The statistical data of hemp production in Turkey is seen in Table 4.1.

Table 4.1 Hemp fiber production data of Turkey (2004–2020) (Turkish Statistical Institute 2021)

Years	2004	2005	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Area cultivated (da)	3750	650	221	157	63	12	10	10	45	46	55	160	101
Yield (kg/da)	160	85	45	102	95	83	100	100	156	152	127	126	94
Production (tons)	600	55	10	16	6	1	1	1	7	7	7	19	9

As seen in Table 4.1, the hemp fiber production has dramatically reduced starting with 2005 season, which come across to the shutdown of the paper factory. Beyond this point, decrease of the hemp fiber production kept going until 2016. A new regulation came into force in 2016 for hemp cultivation and control. Present regulation allows to hemp cultivation in certain regions (19 cities of 81) of the country under the control of local authorities, providing that the permission (Republic of Turkey Ministry of Agriculture and Forestry 2016). In the recent years, hemp cultivation has been promoted by government. In 2020, 70 Euros per decare governmental incentive was paid to the farmers. Yet, Turkey imports hemp seed and hemp fiber due to the lack of sufficient hemp cultivated areas. The hemp fiber import of Turkey was 1.1 tons for 2015, 22.9 tons for 2018, 916 kg for 2019, 619 kg for 2020 and 418 kg estimated in 2021 (Hemp Report of Ordu Commodity Exchange 2021). Recently, domestic Narlısaray variety has been developed to increase seed and fiber yield by the cooperation of Samsun Ondokuz Mayıs University and Blacksea Agricultural Resarch Institute (Baser and Bozoglu 2020).

Aydoğan et al. (2020) applied a specific projection on the economics of hemp cultivation at Vezirkopru/Samsun—Turkey. They investigated 5 production scenarios. In first scenario, hemp is cultivated for both fiber and seed, also, fibers are sold on the stem without decortication. In second scenario, hemp is cultivated only for fiber and fibers are sold as in the first scenario. In third scenario only fiber production is aimed, fibers are decorticated and hurds are sold separately addition to fibers. In fourth scenario fiber and seed production is aimed and hurds are also marketed. The fifth scenario is same with third scenario, but decortication is performed with machine (Aydoğan et al. 2020). According to these scenarios net profits were 211 Euros/da, 186 Euros/da, −103 Euros/da, −125 Euros/da and 20 Euros/da from first to fifth scenarios, respectively. Hemp cultivation has more profit than sunflower, wheat, sugar beet and corn agriculture in the investigated region. In the same study, it was also stated that the cost of 1 kg stem (without decortication) was 0.18 Euro, cost of 1 kg seed was 3 Euros and cost of 1 kg hemp fiber was 2.8 Euros (Aydoğan et al. 2020).

Despite the governmental supports and increasing awareness on sustainable products, hemp fiber production and hemp cultivation areas of Turkey has remained very low. It is thought that lack of conventional hemp production machinery in Turkey in the present results in low domestic demand. Besides, man-made fibers still dominate the composite sector as reinforcement materials. Consequently, farmers and textile producers have hesitations on hemp cultivation in Turkey. However, in the near future, these hesitations are expected to disappear in the long term and the production and consumption rates of hemp fiber are expected to increase gradually.

4.7 Conclusion and Prospects

In addition to its very important features such as biodegradable, environmentally friendly, renewable, natural, and sustainable, hemp fiber is increasing its share in the sector day by day due to its positive and good performance properties which are promising for various textile and composite applications. For this reason, considering the positive contributions of developing technology and innovative processes to hemp fiber, it is thought that the place of hemp fibers in the textile sector and textile economy will increase day by day.

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Chapter 5
Pharmaceutical Applications of Hemp

C. Miyabe Shields and Riley D. Kirk

Abstract Although humans have used the hemp *Cannabis sativa* plant for thousands of years, recently there has been a shift in the availability of hemp products that are high in secondary metabolites while maintaining low levels of the intoxicating phytocannabinoid Δ9-tetrahydrocannabinol (Δ9-THC). Historically, there have been many therapeutic applications of hemp in ethnobotanical formulations for a range of conditions. The primary compound of interest is cannabidiol (CBD), which demonstrates powerful antiepileptic properties and is the rationale behind the change in legal status enabling further production and research of hemp. The plant also contains additional phytocannabinoids, as well as other bioactive molecules including terpenes and flavonoids. There is sufficient preliminary evidence for a molecular mechanism through both the endocannabinoid system and the serotonin system; additionally, there may be non-specific interactions that occur when combinations of complex formulations are administered. The interconnected nature of the endocannabinoid system with other signaling systems in the central nervous system, immune system, and other essential peripheral functions complicates the discrete identification of specific molecular mechanisms. When evaluating the potential pharmaceutical applications of the hemp *Cannabis sativa* plant as a whole, it is found to be well-tolerated in human clinical settings and have vast therapeutic applications across a wide range of symptoms.

Keywords Endocannabinoid system · Cannabidiol (CBD) · Terpenes · Flavonoids · Phytocannabinoids · Cannabigerol (CBG) · Pharmacology

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5.1 Introduction

Humans have been using hemp *Cannabis* for food and fiber from around 10,000 BC; it wasn't until around 2700 BC that we have evidence humans began cultivating medical *Cannabis* bred for secondary metabolites (Pain 2015; Crini et al. 2020). Until recently, there were only two variations of *Cannabis sativa*—separated by the total content of active phytocannabinoids, specifically the percentage of delta-9-tetrahydrocannabinol (Δ9-THC). The industrial hemp *Cannabis* subtype was not used for any therapeutic purposes, and the focus of its cultivation was purely for food or fiber (Russo 2014).

Recent restructuring of the legal landscape regarding hemp *Cannabis sativa* has allowed for renewed interest in selective breeding, resulting in many new chemovars of the plant that contain novel pharmacological profiles. Technically, all *Cannabis sativa* plants that contain trace amounts, <0.2% w/w in the EU and 0.3% w/w in the USA, of Δ9-THC can be classified as hemp and these varieties typically contain significant concentrations of cannabidiol (CBD) as their primary cannabinoid constituent (Hughes 2018; Johnson 2019). However, there are new chemovars emerging with high cannabigerol (CBG) and cannabichromene (CBC) concentrations. Additionally, there are many rare phytocannabinoids that are present in trace amounts as well as other bioactive molecules in the plant that may contribute to the overall therapeutic potential of hemp such as terpenes, flavonoids, and other fatty acids. Many of these may be present in full spectrum hemp extract products currently available to consumers (Erzen et al. 2021).

Evidence suggests that hemp and extracted cannabinoid formulations obtained from hemp, which lack significant concentrations of the main psychoactive component Δ9-THC, can be qualitatively distinguishable from that of traditional high-THC *Cannabis sativa* (Van Dolah et al. 2019). One of the advantages of these new chemovars of hemp is the absence of a psychoactive alteration leading to the absence of negative psychoactive side effects that can accompany high-THC *Cannabis*. This is expected, and can be partially explained by the differences in the individual pharmacodynamic profiles of Δ9-THC and CBD (Zagzoog et al. 2020). While the cannabinoid formulations in hemp consist mainly of CBD and Δ9-THC, they are not the only phytocannabinoids produced by the plant. There is evidence that the presence of multiple cannabinoids in formulation can alter the overall therapeutic efficacy (Nahler et al. 2019). There is preliminary preclinical and clinical evidence for the therapeutic uses of CBD and hemp extracts containing CBD (Table 5.1).

This chapter will provide a review of the known pharmacodynamics and pharmacokinetics behind the main constituents of hemp *Cannabis sativa* by first providing a brief overview of the endocannabinoid system and other relevant biological targets before focusing on individual classes of bioactive molecules in hemp to assess their therapeutic potential.

Table 5.1 Potential therapeutic uses for cannabidiol (CBD) and/or extracts

Therapeutic indication	Form of hemp and/or active constituents	Reference(s)
Human/Clinical evidence		
Anti-epileptic/anti-seizure	CBD isolate	Lattanzi et al. (2018) Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. *Drugs* 78, 1791–1804
Anti-epileptic/anti-seizure	Hemp extract	Suraev et al. (2018) Composition and Use of Cannabis Extracts for Childhood Epilepsy in the Australian Community. *Scientific Reports* 8, 10154 Tzadok et al. (2016) CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. *Seizure* 35, 41–44
Reduction of chronic pain	Formulated THC:CBD extract	Serpell et al. (2014) A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *European Journal of Pain* 18, 999–1012 Überall (2020) A Review of Scientific Evidence for THC: CBD Oromucosal Spray (Nabiximols) in the Management of Chronic Pain. *Journal of Pain Research* 13, 399–410
Substance use disorders	CBD isolate, formulated THC:CBD extract	Morel et al. (2021) Clinical Trials of Cannabidiol for Substance Use Disorders: Outcome Measures, Surrogate Endpoints, and Biomarkers. *Frontiers in Psychiatry* 12, 109

(continued)

Table 5.1 (continued)

Therapeutic indication	Form of hemp and/or active constituents	Reference(s)
Anti-anxiety/Anti-depressant	CBD isolate, hemp extract	Blessing et al. (2015) Cannabidiol as a Potential Treatment for Anxiety Disorders. *Neurotherapeutics* 12, 825–836 Elsaid et al. (2019) Chapter Two—Effects of cannabidiol (CBD) in neuropsychiatric disorders: a review of pre-clinical and clinical findings. *Progress in Molecular Biology and Translational Science* 167, 25–75
Pre-clinical evidence		
Anti-inflammatory (skin)	CBD isolate	Baswan et al. (2020) Therapeutic Potential of Cannabidiol (CBD) for Skin Health and Disorders. *Clinical, Cosmetic, and Investigational Dermatology* 13, 927–942
Anti-inflammatory (gastrointestinal)	CBD isolate	Martinez et al. (2020)

5.2 The Endocannabinoid System

The endocannabinoid system (ECS) is an endogenous signaling system that is present in the bodies of all mammals. The psychoactive component of *Cannabis sativa*, Δ9-THC interacts with the ECS to facilitate the psychoactive effects observed by *Cannabis sativa* users. The ECS plays an integral role in maintaining neurochemical homeostasis both through its own signaling cascades and by responding and regulating the other neurotransmitter systems through retrograde signaling (Cristino et al. 2020). For this reason, it is critical during both neurodevelopment and in the mature brain (Lu and Mackie 2021). Dysregulation of the ECS is a hallmark of many disease pathologies and as a result, the ECS has been investigated as a therapeutic target for a range of conditions such as chronic pain, cancer, metabolic disorders, autoimmune disorders, anxiety and mood disorders, and gastrointestinal disorders (Cristino et al. 2020; Lu and Mackie 2021).

The isolation of Δ9-THC led to the discovery of the cannabinoid receptor 1 (CB1R) and opened the gates for endocannabinoid system research. Currently the core components of the ECS consist of the endogenous signaling molecules, called endocannabinoids, two primary receptors, and the biosynthetic and metabolic enzymes that regulate local endocannabinoid concentrations (Lu and Mackie 2021). However, evidence points towards a much larger ECS network with additional pharmacological targets which includes the recently discovered orphan GPCRs and transport proteins (Cristino et al. 2020).

5.2.1 The Endocannabinoids

Endocannabinoids are polyunsaturated fatty acids derived from phospholipids in the bilayer of cell membranes. The two primary endocannabinoids are N-arachidonoylethanolamide (AEA), or anandamide, and 2-arachidonoylglycerol (2-AG), both of which are derivatives of arachidonic acid (AA) (Fig. 5.1) (Komarnytsky et al. 2021). AEA was the first endocannabinoid to be discovered in 1992. Its name is derived from the sanskrit word "ananda" meaning bliss due to the central role AEA plays in mediating different types of pleasure (Scherma et al. 2019); Ananda was also a disciple of Buddha who is a central figure in Buddhism responsible for memorizing and documenting many teachings of the Buddha after his passing (Hecker 1980). AEA is biosynthesized from the phospholipid N-arachidonoyl phosphatidylethanolamine (NAPE) via several different pathways. One such pathway begins with phospholipase C, an enzyme that is activated by G-protein signaling of many major receptors including serotonin, glutamate, and adrenergic receptors (Yang et al. 2013).

Shortly after the discovery of AEA, 2-AG was identified as another endogenous ligand for the CB1R (Fig. 5.1). 2-AG is biosynthesized from inositol phospholipids (PI) by the enzyme diacylglycerol lipase (DAGL) and is a full agonist at CB1R as

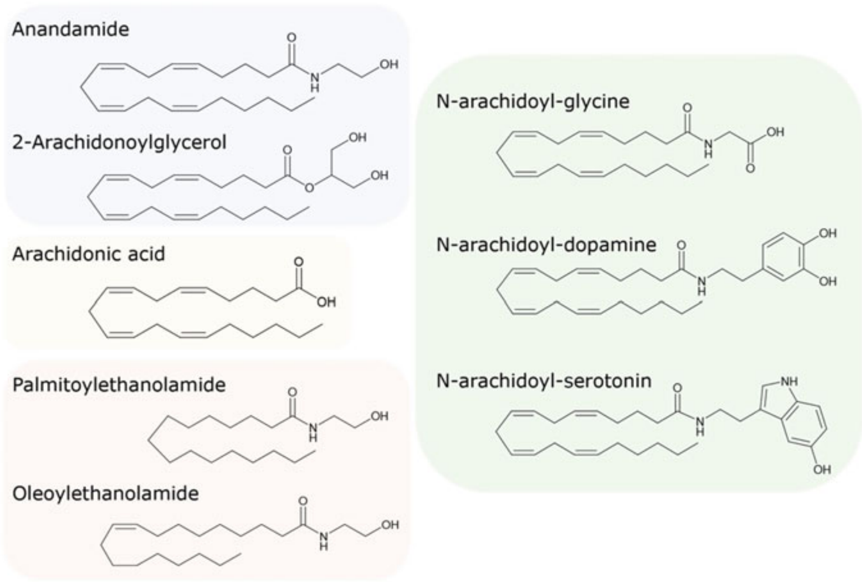

Fig. 5.1 Endogenous cannabinoids (endocannabinoids) and structurally related bioactive lipids

opposed to AEA which is a partial agonist (Bisogno et al. 1997; Baggelaar et al. 2018). 2-AG and AEA work together to regulate the ECS in a delicate balance that is tissue and cell-type specific (Luchicchi and Pistis 2012). Dysregulations of one or both AEA and 2-AG levels have been documented across a myriad of different disease states and animal models supporting the ECS as a therapeutic target for these conditions (Sugiura et al. 2004).

A general model that describes endocannabinoid dysregulation is Clinical Endocannabinoid Deficiency (CED), a theory for the molecular basis of multiple disease states caused by low levels of circulating endocannabinoids. Lower circulating endocannabinoids may cause a lowered threshold for sensing peripheral or central pain, as well as other alterations in homeostatic functions like sleep, mood regulation, or digestion. Currently there is evidence that CED may play a role in many different disease states including migraine, fibromyalgia, irritable bowel syndrome, hyperemesis gravitum, phantom limb pain, infantile colic, glaucoma, post-traumatic stress disorder (PTSD), bipolar disorder, autism spectrum (ASD), and others. However, it remains unclear whether the decreased endocannabinoid tone is the sole cause of the symptoms or a resulting artifact of upstream dysregulation (Russo 2016; Aran et al. 2019; Gunduz-Cinar 2020).

Altered endocannabinoid tone is typically associated with reciprocal alterations in the endocannabinoid receptor densities, namely CB1R and cannabinoid receptor 2 (CB2R) (Aran et al. 2019; Gunduz-Cinar 2020). As these receptors are each linked to many tissue and cell-specific signaling pathways that interact with other important neurotransmitter systems such as serotonin, dopamine, GABA, etc. (Oleson et al.

2021), it both further complicates and supports the theory for CED at the molecular scale.

5.2.2 Endocannabinoid System Receptors

The CB1R is the primary endocannabinoid receptor associated with the central nervous system (Fig. 5.2), but it is located many places throughout the body and across many different tissue and cell types. It is the most abundant G-protein-coupled receptor (GPCR) present in the brain (Chiarlone et al. 2014). The distribution of CB1R is not uniform across cell-types nor across different areas of the brain. In cortical regions of the brain, CB1R is expressed in larger amounts on GABAergic neurons than glutamatergic, but this variation is not seen in the hypothalamic region where the overall CB1R density is lower in both types of neurons (Busquets-Garcia et al. 2018). This variation in CB1R density is similar in the other classical categories of neurons like serotonergic, dopaminergic, and others. Interestingly, there is a paradoxical relationship between the number of CB1R present and the overall prevalence of cannabinoid-dependent signaling (Busquets-Garcia et al. 2018). It's puzzling that the G-protein specific signaling of CB1R is not related to the total concentration of the receptor, but instead regulated by cell-specific characteristics such as the ratios of CB1R and other neurotransmitter system GPCRs that bind and occupy the same available G-proteins as the CB1R (Chiarlone et al. 2014; Busquets-Garcia et al. 2018). To add even more complexity, the CB1R has been shown to heterodimerize with several other GPCRs that have been shown to be colocalized in specific neuron populations, further altering their agonist-dependent signaling cascade (Milligan 2006).

Initial evaluation of the mechanism behind CB1R agonist activity by phytocannabinoids was found to be inhibition of adenylate cyclase (AC) through Gi/o protein signaling. However, when in the presence of D2 dopamine receptors, CB1R has been shown to activate the Gs G-protein signal cascade (Busquets-Garcia et al. 2018). It appears the overall concentrations of Gi/o G-proteins in relation to the available CB1R determines this G-protein specificity based on factors including cell-type and other colocalized GPCRs (Busquets-Garcia et al. 2018). It's also possible that different ligands display biased agonism towards specific G-protein signaling cascades (Khajehali et al. 2015). Discerning between ligand-specific and cell-type specific G-protein signaling activation of CB1R will be important for understanding the mechanism of action of endocannabinoid dysregulation in known disease pathologies.

Additionally, the CB1R has G-protein independent mechanisms mediated through β-arrestin 1 and β-arrestin 2 (Busquets-Garcia et al. 2018). Though primarily associated with GPCR endocytosis and receptor downregulation or upregulation, the β-arrestin proteins also regulate many intracellular kinase cell signaling pathways (Park et al. 2016). Activation of the CB1R can result in alterations in electrolyte ion balances that control the overall voltage potential of the neuron to fire independently of G-protein activation; the mechanism remains unclear for specific ion types in

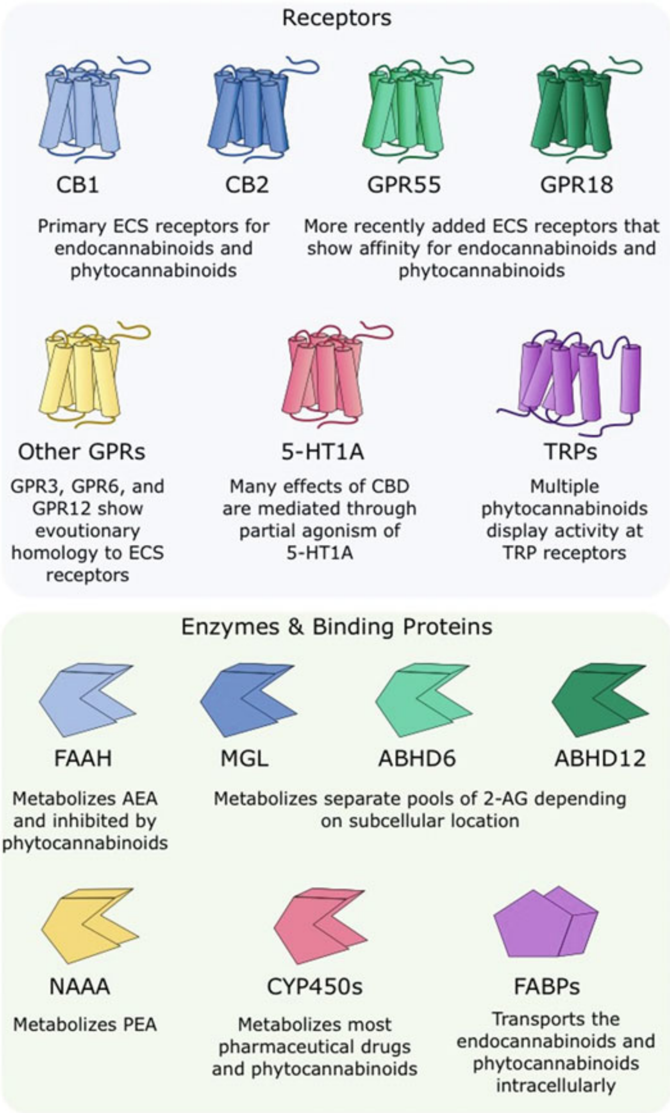

Fig. 5.2 Endogenous targets of hemp *Cannabis sativa* secondary metabolites in the endocannabinoid system and other related systems

specific cell types. There is extensive proof of alteration of ERK kinase and mTor pathway cell signaling by CB1R activation (Busquets-Garcia et al. 2018). Further parsing the role of the downstream signaling pathway of β-arrestin in CB1 functionality will aid in the understanding of its overall mechanistic control of homeostasis signaling.

The final consideration for CB1R pharmacodynamics is the subcellular localization of specific pools of receptors having specific signaling activity. Typically, we associate CB1R activation with the plasma membrane population of CB1R, but there exists entire subcellular populations of CB1R that display distinctive phenotypic effects upon activation (Mendizabal-Zubiaga et al. 2016). Mitochondrial CB1R subpopulations are the most distinctively separate from plasma membrane CB1R signaling and exhibit control over cataleptic behavior, but not antinociception in mouse model (Marsicano 2021). Mitochondria are often deemed the "powerhouse of the cell," and their functionality is especially relevant in the brain as it is the most energy-demanding organ in the body (Brillo et al. 2021). CB1R alteration of mitochondrial functionality represents a new potential therapeutic mechanism of action for specific CB1R mediated effects.

Equally as complicated is the CB2R in its diversity in expression profile throughout both immune and neuronal cell types and its downstream cell signaling pathways. This receptor was originally cloned from human leukemia cells, the CB2R only shares 44% homology to the CB1R (Jordan and Xi 2019). Shortly after it was discovered, the CB2R was associated with the periphery, more specifically immune cells. Though the expression of CB2R mRNA is low in brain regions, immunohistochemical studies have reported its presence in various regions of the brain including the hippocampus, ventral tegmental area, nucleus accumbens, and more (Jordan and Xi 2019). This has been further confirmed in mouse models using electron microscopy paired with selective immunolabeling (Jordan and Xi 2019). While it's clear CB2R has a distinct expression profile from CB1R, it is present in the central nervous system and contributes to endocannabinoid system regulation of the nervous system in processes like behavior, seizure potential, feeding, addiction, reward, learning and memory.

The other main cell-type specific action of the CB2R of interest pharmacologically is through immune system cells, including those in the brain such as microglia (Basu and Dittel 2011). But the CB2R is expressed in many other immune cells such as macrophages, natural killer cells, B cells, and T cells, and participates in many different essential functions both shared by all immune cells and specific to the individual immune system cell subtypes, tissue localization, or pathophysiological mechanism of activation (Basu and Dittel 2011). Chemotaxis or the migration of immune system cells towards areas of interest is one of the central functions of all immune system cells and has been shown to be regulated by the CB2R (Ghosh et al. 2006). Interestingly 2-AG promotes chemotaxis of an array of immune system cells including neutrophils, natural killer cells, B cells, and microglial cells while synthetic CB2R agonists like JWH-015 or O-2137 result in a reduction of migration, an effect that was reversed in the presence of a CB2R antagonist confirming its action at CB2R in the cells (Raborn et al. 2008).

In addition to migration, the CB2R can participate in the overall balance of immune system cells by regulating proliferation, differentiation, and apoptosis of specific immune system cell subtypes. The balance between immunodeficiency, or too few immune system cells, and chronic inflammation or autoimmune disorders caused by too many immune system cells is critical to the proper functionality of the human immune system. The CB2R participates in proliferation in an opposing fashion in B cells versus T cells; CB2R agonism appears to promote differentiation of B cells but inhibits the proliferation of T cells (Basu and Dittel 2011). The CB2R also appears to participate in apoptosis of immune system cells, but the mechanism remains unclear as the apoptotic-promoting effects of CB2R agonism were only partially reversed by selective antagonists and occurred at high doses where receptor-independent mechanisms may have contributed (Do et al. 2004). Finally, the CB2R participates in immune system regulation by altering the production of pro-inflammatory cytokines and other highly specific immune system activities such as the conversion of B cell immunoglobulin production from IgM to IgE (Correa et al. 2009). However, a vast majority of the immune system activity of CB2R has been determined in vitro and, given the complexity of human immune system connectivity at the tissue and organ scale, many contributing factors to immune cell regulation may be lost in the assumptions necessary for in vitro analysis.

As with the CB1R, the CB2R cell signaling pathways are highly dependent upon the cell-type and other GPCRs colocalized on the cells, but primarily associated with Gi G-protein activation (Basu and Dittel 2011). In immune system cells, the activation of the AC pathway is typically associated with the transcription of the IL-2 gene through increased intracellular concentrations of cAMP and subsequent protein kinase A (PKA) activation. Through an unclear mechanism, CB2R modification of AC activity has been shown to be dependent upon the incubation time of the ligands (Basu and Dittel 2011). This effect is at least partially believed to be through crosstalk with T-cell receptors. Furthermore, the CB2R has been shown to regulate all three pathways of mitogen-activated protein kinase (MAPK) signaling and the Rho/Rac and Rap family of signaling proteins, which participate in many fundamental functions of cell viability such as cytoskeletal rearrangement and cell cycle progression (Shoemaker et al. 2005). The complexity of cell signaling pathways for GPCRs cannot be overstated and the cannabinoid receptors are no exception to this.

While CB1R and CB2R have been the most extensively researched receptors in the endocannabinoid system, the family of receptors tentatively included as part of the "endocannabinoidome" has expanded to include GPR55 and GPR18 (Fig. 5.2). Both GPR55 and GPR18 have been shown to interact with both endogenous and exogenous cannabinoid ligands and, as such, have earned the designation of putative endocannabinoid system receptor targets (Tuduri et al. 2017). However, other class A orphan GPCRs like GPR3, GPR6, and GPR12 share a close evolutionary relationship with the cannabinoid receptors (Morales and Reggio 2017). For a comprehensive review of the endocannabinoid-related orphan GPCRs see recent review by Morales and Reggio (2017).

Although technically part of the vanilloid family, the transient receptor potential vanilloid 1 (TRPV1) receptor (Fig. 5.2) participates extensively in endocannabinoid system dynamics (Tominaga and Tominaga 2005). The TRPV1 receptor is a polymodal ion-channel that is activated by capsaicin, heat, variations in pH, and many lipid signaling molecules, including AEA (Tominaga and Tominaga 2005). TRPV1 is also activated by exogenous phytocannabinoids and synthetic cannabinoids, which causes an influx of Ca^{2+} ions and triggers several calcium-dependent signaling pathways in a cell-specific manner. Additionally, TRPV1 signaling has been shown to display a relatively unique homeostatic desensitization mechanism where after activation the receptor can no longer respond to stimuli for a set time period (Muller et al. 2018; Ryskamp et al. 2014). This activation and desensitization mechanism plays an important role in neuropathic pain and inflammation. The phytocannabinoids have been shown to interact with other TRP receptors as well, for more information see review by Muller et al. (2018).

5.2.3 Endocannabinoid-Metabolizing Enzymes

Acting in synchrony with the cannabinoid receptor dynamics is the regulation of circulating endocannabinoids by endocannabinoid-metabolizing enzymes (Fig. 5.2). The two endocannabinoids AEA and 2-AG are metabolized primarily by Fatty Acid Amide Hydrolase (FAAH) and Monoacylglycerol Lipase (MGL), respectively. In neuronal cells, these two enzymes are in separate populations with FAAH in the post-synaptic cell at the site of endocannabinoid synthesis and MGL in the pre-synaptic cell colocalized with the cannabinoid receptors (Gulyas et al. 2004). While differences in specific endocannabinoid levels have been linked the pathophysiology of various disorders (Russo 2016; Aran et al. 2019; Gunduz-Cinar 2020) the exact nature of the balance between AEA and 2-AG signaling, and the role of the metabolizing enzymes has yet to be fully elucidated. Increasing endocannabinoid tone through inhibiting the endocannabinoid metabolizing enzymes has been linked to therapeutic potential without negative psychoactive cannabinoid receptor-related effects (Saario and Laitinen 2007).

FAAH is a type I—single transmembrane domain integral membrane protein that can be found in both the plasma membrane and the endoplasmic reticulum; its main role is to metabolize AEA (Ahn et al. 2009). While FAAH has been shown to break down 2-AG in vitro, this has never been confirmed in vivo. FAAH has both esterase and amidase activity and breaks down other similar fatty acid amides such as oleamide, N-palmitoylethanolamine or N-oleoylethanolamine (Bisogno et al. 2002) (Fig. 5.1). Inhibition of genetic knock out of FAAH leads to elevated levels of AEA and other N-ethanolamines and N-acyltaurines across many different tissue types (Ahn et al. 2009; Kailash and Tripathi 2020). The phenotype of human and mouse model downregulation of FAAH displays anxiolytic and antinociceptive therapeutic potential. FAAH-specific inhibitors have entered clinical trial for a range of applications generally associated with neurological or neuropsychiatric disorders such as anxiety, mood disorders, Tourette syndrome, etc. Thus far they have outpaced their sister molecules, the MGL inhibitors, in clinical trial, however, none have made it to market (Kailash and Tripathi 2020).

MGL is a membrane-associative serine hydrolase that is responsible for most of the metabolism and deactivation of 2-AG. The structure of MGL consists of an alpha beta hydrolase domain fold basket with a relatively small lid domain (Gil-Ordonez et al. 2018). Created by the interface of the basket and lid domain, the binding pocket determines substrate specificity for hydrolysis. Inhibition of MGL leads to increases in 2-AG and decreases in arachidonic acid (AA) (Fig. 5.1), as 2-AG is the major precursor for AA (Gil-Ordonez et al. 2018). As prostaglandins and other inflammatory lipids are synthesized from AA (Hanna and Hafez 2018), the inhibition of MGL leads to increases in 2-AG which activates both cannabinoid receptors while simultaneously decreasing the prevalence of systemic inflammatory factors. For that reason, MGL is an attractive therapeutic drug target for a myriad of applications like pain, anxiety, neuroinflammation, and cancer (Gil-Ordonez et al. 2018).

Much like the cannabinoid receptors, the family of endocannabinoid metabolizing enzymes has been growing to include more recently discovered hydrolases and amidases. Alpha/beta hydrolase domain 6 (ABHD6) is a serine hydrolase in the same superfamily as MGL, though it does not share a high sequence homology; ABHD6 is an integral membrane protein with a single N-terminal transmembrane domain that is located post-synaptically at the site of 2-AG biosynthesis (Thomas et al. 2013). Depending on the cell type and assay, ABHD6 controls between 4 and 20% of 2-AG metabolism and has been shown to act upon a unique pool that directs specific downstream effects. Recently ABHD6 has been shown to play a pivotal role in energy homeostasis as the downregulation through pharmacological inhibition or genetic knockout result in the complete prevention of obesity and diabetes (Thomas et al. 2013). In the same family of serine hydrolases, ABHD6 also participates in the regulation of the immune system and controls the surface expression of specific NMDAR subunits. Closely related but located pre-synaptically with the cannabinoid receptors and MGL is alpha/beta hydrolase domain 12 (ABHD12). While there is limited information on ABHD12 functionality, it has been linked to 2-AG hydrolysis and neurodegenerative disorders (Kind and Kursula 2019). Most recently N-acylethanolamine acid amidase (NAAA) has earned a place in the endocannabinoid system family. This fascinating enzyme self-proteolysis to expose the catalytic cysteine residue in an adjacent subunit of tertiary structure (Gorelik et al. 2018; Piomelli et al. 2020). Inhibition of NAAA is being investigated for analgesic and antiinflammatory potential. Together, MGL, FAAH, ABHD6, ABHD12, and NAAA make up a vast majority of endocannabinoid metabolism and deactivation, but their specific expression profiles throughout the body and variations in membrane composition across cell-types determine the balance of their signaling (Kailash and Tripathi 2020, Thomas et al. 2013; Savinainen et al. 2012 Piomelli et al. 2020).

5.2.4 Fatty-Acid Binding Proteins

While traditionally not included in the formal definition of the endocannabinoid system family, the fatty acid binding proteins (FABPs) that solubilize and transport the endocannabinoids throughout the cytoplasm of the cell like FABP1, FABP3, FABP5, and FABP7 can alter overall endocannabinoid system functionality (Fig. 5.2) (Kaczocha et al. 2012). Inhibition of FABPs leads to increases in AEA likely due to the lack of transport of the substrate to the metabolizing enzyme (Kaczocha et al. 2012). FABPs have been shown to bind to Δ9-THC and CBD which could be a contributing factor in the increase in AEA levels seen after cannabis use (Elmes et al. 2015).

5.3 Downstream and Crosstalk of ECS with Other Systems

When considering the pharmacological activity of cannabinoids on ECS targets, the considerable synchronous and downstream interactions with other systems cannot be overlooked. As the only regulatory system in the body that operates by retrograde signaling, the ECS is positioned to exert control over many central and peripheral functions (Cristino et al. 2020, Lu and Mackie 2021). Even the metabolism and deactivation of endocannabinoids produces the scaffold and begins one of the most complex lipid-signaling cascades in the human body with therapeutic applications ranging from cancer and angiogenesis to anti-inflammatory, cardiovascular, and blood-pressure regulation effects.

When AEA or 2-AG is hydrolyzed, AA is released. AA is the base molecule of an entire signal cascade of bioactive lipids called eicosanoids (Hanna and Hafez 2018). The AA signaling cascade includes many well-known pro-inflammatory factors like prostaglandins and is the mechanism of action for pharmaceutical antiinflammatory cyclooxygenase (COX) COX1 and COX2 inhibitors such as ibuprofen, naproxen, and celecoxib (Hanna and Hafez 2018). Alterations in the ECS directly affect the downstream AA cascade as the available parent molecule is sourced from endocannabinoid hydrolysis (Cascio and Marini 2015).

Another significant class of enzymes that the phytocannabinoids interact with are the cytochrome P450 (CYP) enzymes (Fig. 5.2) (Yamaori et al. 2010). The CYP enzymes are a large class of metabolic, mainly oxidizing, enzymes that are responsible for the metabolism of most major pharmaceutical drugs (Manikandan and Nagini 2018). The competition of phytocannabinoids with other major pharmaceuticals may contribute to drug-drug interactions and potentiating effects.

Also noteworthy are the other N-arachidonoyl lipid signaling molecules found to interact with ECS targets such as N-arachidonoyl serotonin, N-arachidonoyl dopamine, and N-arachidonoyl glycine (Fig. 5.1). These AEA analogs are called elmiric acids and are emerging as key regulators of endocannabinoid system functionality through unique pathways, adding nuance and subtlety to overall signaling in a cell-specific or tissue-specific manner (Burstein 2008).

There are about 40 identified elmiric acids that have a range of bioactivities and therefore therapeutic applications such as pain, inflammation, cell proliferation, and calcium-dependent signaling (Burstein 2008). Altogether these ECS protein targets and the vast array of lipid signaling molecules act together to conduct the homeostatic orchestra of endocannabinoid signaling.

In addition to endocannabinoid-related signaling molecules, the regulation and modification of other neurotransmitter systems and lipid signaling systems by ECS signaling, including heterodimerism of cannabinoid receptors with other GPCRs to alter the agonist-driven responses is significant (Sleno and Hebert 2019). The ECS directly affects serotonin, dopamine, GABA, glutamate, opioid, and oxytocin signaling systems and likely indirectly affects every neurological process in the brain (Lu and Mackie 2021). The deeply embedded nature of the ECS within and around other systems is what creates such large and vast therapeutic potential as a drug target.

Of specific interest to hemp pharmacology is the 5-HT1A serotonin receptor (5HT1AR). The functionality, not expression level, of this receptor has been shown to be dependent upon CB1R signaling and it has been a general therapeutic target for mental health disorders for over 50 years (Mato et al. 2007). The 5HT1AR is a GPCR that is located in both presynaptic and postsynaptic cells (Albert and Vahid-Ansari 2019). In a similar fashion to both cannabinoid receptors, the 5-HT1AR is primarily associated with Gi/o G-protein signaling, however, this has been shown to be highly dependent upon cell type, other GPCR colocalization, and can even display ligand specificity (Albert and Vahid-Ansari 2019). The overall regulation of the serotonin system by the endocannabinoid system has been extensively researched (Haj-Dahmane and Shen 2012), but the tangible applications of pharmacological targeting remains an enigma. While it's clear that ECS activity regulates the release of serotonin, different serotonin receptor subtypes, and receptor functionality, the exact nature of the cross-talk between these two systems is highly dependent on cell-type, tissue-type, or adaptive response being investigated (Haj-Dahmane and Shen 2012).

The last thing worth mentioning is the relationship between the endocrine and endocannabinoid systems. Hormones are another class of signaling molecules encompassing sterols, which are lipid signaling molecules synthesized from cholesterol, and small peptides like oxytocin or prolactin. Hormones mediate many significant functions in human homeostasis, a significant portion of which overlap with and have been shown to be modified by the endocannabinoid system (Hillard 2015; Santoro et al. 2021). Prolactin is the hormone that mediates lactation, but also contributes to other functions such as immune system regulation and hematopoiesis; generally, the activation of the endocannabinoid system is associated with a reduction in prolactin (Hillard 2015). Oxytocin is often referred to as the "love hormone" and primarily associated with social reward, which has more recently been shown to be completely mediated through endocannabinoid signaling (Wei et al. 2015). The ECS also participates in sex hormones like estrogen and testosterone regulation through gonadotropin-releasing hormone (Santoro et al. 2021). This interaction between the endocrine system and ECS has been shown to be significant across multiple physiological functions from reproduction to stress, memory, and learning.

The substantial interplay of the ECS with other tangential, opposing, and synchronous signaling systems makes it a promiscuous yet ubiquitous pharmacological target. The ECS is involved in virtually every step of maintaining both central and peripheral homeostasis (Lu and Mackie 2021). Therefore, it's not surprising that dysregulations in ECS functionality have been observed across a myriad of disease pathologies. These variations can be a result of biodiversity or neurodiversity, environmental factors, trauma, or a combination, and can cause an array of symptoms ranging from benign to severely disabling. The manipulation of the ECS and related systems through phytocannabinoids, terpenes, flavonoids, and other bioactive molecules present in hemp *Cannabis sativa* has vast therapeutic potential, especially for mental health, inflammation, neurological disorders, chronic pain, and gastrointestinal disorders.

5.4 Phytocannabinoids

Until very recently, hemp *Cannabis sativa* was not cultivated for its secondary metabolites and, thus, had relatively low concentrations of cannabinoids in comparison to medical high-THC *Cannabis* (Russo 2014). However, even in plants cultivated purely for fiber, the flowers still contained significant amounts of cannabidiolic acid (CBDA) and minimal amounts of Δ9-tetrahydrocannabolic acid (THCA). These carboxylic acid derivatives of their better-known partners, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC) respectively, make up a majority of secondary metabolites present in hemp *Cannabis sativa* (Russo 2014). The carboxylic acid moiety adds a negatively-charged substituent that significantly alters the pharmacology and permeability of the molecule, creating unique therapeutic profiles.

5.4.1 Carboxylic Acid Biosynthetic Precursors

The biosynthetic parent molecule of both CBDA and THCA is cannabigerolic acid (CBGA). This molecule has a single phenol ring substituted with a carboxylic acid, two alcohol groups and two carbon chains, an alkyl group and an alkene group. CBGA is structurally very distinct from CBDA and THCA in that it has two flexible hydrophobic chains which contributes to its unique pharmacology. Thus far, CBGA appears to block TRP family receptors, specifically TRPV3, TRPV4, and TRPM8 (De Petrocellis et al. 2011). Notably, CBGA desensitized these receptors to noxious stimuli, which is a potential mechanism for pain reduction (De Petrocellis et al. 2011). CBGA has also been shown to have antiepileptic properties in animal models (Anderson et al. 2021). More recently novel chemovars of hemp *Cannabis* have emerged that contain significant CBGA concentrations (Erzen et al. 2021). While CBGA does display unique therapeutic potential, the enzyme-facilitated cyclization into CBDA has been the primary focus of past research and more research on CBGA pharmacology is needed to further explore its therapeutic potential.

CBDA is the main secondary metabolite present in hemp *Cannabis* flower. While the carboxylic acid increases the hydrophilicity of the compound and, thus, is expected to decrease blood–brain barrier permeability, CBDA shows an increased affinity to both CB1R and CB2R in comparison with CBD in competition binding assays (Zagzoog et al. 2020). This correlated with increased potency of CBDA over both CBD and THC in cell signaling assays evaluating decreases in cyclic-AMP (cAMP) caused by CB1R activation (Zagzoog et al. 2020). It appears that CBDA would have increased potency over CBD in peripheral CB1R and CB2R-related effects, which include inflammation and immune system regulation. Additionally, CBDA has displayed strong biased agonism in the CB1R towards the β-arrestin pathway, however, a separate experiment has contradicted this finding, further complicating its mechanism of action (Navarro et al. 2020). Interestingly this affinity to CB1R and CB2R has not yet been attributed to any physiological functions directly. Indirectly, CBDA has been shown to inhibit MDA-MB-231 breast cancer cell migration through a reduction in cAMP-dependent protein kinase A activity which is a potential effect of cannabinoid receptor activation (Takeda et al. 2012). CBDA has also been shown to eliminate trauma-induced general anxiety behavior in mouse model (Assareh et al. 2020); modulation of trauma and fear responses through endocannabinoid manipulation of the amygdala is well-established (Gunduz-Cinar 2021). Outside the ECS, the antiemetic properties of CBDA has been shown to be facilitated through the serotonin 5-HT1AR (Bolognini et al. 2012). Downstream of the ECS, CBDA has been shown to inhibit COX2 enzymes associated with inflammatory disorders like rheumatoid arthritis (Takeda et al. 2008). This is expected as the molecular structure of CBDA contains salicylic acid which is a COX2 inhibitor. This COX2 inhibition has also been linked to a decrease in the total expression levels of COX2 enzymes in MDA-MB-231 breast cancer cell lines—potentially elucidating an additional mechanism of CBDA in inhibition of breast cancer cell metastasis (Takeda et al. 2014).

While THCA is present in much smaller concentrations than CBDA, it is still a component in full spectrum hemp *Cannabis* extracts and as such its pharmacology is significant especially in a potential synergy with CBD and CBDA. THCA displays affinity and pharmacological activity for a myriad of targets in the ECS: CB1R, CB2R, MGL, FAAH, NAAA, TRPV1, as well as others outside the ECS like PLC, COX1, COX2, and others (Zagzoog et al. 2020; Moreno-Sanz 2016). THCA has been shown in vitro and in vivo laboratory settings to have anti-inflammatory, immunomodulatory, antiemetic, neuroprotective, and antiepileptic properties (Moreno-Sanz 2016). Both CBDA and THCA show therapeutic potential through modulation of the ECS and inhibition of inflammatory enzymes.

5.4.2 Cannabidiol (CBD) and Related Cannabinoids

Although the plant itself creates most of its secondary metabolites in the acidic form, decarboxylated CBD has been identified as the primary therapeutic agent in hemp *Cannabis*. CBD has a more flexible molecular structure in comparison to Δ9-THC due to the free rotation of the two ring structures. This makes CBD a promiscuous ligand that has been predicted to interact with over 60 targets in the body including members of the ECS, the TRP receptor family, serotonin system, opioid system, gamma aminobutyric acid (GABA) system, glycine system, and metabolic and synthetic enzymes (Ibeas Bih et al. 2015). While this promiscuity complicates elucidating specific molecular mechanisms for CBD, it also is what gives CBD such versatility in therapeutic applications.

Initially CBD was believed to be a neutral antagonist at CB1R and an inverse agonist at CB2R, but at very low affinity that it was uncertain whether it was physiologically relevant (Zagzoog et al. 2020). It's certainly possible that at very high doses, CBD displays antagonist and inverse agonist properties that reduce ECS tone. More recently, CBD was shown to be a negative allosteric modulator at CB1R, also reducing ECS signaling. However, this effect may be negated or even fully overcome by the fact that CBD inhibits the endocannabinoid-metabolizing enzyme FAAH and likely also inhibits MGL, ABHD6, and ABHD12. Inhibition of these enzymes results in an increase in AEA and 2-AG that would be associated with an increase in overall ECS signaling through all ECS receptors. Increasing circulating endocannabinoids has been shown to have anti-anxiety, anti-inflammatory, and antinociceptive effects and endocannabinoid-hydrolyzing enzymes have been viewed as an amenable pharmacological target for the development of novel pharmaceuticals for some time.

Possibly acting in synergy to these effects is the interaction of CBD with the serotonin system. CBD has been shown to be a full agonist at 5HT1AR and a partial agonist at 5HT2AR, increasing serotonin signaling (Russo et al. 2005). The activation of 5HT1AR by CBD has been linked to both its anxiolytic and antiepileptic effects in murine models (Resstel et al. 2009). Alteration in serotonin system functionality has been a well-documented therapeutic mechanism of action for multiple mental health disorders and symptoms such as general anxiety, depression, bipolar disorder, schizophrenia, and ASD. Many of the current psychopharmaceuticals prescribed for antidepressant, antipsychotic, mood stabilization, and anxiolytic indications show 5HT1AR agonist activity. In addition to this mechanism, there is a strong potential for synergy between the ECS and serotonin system, especially given the nature of CB1R and 5HT1A, 5HT2A heterodimerism (Galindo et al. 2018).

The most significant therapeutic application of CBD, and by direct extension hemp *Cannabis,* is its powerful antiepileptic properties (Consroe and Wolkin 1977; Cunha et al. 1980). The antiepileptic properties of CBD have been known for decades, but a 2014 case report of Charlotte Figi, who had Dravet syndrome, documented the remarkable decrease in the number of daily seizures (Maa and Figi 2014). The impact of the efforts of Charlotte's mother, Paige Figi, to share Charlotte's story and to advocate for the medical applications of CBD and hemp *Cannabis* cannot be understated. CBD shows strong antiepileptic properties and can be effective in patients that do not respond well to other antiepileptic drugs (Silvestro et al. 2019). Currently there is a pharmaceutical formulation of CBD by GW Pharmaceuticals called Epidiolex that is prescribed for epilepsy. While CBD isolate that is >98% pure derived from hemp is commercially available, in general Epidiolex is formulated at higher concentrations and the suggested dosage is significantly higher than a vast majority of commercial products.

As other antiepileptic pharmaceuticals generally share applications in other neurological and mental health disorders, it is not surprising that CBD also displays therapeutic effects for a number of mental health disorders including schizophrenia, PTSD, attention deficit hyperactive disorder (ADHD), ASD, anxiety, insomnia, and Tourette syndrome (Khan et al. 2020). Studies evaluating doses of CBD between 200 and 1500 mg per day showed it was able to alleviate symptoms of psychosis in schizophrenia and Parkinson's disease (Khan et al. 2020). Interestingly the dose of CBD alters the therapeutic profile significantly for psychosis, which is defined as having two separate categories of positive and negative symptoms. A lower dose of 300 mg/day was shown to improve cognitive impairment where a higher dose of 600 mg/day did not; a higher dose of 800 mg/day was shown to be comparable to amisulpride in improving symptoms and associated with elevated levels of AEA (Hallak et al. 2010). In a study dosing CBD at 1000 mg/day, positive symptoms of schizophrenia were reduced with no change in negative symptoms (McGuire et al. 2018). This variability and apparent contradictions in dose-dependency of CBD may have to do with the delicate interplay between CB1R and 5HT1AR-related effects. Overall, there is strong evidence that CBD may be therapeutic for reducing symptoms of psychosis.

Of the other clinical investigations of CBD and mental health disorders, the study evaluating ASD and other comorbidities is of significance, namely due to lack of understanding in underlying molecular mechanism of neurodiversity. At a median dose of 90 mg/day over an average of 66 days CBD was able to reduce anxiety, hyperactivity, insomnia and self-injurious behaviors in children with ASD (Barchel et al. 2019). The reduction in anxiety, insomnia, and self-injurious behaviors may be through CBD's action as a positive allosteric modulator of GABA-A receptors (Bakas et al. 2017). This is the same molecular mechanism as benzodiazepines, a major class of anxiolytic pharmaceuticals that are currently prescribed to treat these symptoms. It should be noted that this study involved low concentrations of Δ9-THC (approximately in a 20:1 ratio of CBD:Δ9-THC), which may have contributed to the beneficial effects.

In addition to mental health disorders, CBD has shown therapeutic potential for both inflammatory and neuropathic pain in animal models. This aligns with ECS and serotonin system modulation which have both been pharmaceutical targets for pain and for replacement options over opioid system pain management, which has clear disadvantages. In a survey of volunteer patients in pain clinics, 90.8% of patients responded that CBD was able to reduce their pain with 59% of patients stating that it was "a lot" to "completely" reduced (Schilling et al. 2021). These patients had a wide array of symptoms ranging from back pain, neck pain, limb pain, neuropathic pain, fibromyalgia, or migraines. Despite promising qualitative results for pain management in the general public, the efficacy of CBD for migraines, fibromyalgia, rheumatoid arthritis (RA), and pain in geriatric populations has shown a large amount of variability (Berger et al. 2020; Hendricks et al. 2019). This is likely due to the complex and multifaceted signaling mechanisms regulating pain combined with variations in ECS tone from patient to patient.

Due to the inflammatory pathology of most gastrointestinal (GI) disorders and extensive qualitative evidence for therapeutic benefits of *Cannabis* and its secondary metabolites, CBD's efficacy for the treatment of various GI symptoms has been under investigation. CBD was shown to normalize GI motility in multiple murine models of intestinal irritation and inflammation; not only curative, CBD showed potential as a preventative treatment for inflammation-based GI disorders through histophathological studies in murine models (Martinez et al. 2020). These findings have yet to be confirmed by clinical trial, though there is one study that did not reach its endpoint that showed therapeutic promise for CBD for ulcerative colitis. As the communication between the GI system and the nervous system has been shown to be integrally linked to ECS and serotonin system interplay, it's not surprising that CBD shows promise for GI disorders. The fact that CBD modifies both the ECS and key serotonin system receptor targets makes it an attractive and unique pharmacological ligand that has vast therapeutic potential. Furthermore, CBD has been shown to be well-tolerated across multiple studies in human clinical settings, indicating that it poses relatively low risk for negative side effects, making it even more attractive.

Sharing almost entirely the same structure as CBD, cannabidivarin (CBDV) has a shortened alkyl chain substituent—CBDV contains a propyl group as opposed to CBD's pentyl side chain on the phenol ring. Thus far, the most significant pharmacological target of CBDV appears to be the TRP receptor family; CBDV is an agonist at TRPA1, TRPV1, TRPV2, TRPV3, TRPV4, and an antagonist at TRPM8 (Zagzoog et al. 2020). The TRP receptor family contributes to many different sensory processes, making CBDV a potential ligand of interest for different types of pain. Additionally, CBDV has been shown to modify the ECS through inhibiting AEA uptake and inhibiting 2-AG synthesizing enzyme diacylglycerol lipase (DAGL) (Martinez et al. 2020). Although the molecular mechanism remains unclear, CBDV displays antiepileptic and neuroprotective effects (Huizenga and Forcelli 2018). CBDV is currently under clinical investigation for both ASD and epilepsy (Zamberletti et al. 2021).

Often overlooked, but significant in terms of high-heat transformation of CBD when hemp *Cannabis* is smoked or vaporized, is cannabinodiol (CBND)—a dehydrogenation product of CBD that has been identified in the plant matter and as a component of hashish (Van Ginneken et al. 1972). Previously reported to be a degradation product of Δ9-THC, recently CBND has been shown to be a heat transformation product of CBD from hemp. It was originally believed to be a minor yet psychoactive component of the plant present in insignificant amounts, but a renewed interest in CBND pharmacology should arise from its prevalence in high-temperature methods of administration of hemp *Cannabis* such as smoking or vaporization. Synthetic analogs of CBND have been shown to be highly selective for CB2R, which provides unique therapeutic benefits over pan-CB receptor ligands (Banister and Connor 2018). It's highly likely that a significant portion of CBD's therapeutic versatility can be attributed to its structural flexibility. As such, rare phytocannabinoids that share this core structural feature share this potential promiscuity in application. It's possible that high-heat transformation of cannabinoids creates an abundance of structurally similar, oxidated, dehydrated, or otherwise derivatized phytocannabinoids that contribute to the overall therapeutic formulation present in smoke.

5.4.3 Δ9-Tetrahydrocannabinol (Δ9-THC) and Related Cannabinoids

While the definition of hemp *Cannabis* mandates that there be minimal concentrations of Δ9-THC, it should not be overlooked that hemp flower and full spectrum products contain Δ9-THC as part of the delivered formulation (Erzen et al. 2021). Δ9-THC has been investigated extensively for therapeutic indications ranging from chronic pain, antiemetic, antiepileptic, antitumorgenic, anti-inflammatory, and more (Russo 2014). There's evidence that the presence of CBD mitigates some of the negative risk effects of Δ9-THC, making the low concentrations present in hemp in comparison to high concentrations of CBD desirable therapeutic formulations (Boggs et al. 2018).

In addition to trace amounts of Δ9-THC present in flower, Δ8-tetrahydrocannabinol (Δ8-THC) has recently emerged as a commercially available cannabinoid in the United States that is found in trace amounts in the plant (Mechoulam and Gaoni 1967), but can also be synthesized in bulk from CBD. Δ8-THC is a structural isomer of Δ9-THC, meaning the two only differ in the position of a single double bond in the top ring (Mechoulam and Gaoni 1967). This shift did not cause any changes in CB1R affinity in animal models but resulted in an apparent decrease in potency at CB1R as determined by an early experiment involving human volunteers (Bow and Rimoldi 2016; Hollister and Gillespie 1973). Generally, Δ8-THC displays comparable therapeutic potential to Δ9-THC displaying antiemetic effects and a reduction in opioid withdrawal symptoms in animal models (Yamaguchi et al. 2001; Abrahamov et al. 1995). However, never before have such large doses of Δ8-THC been available to the general public and as Δ8-THC continues to be available in the market, more research is needed to elucidate the possible therapeutic implications as well as risk factors.

Another recent addition to the commercially available cannabinoids derived from hemp in the United States is cannabinol (CBN). CBN is a dehydration product of both Δ9-THC and Δ8-THC, making it a tri-cyclic molecule with two phenyl moieties (Zagzoog et al. 2020). Early experimentation in animals showed CBN had potential to prolong the total sleep time of mice that were tranquilized with phenobarbital (Yoshida et al. 1995). CBN shows decreased potency to CB1R in both in vitro and human experimentation (Zagzoog et al. 2020). CBN does appear to display unique therapeutic effects as marked by opposing effects on feeding behaviors from CBD (Farrimond et al. 2012). Many commercially available products containing CBN are marketed as sleep-aids, however, this effect has not been confirmed in human trials. More research is needed on the effects of CBN on sleep, specifically. While the tricyclic psychoactive phytocannabinoids only make up a small percentage of the secondary metabolites present in hemp *Cannabis* flower, both Δ8-THC and CBN are becoming more and more prevalent in the market space. The therapeutic value of these molecules alone and in combination with CBD should be further evaluated.

5.4.4 Other Rare Cannabinoids

Cannabigerol (CBG) is the decarboxylated version of CBGA and structurally unique from CBD or THC in that it only contains a single di-phenol ring with two significant alkyl chain substituents (Zagzoog et al. 2020). However, CBG shares the promiscuity of all cannabinoids and acts as a partial agonist at both CB1R and CB2R with weak affinity, and a full agonist at alpha2-adrenergic receptors (Zagzoog et al. 2020); CBG also activates the TRPA1, TRPV1, and TRPV2 receptors and acts as an antagonist at 5HT1AR and TRPM8 (Muller et al. 2018). While CBG has weak affinity for the CB receptors, it inhibits MGL and alters AEA uptake, which may contribute synergistically to ECS modulation by CBG (De Petrocellis et al. 2010). Thus far, CBG has been shown to have anti-inflammatory, antioxidant, and neuroprotective effects. CBG has also been shown to have therapeutic potential for inflammatory bowel disease (IBD) and symptoms associated with Huntington's disease (Borrelli et al. 2013, Valdeolivas et al. 2015). Further research into the pharmacology of CBG will aid in elucidating the full extent of its therapeutic potential.

Cannabichromene (CBC) was one of the earliest phytocannabinoids to be discovered and has been considered to be one of the main constituents of *Cannabis* for some time (Pollastro et al. 2018a). The main pharmacological target for CBC in the body is the TRPA1 receptor, which CBC displays affinity for (Zagzoog et al. 2020; De Petrocellis et al. 2010). CBC has anti-inflammatory properties and has been shown to have therapeutic potential in animal models of colitis and acne (Wirth et al. 1980; Romano et al. 2013; Olah et al. 2016). CBC also displays high antibacterial and antifungal activity (Turner and ElSohly 1981). Interestingly, CBC has been shown to increase the brain penetration of Δ9-THC when co-administered, giving it an additional therapeutic mechanism of action when given in full spectrum formulations (Pollastro et al. 2018a).

There is limited information on both cannabicitran (CBT) and cannabicyclol (CBL), but they are notable due to their prevalence in many different strains of *Cannabis sativa* hemp flower and, thus, their exposure to consumers through full spectrum extracts. The only evaluation to date showed that neither had therapeutic antidepressant effects in forced-swim tests in murine model (Ivy et al. 2008). While their pharmacology has yet to be investigated and neither have been linked to specific therapeutic effects, both CBT and CBL contain complex multi-ring structures as opposed to the planar ring structures of all other phytocannabinoids that in theory should lead to unique binding properties for both (Kane et al. 1984).

While the rare cannabinoids make up a small portion of the total cannabinoid formulation, their contributions to the overall therapeutic effect of hemp should not be overlooked. Additionally, they represent unexplored potential for variations in therapeutic responses across many different disease pathologies, namely anti-inflammatory, antibacterial, antifungal, and neuroprotective effects. Besides the traditional receptor-related effects of cannabinoids, there is mounting evidence that the cannabinoids contribute to receptor-independent molecular mechanisms that are phenotypically significant (Martin et al. 2021). One such mechanism is through alterations in membrane fluidity, elasticity, phospholipid stability, and allosteric interaction at the interface of the receptor and membrane (Mavromoustakos et al. 2001). The phytocannabinoids are amphipathic molecules that are structurally similar to cholesterol. As such, they are likely to display similar alterations in membrane mechanics as cholesterol, which has been known to contribute significantly to receptor kinetics and dynamics (Tiburu et al. 2009). It's possible that these membrane mechanics are cumulative, meaning the total phytocannabinoid concentration is equally significant than the presence of any single specific phytocannabinoid. Altogether, the minor phytocannabinoids in hemp *Cannabis* represent a large class of potential therapeutic ligands that have yet to be fully characterized or explored.

5.5 Terpenes

The terpene content of hemp *Cannabis sativa* is highly variable between the different genetic chemovars or "strains." Although the total terpene content of *Cannabis* does not typically exceed 3% by weight, the volatile compounds contribute significantly to the aroma, experience, and preference of the consumer (Lowe et al. 2021; Nuutinen 2018). Qualitative observation of the putative synergy between phytocannabinoids and terpenes that determine strain-specific effects has been described as "the entourage effect." (Nahler et al. 2019) Though the significance of this effect beyond placebo has yet to be confirmed, there is evidence in the literature of pharmacological significance for the terpenes and terpenoids present in hemp *Cannabis* for an array of therapeutic effects such as antimicrobial, anti-inflammatory, anxiolytic effects, and others.

5.5.1 Monoterpenes

Terpenes are created by linking isoprene units together into chains that can then be restructured into rings and other more complex geometries (Nuutinen 2018). Monoterpenes are comprised of two isoprene units; many monoterpenes serve as building blocks for more complex molecules like the phytocannabinoids. Common monoterpenes in hemp *Cannabis* include myrcene, pinene, limonene, terpinolene, and the terpenoid linalool (Booth and Bohlmann 2019).

Myrcene is one of the most common terpenes present in many *Cannabis* strains and has displayed therapeutic antioxidant and anti-inflammatory potential in cell-based assays. These beneficial effects were translated over to animal models in multiple tissue types including the gut and brain (Nuutinen 2018). Pinene is the most common terpene in nature due to its presence in conifer trees. There are two different isomers of pinene, alpha and beta, that differ in the position of the double bond. Pinene has antibacterial, antioxidant, antitumorigenic, and anti-inflammatory properties (Nuutinen 2018). Although it is still debatable whether the bioavailability and metabolism of pinene enables it to have efficacy when orally administered in edibles, there is ethnopharmacological evidence for pinene in medicinal smoke. Many indigenous communities have been burning parts of pine trees for therapeutic purposes for hundreds of years (Pennacchio et al. 2010).

Another common monoterpene in nature is limonene which is found in citrus fruits (Booth and Bohlmann 2019). Limonene has displayed a vast array of therapeutic potential from anxiolytic, antidepressant activity to wound healing, muscle spasms, and antiviral activity (Nuutinen 2018). The terpineol isomers are often synthesized from limonene and all display anticancer activity (Pennacchio et al. 2010). Terpinolene and the terpineol isomers are all structurally related to one another. Terpinolene can be the predominant terpene present in specific chemotypes and has been shown to be anti-tumorigenic, anti-inflammatory, anti-nociceptive, antioxidant, and have sedative effects (Pennacchio et al. 2010).

Other oxidized terpenes, called terpenoids, include linalool and geraniol. Though linalool is often only present in smaller concentrations, it has significant biological activity and has been more thoroughly researched in comparison to other terpenes (Kamatou and Viljoen 2008). It displays many different therapeutic indications that the other monoterpenes share including anti-inflammatory, antioxidant, antibacterial, neuroprotective effects, and others (Kamatou and Viljoen 2008). This has been linked to modifications across multiple systems including the serotonin system and the 5HT1A receptor. There are many additional monoterpenes that may be present in hemp *Cannabis* depending on the chemovar including geraniol, ocimene, thujone, carene, and cineole (Nuutinen 2018).

5.5.2 Sesquiterpenes

Sesquiterpenes are synthesized from three isoprene units, are larger, and as such generally more complex in structure (Booth and Bohlmann 2019). The most notable sesquiterpene is β-caryophyllene due to its general abundance across a majority of chemovars and its documented activity at the CB2 receptor. β-caryophyllene has shown high affinity for the CB2 receptor in vitro and displays full agonist functionality with competitive binding against standard CB2-selective ligands. β-caryophyllene has therapeutic potential specifically for neuroinflammatory conditions like multiple sclerosis or Parkinson's disease through its neuroprotective, anti-inflammatory, and anti-convulsive properties, though it has also been shown to participate in neuroprotection through the dopaminergic system, alterations in microglia and astrocyte functionality, addiction, feeding behaviors, and nociception. Though the selective CB2 agonism has been linked to its anti-inflammatory effects, some of the effects of β-caryophyllene may be mediated through the opioid, serotonin, and acetylcholine systems (Gertsch et al. 2008).

Sometimes referred to as α-caryophyllene, another sesquiterpene that is very similar in structure to β-caryophyllene with biological activity and present in significant amounts in hemp *Cannabis* is α-humulene (Nuutinen 2018). Humulene displays anti-inflammatory and anticancer therapeutic potential, but more studies are needed to elucidate the molecular mechanism and specific endogenous targets. However, from an ethnopharmacology perspective, natural medicines made from plants that are high in humulene have historically been used for mental health and gastrointestinal disorders (Pennacchio et al. 2010).

Although terpenes and terpenoids show therapeutic potential, it's unclear if the doses used in vitro or in vivo are physiologically relevant given the relatively low terpene content in the plant matter and depending on the method of administration and metabolism (Nahler et al. 2019). More research is needed to further elucidate the contribution of terpenes to the overall therapeutic effects profile of hemp products. Despite the structural differences between the classes of compounds found in the Cannabis plant, terpenes, cannabinoids, and flavonoids have one consistent biosynthetic building block hat is the repeating presence of isoprene units, which make up all terpenes. Cannabinoids like Δ9THC, and flavonoids such as cannflavin A/B both contain sections of the molecules with two isoprene units, resulting in the presence of a monoterpene in each structure.

5.6 Flavonoids

Among the other phytochemicals in the cannabis plant such as terpenes and cannabinoids, flavonoids are an understudied class of compounds. Flavonoids are widely abundant in higher plant species and are characterized within the polyphenol class of compounds (Yu et al. 2021; Panche et al. 2016). They are present in all parts of the cannabis plant, apart from the roots and seeds (Frassinetti et al. 2018; Flores-Sanchez and Verpoorte 2008). Over 20 flavonoid compounds have been identified in cannabis, some of them are unique to only this plant. Their presence is responsible for many of the vibrant colors seen in nature, especially in flowers and fruits; The red of raspberries, the blue of blueberries, and the black of blackberries are all due to the presence of flavonoids. Biologically, flavonoids help attract pollinators and herbivores that will spread seeds after consumption. Biochemically, the flavonoids help plants screen UV light and counteract microbial diseases (Mierziak et al. 2014).

Flavonoids are UV-screening molecules in plants, acting as pigmented sunscreens to prevent the generation of reactive oxygen species, which lead to cell damage (Agatia et al. 2012; Bilodeau et al. 2019). This is consistent with the accumulation of flavonoid molecules in the appendages of plants such as the trichomes where they will be exposed to the most UV radiation (Agatia et al. 2012). They have also been shown to control genes associated with light sensitivity and growth. However, the

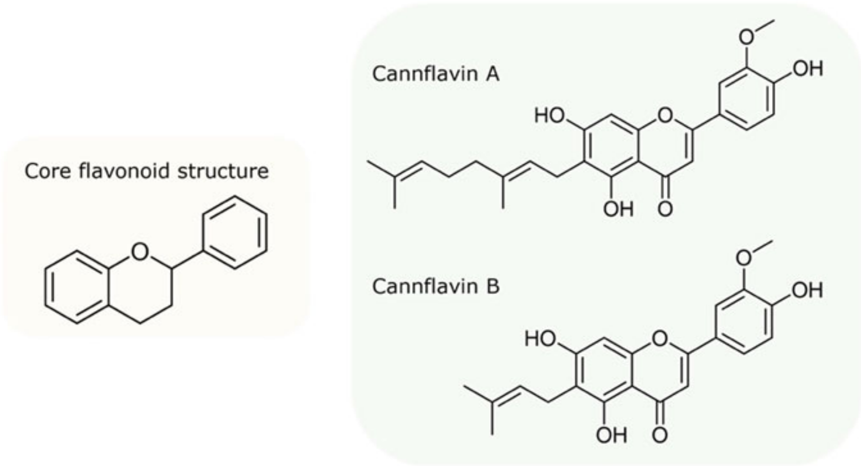

Fig. 5.3 Core structure and variations in cannflavin A and cannflavin B molecules

pigments are likely not directly involved in the primary photosynthetic processes in the plant (Agatia et al. 2012).

Flavonoids can be subdivided into subclasses of molecules based on their core structure. These subclasses include flavones, flavanones, flavanols, isoflavones, chalcones, flavonols, and anthocyanins (Bilodeau et al. 2019; Panche et al. 2016). The subclasses of flavonoids mainly differ by level of unsaturation, presence and position of hydroxyl groups, and type of heterocycle involved. Despite the small differences, each flavonoid subclass contains a three membered ring system with fused A and C rings and a branched B ring (Fig. 5.3). In the cannabis plant, the flavonoid compounds mainly belong to the flavones and flavonols subclasses (Upton et al. 2013; Pollastro, et al. 2018b). Interestingly, a group of flavonoids isolated from the cannabis plant, named the cannflavins are unique such that the core structure containing three rings is consistent with other flavonoids, however, these metabolites are prenylated, meaning there is the addition of a monoterpene tail on the metabolite. The addition of the prenylated side chain increases the lipophilicity of these metabolites leading to an increased affinity for biological membranes and protein interactions (Yang et al. 2015).

The purple color of some cannabis cultivars is due to the presence of flavonoids in the anthocyanin class (Khoo et al. 2017). Purple cannabis is often sought after for curb appeal, and it is often associated with higher quality flower. Although it is not believed that every cultivar of cannabis can induce the switch to purple, it is commonly observed in the leaves and flower buds of hybrid plants once introduced to colder temperatures. When colder temperatures are present, the other dominating plant pigments such as chlorophyll will be removed, and the minor pigments will begin to display.

This phenomenon is similar to what happens to deciduous trees in the fall, resulting in a myriad of colors. However, the anthocyanin rich, completely purple cannabis cultivars are only possible if the plant contains the genetic code to produce high levels of flavonoids (Werz et al. 2014).

Flavonoids are medicinally valuable as phytochemicals for their anti-inflammatory, antioxidant, anti-microbial, and neuroprotective properties (Pellati et al. 2018). The prenylated flavonoids identified in the cannabis plant named the cannflavins, are mainly hemp specific, although cannflavin A has been isolated from other plant sources (Salem et al. 2011). Experiments in the 1980s identified a cannabis extract lacking cannabinoids to have potent anti-inflammatory activity. This led to the discovery and structure elucidation of cannflavin A and cannflavin B (Fairbairn and Pickens 1981). These cannflavins possessed 30 times as potent anti-inflammatory activity as aspirin and it was hypothesized that these compounds were capable of inhibiting prostaglandin E2, a marker of inflammation. These results have been confirmed in mice and human rheumatoid synovial cells (Barrett et al. 1985). It was later discovered that the enzymatic target of the cannflavins is prostaglandin E2 synthase-1 and 5-lipoxygenase which reduce the production of inflammatory molecules leading to overall anti-inflammatory activity (Barrett et al. 1985). Many non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen and Aspirin work by inhibiting the COX enzymes, which are critical to the inflammatory response in the body as well as other essential functions. The inhibition of COX enzymes can lead to adverse effects such as gastrointestinal erosion, irritation, and bleeding (Harirforoosh et al. 2013). The cannflavins have shown only weak inhibition of these enzymes.

Another potential therapeutic effect of cannflavins is as antioxidants. Antioxidants work by donating an electron to a free electron that is causing cellular damage. For a compound to be considered a good antioxidant it needs to be capable of donating an electron to the radical molecule that is causing damage. Double and triple bonds are electron rich, and conjugated systems such as the cannflavins are electron heavy systems. This trait allows the metabolites to donate electrons when radicals are nearby. Although flavonoids in general are good antioxidants, it should be noted that smoking the pure cannflavins would likely have no antioxidant effects on humans and should be taken orally or topically for medicinal benefits.

Flavonoids have shown promise as neuroprotective compounds by combating amyloid β protein induced neurotoxicity, which is a hallmark of Alzheimer's disease (Eggers et al. 2019). When tested at concentrations below 10 μM cannflavin A has shown anti-aggregatory activity, however, at higher concentrations cannflavin A induced neurotoxicity (Eggers et al. 2019).

The yield is typically low for extracting the cannflavins from the *Cannabis sativa* plant, resulting in bottlenecks for assessments in humans and animals (Jin et al. 2020). However, the biosynthetic pathway of cannflavin A and B has been partially elucidated (Rea et al. 2019). These findings show promise for synthetic biology mechanisms to increase the yield of the cannflavins for research and future studies. Further, the level of flavonoid production will vary depending on a variety of stress factors such as temperature, humidity, moisture, and solar radiation (Calzolari et al.

2017). Future cultivation strategies that specifically focus on flavonoid production could be implemented in the future such as exposure to UV, blue, and FR wavelengths.

5.7 Discussion and Conclusion

5.7.1 Exploring the Molecular Mechanisms Behind Hemp Cannabis Sativa Pharmacology

The large number of bioactive molecules in hemp *Cannabis sativa* may provide unique therapeutic benefits alone or in combination. Through modifying the ECS, other signaling systems, and potentially non-specific mechanisms, the secondary metabolites exhibit a large range of different effects on different targets. The formulations that are delivered in commercially available hemp products can range from being pure isolated compounds, like CBD isolate, to containing mixtures of phytocannabinoids, terpenes, flavonoids, and others like in full spectrum extracts.

In terms of the ECS, there are many potential molecular mechanisms of action. Various compounds present in hemp *Cannabis sativa* display the potential for ECS modification by both directly binding to the cannabinoid receptors and by indirectly altering the concentrations of circulating endocannabinoids through inhibition of endocannabinoid-metabolizing enzymes or competitive binding to FABPs. ECS manipulation displays potential therapeutic efficacy for mental health, chronic pain, gastrointestinal disorders, autoimmune disorders, cancer, neurodegenerative disorders, and inflammatory disorders. The major roadblock to establishing modifications of the ECS by hemp *Cannabis sativa* remains the lack of research into specific interactions of minor and rare components of the plant with ECS targets. An additional limitation is the lack of research done on minor and rare components of the ECS like the enzymes ABHD6, ABHD12, NAAA, the FABPs, and the orphan GPCRs in general; much of the general molecular mechanism for the overall function of these proteins within the ECS has yet to be fully elucidated.

There also exists important cross-talk, synchronistic, synergistic, and antagonistic activity between the ECS and other homeostatic signaling systems. This overlap in functionality creates recursive pathways of alteration for many of the bioactive molecules that have yet to be teased apart. Specifically, the interplay between the serotonin system and the ECS appears to have synergistic potential through both ECS modification of serotonin metabolism and release and heterodimerism of CB1R with serotonergic receptors like 5HT1A or 5HT2A/C. This further broadens the potential applications of hemp though it simultaneously complicates the full picture in regards to its mechanistic source. Despite this lack of clarity, there is sufficient evidence to support the therapeutic potential of hemp *Cannabis sativa* extracts.

5.7.2 Initial Evaluations of the Therapeutic Applications of Hemp

Since the 2018 Farm Bill removed hemp *Cannabis sativa* from the Controlled Substances Act, there has been a significant increase in the number of clinical studies evaluating commercially available hemp products. The safety and tolerability of hemp performed well across all studies, indicating that the risk for negative adverse side effects is minimal. Unfortunately, these studies lack standardization of methodology which prevents them from being directly comparable to one another. There is significant variability in almost every aspect of the studies from the source of the hemp extract, the overall formulation of secondary metabolites contained, method of administration and dosage schedule, sample population, and quantification of outcomes. Regardless it is worth summarizing the clinical findings that have evaluated hemp extracts in human populations. For a summary of the possible therapeutic applications of hemp see Table 5.1.

Studies evaluating the antiepileptic properties of CBD in human trials reproducibly find that it displays therapeutic potential for treatment-resistant epilepsy across both adult and pediatric epilepsy. This is heavily supported by studies in animal models. However, many studies evaluating the efficacy of CBD for antiepileptic properties use CBD as an add-on treatment, meaning that the patients are still taking other antiepileptic medication concurrently during the evaluation. This muddies the waters as it has been proposed that one of the possible contributing mechanisms to CBD's antiepileptic properties is its inhibition of metabolic enzymes that then prolong and potentiate the other antiepileptic medications that the patient is taking. It also complicates evaluation of the hepatotoxicity of CBD when taken chronically, as a recent study has shown there is possibility of liver damage from chronic CBD, however, these patients were all concurrently taking antiepileptic medication that is shown to be hepatotoxic on their own. Additionally, there still remains a small, but significant population of patients whose seizures are not reduced by CBD treatment.

Unsurprisingly there is an overlap between CBD's efficacy as an antiepileptic and other mental health symptoms that can be applied to a range of diagnoses including anxiety, mood disorders, PTSD, autism, schizophrenia, and more. While there is evidence of positive therapeutic effects from CBD across multiple studies, they lack consistency of dose and dose scheduling; many of these studies show conflicting results at differing doses. Additionally, the form factor of the CBD varies from study to study which may have a significant effect on the overall potency and efficacy depending on the final formulation delivered to the patients. Though reproducibility of these results should be further investigated, there is clear potential for positive therapeutic effects for mental health.

Other therapeutic applications for hemp *Cannabis sativa* include antimicrobial activity, anti-inflammatory, antitumorigenic, and neuroprotective effects. Aside from the antimicrobial activity, which is displayed by a vast array of natural products and linked to non-specific pro-apoptotic mechanisms, there is evidence for all other therapeutic applications to be linked to the ECS. However, it's also possible for it to be through non-specific mechanisms or synergistic interactions between multiple systems in complex formulation. To fully understand and exploit the full pharmaceutical potential of hemp *Cannabis sativa* the individual and combinatorial pharmacology will need to be further developed. Prior literature supports a large scope of therapeutic indications for this natural product that is well worth investigating.

5.7.3 Future Directions and Further Research

In terms of molecular mechanism, there is still a gap in basic pharmacological data on many specific secondary metabolites that are present in commercially available extracts in isolation such as CBG, CBN, and CBC. While binding affinity has been established at potential targets, this has yet to be directly linked to any therapeutic effects. Furthermore, the potential contribution of terpenes, flavonoids, and other bioactive molecules in the overall therapeutic effects of the delivered formulation has yet to be investigated in a systematic yet comprehensive manner. Ideally studies would first investigate the effects of each secondary metabolite in isolation, then add in additional secondary metabolites one by one. Clearly this should not be the immediate priority for the entirety of the hemp *Cannabis sativa* metabolome as that would encompasses too large a scope, however, it is possible to begin systematically with the largest and most prevalent molecules first. Connecting physiological and phenotypic therapeutic effects to specific pharmacological targets will aid in understanding the full picture of controlling or reducing specific symptoms through hemp products.

At a larger scale, the inconsistency in dosing and dose schedule for CBD and hemp extract evaluation is a major roadblock to determining standardized treatment for specific disease pathologies. This variability in delivered formulation is further impacted by inconsistent sourcing of CBD and processing methods of hemp extracts used in clinical settings. There should be established standard general purity requirements for CBD isolate, methodology for hemp extract generation, and dosages to be evaluated as “low,” “mid,” and “high” dose levels depending on the population and therapeutic indication being evaluated. In addition, there should be standard dose schedules as determined by previous literature that is replicated across multiple studies. Admittedly this level of rigor will require extensive coordination; but by reducing the variability in formulation, dosages, and dose schedules, compounding conclusions can be drawn across multiple studies that investigate complementary molecular mechanisms, animal models, or clinical disease pathologies.

Another often overlooked aspect of the therapeutic applications of hemp in humans is the large population in the general public who are consuming by smoking the plant flower at high temperatures. Many of the bioactive molecules covered in this chapter are susceptible to degradation, dehydration, dehydrogenation, isomerization, and derivatization upon exposure to high heat in both anaerobic or aerobic conditions. This means that those who are using administration methods that involve heat are taking in additional, more complex formulations of compounds, many of which have not been investigated in isolation or in combination. Understanding the uncharacterized components will be additive on two fronts: to identify any potential hazardous byproducts and to identify any potential novel therapeutic compounds.

The final consideration for future direction of research of hemp applies to the potential therapeutic indications for all natural products and crude extracts in general; typically these commercially-available products contain complex formulations of bioactive molecules of various chemotypes. However, there has been limited effort to further optimize these natural products either by concentration of specific chemotypes or by identifying synergies for specific disease pathologies at the mechanistic scale. The further investigation of the role of chemodiversity in the efficacy of natural products extracts is essential to the further potentiation of the medicinal value of natural products as pharmaceutical agents.

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Chapter 6
Hemp Usage as Regular Food and in Nutraceutical Industry

Sanusi Shamsudeen Nassarawa and Munir Abba Dandago

Abstract The growing demand for plant proteins has prompted the food and nutrition industry to investigate alternative protein sources. Hempseed has sparked a lot of attention in the scientific and industrial sectors due to its high nutritional content and digestibility. In this chapter, hemp will be introduced, focusing on the usage of hemp as regular food, Potential health benefit of hemp, Production of Hemp, Industrial application of hemp, Future perspectives of hemp will be availed.

6.1 Introduction

Hemp (*Cannabis sativa L.*) has been used as a food, fiber, medicine, and hallucinogenic stimulant for thousands of years. Because of the psychoactive ingredient tetrahydrocannabinol, hemp production has been prohibited in the past. In 1990 many countries legalized the cultivation and processing of hemp cultivars with much lower THC levels (Ingrao et al. 2015). Hempseeds are produced in large quantities in Canada, Australia, China, the United Kingdom, France, and Spain (Vasantha Rupasinghe et al. 2020). Hemp is one of the first plants to be cultivated for its nutritional and therapeutic properties. Traditional oriental medicine has used hemp to heal and prevent ailments. In recent years, some US states, including North Dakota and Kentucky, have passed legislation allowing its production (Wang and Xiong 2019). This chapter examines the potential of hemp as a regular food and in the nutraceuticals industry, the composition of hemp, which includes nutritional components, bioactive phytochemicals, and health benefits. It also covers hemp seed as a source

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of value-added or functional dietary elements, as well as its components and their roles in illness and disease prevention and treatment.

6.2 Production of Hemp

Since the mid-eighteenth century, hemp has been farmed commercially in North America as a fiber crop. Hemp was dubbed "marijuana" in the 1930s, and its growing in Canada was rendered illegal. In the United States, production acreage, industry, and industry all fell dramatically (Adesina et al. 2020; Callaway 2004; Campiglia et al. 2017; Tang et al. 2006). When other sources of fiber became unavailable due to the outbreak of world war 2, the embargo was temporarily repealed. The United States Department of Agriculture (USDA) produced an educational film called "Hemp for Victory" to encourage farmers to grow hemp. After the war, the embargo was resumed, and the focus was switched to other crops, investment in the industry continued to drop (Vasantha Rupasinghe et al. 2020). In the nineteenth century, hemp output dropped in Europe and the America due to a variety of factors. The availability of abaca fiber and rope, as well as the replacement of sail ships by steamships, contributed to the drop. In the 1930s and 1940s, synthetic fibers such as polyester, nylon, and acrylic were developed (Yang et al. 2017). Hemp production was legalized in 1998, after a 60-years prohibition, and hemp cultivation began in Canada under the Industrial Hemp Regulation Program (Vonapartis et al. 2015). Hemp fiber and grain are currently marginal crops in many parts of the world. Hemp has, nevertheless, become one of the most valuable crops in recent years due to the production of cannabidiol (CBD). In various states in the United States, CBD hemp is becoming a significant commodities crop. Furthermore, the rising usage of Cannabis as a psychotropic modulatory drug in the Western world has altered public perceptions about hemp.

6.2.1 Hemp Products

Hemp is an excellent option for carbon sequestration since it can be produced in various agro-ecological situations and proliferates (Matthäus and Brühl 2008). Hemp can be cultivated in sandy loam that retains water well and drains well. To achieve higher branching and flower yields, oilseed and CBD hemp should be planted widely apart. Hemp thrives in temperatures ranging from 16 to 27 degrees Celsius, making it a great growing environment (Adesina et al. 2020). Hemp is grown for a multitude of reasons, including fiber, seeds, and inflorescence (flowering buds), but it is also grown for its psychoactive properties. The cultivar selected, as well as the amount of nutrients and moisture in the soil, have an impact on the final yield (Datwyler and Weiblen 2006). Hemp produces 250 % more fiber than cotton and is a high-yielding fiber crop. Hemp is a chemical-free natural weed killer that may be grown without the use of pesticides (Ranalli and Venturi 2004). Hemp is a vital part of the plant family that aids in the improvement of soil quality. During the growing season, leaves are shed continuously, adding moist organic matter to the soil. As a result, hemp can be utilized in crop rotation plans to boost the main crop's output (Shahzad 2012).

Hemp can be used for a variety of industrial or commercial purposes. Fiber hemp is a specialized crop that can only be produced in temperate areas right now. Consumers are becoming more interested in hemp seed and its derivatives. Hemp fiber is in high demand for rope, paper, construction, and reinforcement materials. Textiles, clothing, home furnishings, industrial oils, cosmetics, food, and pharmaceuticals are all made from hemp (Andre et al. 2016). Hemp seeds offer a lot of nutritional and pharmacological benefits. Hemp seed products now comprise a wide range of meals and beverages, nutritional supplements, alternative protein sources, and medications, among other things. Hemp seed's use as a functional food ingredient brings back old therapeutic uses, as its metabolites have been demonstrated to have substantial biological effects (Andre et al. 2016).

6.3 Composition of Hemp

Hemp seed is a well-balanced health food that contains bioactive components that aid in health and provide essential nourishment. According to the World Health Organization, hempseed cultivation has recently generated interest due to its macronutrients and phytochemicals (WHO) (Vonapartis et al. 2015). The major component of hempseed includes high in protein, fatty acids, lipids, carbohydrates and are high in insoluble fiber (Silversides and Lefrançois 2005). Hemp seed can be consumed by both humans and animals. It consists primarily of high-quality, easily digested proteins such as edestin and albumin, as well as essential amino acids (Tang et al. 2006). Linoleic acid and alpha-linolenic acid are good sources of PUFA and are considered balanced for human nutrition in a 3:1 ratio (Ditrói et al. 2013). Linoleic acid makes up 64 to 72 % of total fatty acids. Different hemp cultivars, cultivation practices, and processing and storage conditions can contribute to this wide range. Because these fatty acids are essential for healthy nutrition but cannot be generated by the body, they must be received from dietary sources (Schultz et al. 2020). According to nutritional guidelines, fats should account for 15–20 % of daily calories, with essential fatty acids accounting for roughly one-third of these fats in a 3:1 ratio. Three tablespoons of hemp seed oil are thought to be sufficient to achieve this dietary objective (Kittiphoom and Sutasinee 2013).

Phytocannabinoids, which are naturally occurring cannabinoids found solely in the Cannabis plant, are abundant in hemp flowers and herbage (Kittiphoom and Sutasinee 2013). THC, CBD, and other cannabinoids are present in all hemp cultivars, albeit the quantities in certain kinds are meager to non-detectable. Hemp has a notably high CBD concentration and a low THC content in northern latitudes (Russo 2011). CBD is more potent than THC, and CBD can be found in hemp seed oil in relatively low amounts. This is due to the amount of resin retained by the seed coat during processing, as well as different hemp strains and growing conditions around the world for different purposes (Petrović et al. 2015). Even trace levels of CBD are regarded to be beneficial to one's health. The formation of olivetolic acid and geranyl diphosphate is the first step in the biosynthesis of CBD (Leizer et al. 2000; Russo 2011). Although CBD is the most well-known of hemp's health advantages, over 100 cannabinoids have been found in Cannabis species (Grof 2018). Humans have an endogenous signaling system called the endocannabinoid system. Endocannabinoids are fatty acid-based neurotransmitters that function as signal molecules in all physiological systems. Diet, sleep, exercise, and stress have all been shown to have an effect on the body (Di Marzo and Piscitelli 2015). Cannabinoids are chemicals that interact with the endocannabinoid system in humans. Cannabinoid receptors are G-protein-coupled receptors with 7-transmembrane domains. The central CB1 receptor and the peripheral CB2 receptor have been identified as cannabis receptors (Freeman et al. 2019; Kumar et al. 2019; Massi et al. 2004). Natural antioxidants known as tocopherols have been shown to reduce the risk of oxidative damage. Flavonoids including flavanones, flavonols, and isoflavones are the most common phenolic compounds found in hemp seed oil (Oomah et al. 2002; Smeriglio et al. 2016).

6.4 Potential Health Benefits

CBD possesses properties that make it a promising therapy for central nervous system illnesses such as epilepsy and multiple sclerosis. The seeds are high in omega-6 and omega-3 fatty acids, which can help to improve cardiovascular health (Burstein 2015). Hemp seed has been studied as a dietary supplement to support cardiovascular health. After four weeks of supplementing the human diet with 30 mL of hemp seed oil daily, the blood lipid profile improved (Schwab et al. 2006). After 12 weeks, rats fed a diet supplemented with 5 % or 10 % hemp seed had higher plasma LA and ALA levels, according to another study (Al-Khalifa et al. 2007). The ability of the heart to recover from an ischemia–reperfusion insult has been found to be improved by hemp seeds. According to study published in the journal Cell Metabolism, there may be fewer myocardial infarctions and strokes as a result (Richard et al. 2007). In rabbits, ingesting hemp seed boosted PUFA plasma levels and reduced platelet aggregation and myocardial infarction, according to a study. Hemp seed supplementation resulted in lower cholesterol, low-density lipoprotein, and triglyceride levels (Kaushal et al. 2020; Prociuk et al. 2008).

In mice given cannabidiol (CBD), the treatment has been demonstrated to delay the onset of diabetes and diminish leukocyte activity. CBD suppresses immunological responses, cellular and humoral immunity, and causes lymphocyte death, all of which are helpful in the treatment of inflammatory illnesses (Lehmann et al. 2016; Nichols and Kaplan 2020). Using an experimental mouse model, proved that hemp seed has anti-neuroinflammatory effects (Zhou et al. 2018). Pain management is another area where hemp's advantages are being studied. Various pain conditions, such as fibromyalgia, are believed to be caused by an endocannabinoid deficiency. CBD is a widely used symptom reliever for a variety of ailments. Cannabis has been utilized to treat a variety of chronic pain conditions that are not believed to be related to the shortage (Baron 2018; Russo 2016). Cannabinoids work by reducing neurotransmitter release from presynaptic neurons, which reduces pain. Terpenes inhibit inflammation in the brain by activating pain-suppressing pathways. A key stumbling barrier in treating any of the aforementioned disorders is the paucity of long-term trials (Baron 2018; Vasantha Rupasinghe et al. 2020).

6.5 Applications of Hemp in Food Product and Nutraceutical

Consumers are becoming more interested in how their diet might help them deal with health problems and improve their overall well-being. Two-thirds of grocery shoppers stated that their desire to prevent, manage, or treat a specific health concern had a substantial impact on their purchases a decade ago (Lutterodt et al. 2011). From its plant-based constituents, hemp seed oil has established a reputation for having medical and nutraceutical benefits, as well as culinary and nutritional benefits (Uluata and Özdemir 2012). Cosmetics, salad dressings, and dietary supplements all contain hemp seed oil. Hemp seed oil is particularly susceptible to rancidity when exposed to heat or stored for an extended period of time. In the food and nutraceutical industries, hemp seed oil has a lot of potential (Montserrat-De La Paz et al. 2014). Hemp seed flours are being used to develop functional foods that increase high-density lipoprotein (HDL) levels while stabilizing other glycerides and lipoproteins, helping to avoid illnesses. When hemp milk is pasteurized, a method was established to ensure that it does not change color or become bitter (Cerino et al. 2021; Frassinetti et al. 2018; Lutterodt et al. 2011). Bioactive components in hemp seeds and sprouts have antioxidant action in vitro and in vivo. When added in alcoholic beverages, hemp juice is help in digestion. Hemp contains terpenes, which have anti-inflammatory and anti-allergic characteristics (Frassinetti et al. 2018).

6.5.1 Microencapsulation Technologies

Microencapsulation is a strategy for preventing oxidation of unstable food components like PUFAs. Spray drying, freeze-drying, and fluidized bed coating are the most prevalent methods for microencapulation. Complicated coacervation, ionotropic gelation, liposome entrapment, and electro spraying are some of the other procedures used (Anwar et al. 2010; Arslan et al. 2015; Belščak-Cvitanovic et al. 2016; Coghetto et al. 2016; Desai and Park 2005; Timilsena et al. 2016). Hemp seed oil is an excellent approach to increase hemp's nutritional content and advantages. The low water solubility, bioavailability, volatility, and stability of high-value oils can all be improved via nanoencapsulation. The method, type of core material, and end use are all important factors in the development of a new bio-nutritive isolate (Augustin and Hemar 2009; Prakash et al. 2018). Hemp fiber processing waste, also known as hemp fiber meal, was used to extract and encapsulate bioactive components. Using food-grade polysaccharide digesting enzymes, hemp fiber meal can be utilized to isolate important amino acids, particularly arginine. It can then be ultrafiltered and removed in order to concentrate the protein content (Malomo and Aluko 2015). Before hemp seed oil can be used as an useful food ingredient, more research is required. The hemp food sector with added value is expanding. Over the next few years, hemp seed oil's health applications are likely to rise, as well as its food applications (Malomo and Aluko 2015).

6.6 Future Prospects

Hemp has been grown for its nutritional and therapeutic properties since the beginning of time. Hemp has been demonstrated to have viable, value-added food and nutraceutical applications under recent legalization with tight production rules. Many studies have recently shown that hemp's nutrient and bioactive makeup helps to prevent and treat a variety of illnesses, indicating that it could be a useful functional food element. The crop's expansion is aided by its ease of production and adaptability to a wide range of climatic and geographic conditions. Many universities and breeding centers in North America and Europe are cultivating hemp. Growing hemp could help it develop faster and gain more customers while eliminating regulatory restrictions. The technique for extracting hemp seed oil has evolved tremendously, as have the nutritional benefits of hemp seed oil. Gastronomic possibilities abound when hemp seed oil is incorporated into typical value-added and supplemented foods. The establishment of standardized hemp seed and hempseed oil manufacturing procedures will assist quality control. Byproducts from hemp processing could be used in a number of meals, feeds, and industrial applications. For bioactives like CBD, analytical procedures must be standardized. Clinical studies that are well-designed, randomized, placebo-controlled, and double-blind are required.

6.7 Conclusion

Hempseeds, a protein-rich plant material gaining popularity in the food and nutraceutical industries, quickly become a viable alternative protein source. The market for hemp seed is predicted to increase fast as consumer interest in ingredients sourced from natural sources grows around the world. Although research into the chemical composition, nutritional and health advantages, processing capabilities, and functional behavior of hempseed in food processing has progressed in recent years, there is still a lot to learn. Despite its nutritious importance, natural hempseed limited solubility limits its specialized activities and applications in the food industry. An additional study employing molecular, cellular, and animal models is also required to investigate the health advantages.

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Chapter 7
Hemp Usage in Cosmeceutical and Personal Care Industry

Sanusi Shamsudeen Nassarawa, S. Dutta Gupta, and Munir Abba Dandago

Abstract Hemp is grown in more than 30 nations, with China being the major producer and exporter. Hemp can be used for various human and animal applications, from textiles to bio-pharmaceuticals. They can also be used in beverages and nutraceutical goods: cosmetics and personal care products. Pharmaceuticals are becoming more prevalent in a variety of areas, including food and nutrition, cosmetics, and the automobile industry. acoustic domain, biofuels, biotechnology, phytoremediation, and wastewater treatment, are just a few examples of novel uses that could help these items reach new markets. In this chapter, hemp will be introduced, focusing on the usage of hemp in cosmeceutical and personal care industry production.

7.1 Introduction

Hemp is a plant belonging to the Rosales order, Cannabaceae family, and Cannabis genus. Hemp is one of the world's oldest crops, originating in Asia. It was first cultivated in China 4500 years ago to produce fiber, seeds, and oil (Crini et al. 2020). Hemp fibers have been utilized for various human and animal purposes for thousands of years. The leaves were also utilized as mulch, compost, animal bedding,

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and agricultural machinery fuel (Bertoli et al. 2010). In the 1930s, hemp production was deemed illegal in the majority of Western countries and North America, and it is still prohibited in many parts of the world today (Crini et al. 2020). *Cannabis sativa L.*, or hemp, has become a problematic crop due to its genetic similarities to THC-producing plants. THC, or delta-9-tetrahydrocannabinol, is the molecule in marijuana that gives it its intoxicating characteristics. Marijuana, often known as medical cannabis, has a THC content of 10–30%. Hemp, often known as industrial hemp, has a low THC content and a high cannabidiol content (CBD) (Bertoli et al. 2010).

Industrial hemp, often known as industrial hemp, is a valuable crop with unique agronomic characteristics that provides raw ingredients such as fibers and oil in a variety of ways. For example, hempcrete was gaining traction as a potential alternative to traditional building materials (Kittiphoom and Sutasinee 2013). Hemp-based insulation and construction materials were an effective approach to cut carbon emissions. To create automobiles, hemp fibers were mixed into bio composites that were lighter and stronger than steel. Another potential area is bioplastics, which are biodegradable and non-toxic plastics made from hemp (Bertoli et al. 2010). Hemp oil was also used in cosmetics and personal care products. These regions are still in use today, and hemp-based materials and products have a variety of other active and innovative industrial applications. Hemp is a low-cost, environmentally friendly, long-lasting, and versatile plant. There are about 25,000 products in the worldwide industrial hemp market, divided into nine submarkets. Felt fibers, shives, powders, and seed commodities like oil, seeds, and oil cake are among the things available (Crini et al. 2020). The traditional and contemporary applications of industrial hemp are discussed in this chapter. Also, it provides a complete overview of hemp in the cosmeceutical and personal care industry.

7.2 Hemp for Cosmetics

Due to the numerous benefits associated with hemp, hemp seed oils have a high market value. Cosmetics, aromatherapy, and medicine are all likely to expand their use beyond human food and nutritional supplements (Adesina et al. 2020). Many chemicals found in petroleum-based lotions and cosmetics can be replaced with hemp oil. For skin hydration and hand protection, it's commonly accessible in health and beauty stores. It is intended for people who are worried about their health as well as the environment (Russo 2016). Hemp is a wonderful resource for green cosmetics in cosmetology because of its high concentration of oil containing intriguing chemicals for skincare. Due to their high quantity of fatty acids, minerals, and vitamins, hemp oils are particularly appealing as natural ingredients/additives. Hemp oils and extracts have piqued interest because of their great antioxidant potential. Cold-pressed natural oils can be applied on the skin, face, and body (Smeriglio et al. 2016; Zhou et al. 2018). Industrial hemp inflorescences are a common by-product of cultivation that is often overlooked. Because of its high availability, it might be used as a supplementary resource at the industrial level to develop specialty goods for the food, cosmetics, and pharmacy industries, among others. Essential oils found in hemp flowers and leaves are used to scent perfumes, soaps, and candles. They contain antibacterial and insecticidal properties as well (Lutterodt et al. 2011).

7.3 Hemp in the Personal Care Industry

Hemp oil, as well as other cannabidiol (CBD) oils, are quite popular right now. CBD oils are well-known for their pain-relieving and anti-inflammatory properties. Cannabis sativa seed oil and hemp oil have become "go-to" ingredients in natural beauty products (Lehmann et al. 2016). However, from lip balms to bath salts to lotions, the natural element is increasingly being included into more products across the beauty categories (Campiglia et al. 2017). Cannabidiol (CBD) and hemp-infused beauty products have established themselves as a distinct market sector in the cosmetics industry. Despite the fact that demand for hemp cosmetics is increasing and global legal reforms are in the pipeline, the plant still has a negative reputation that makes it difficult for businesses to get traction. However, as we will explain below, this should not prevent enterprises from using hemp oil.

7.4 Confusion About Hemp Oil

The seeds of the Cannabis Sativa (Industrial Hemp) plant are used to make hemp oil. It's also known as hemp seed oil or cannabis sativa seed oil. Industrial Hemp is one of the most frequent types from which we produce hemp oil and CBD oil (Schultz et al. 2020). Industrial hemp oil contains higher levels of non-intoxicating component Cannabidiols (CBD) and no or very low levels of tetrahydrocannabinol (THC). Cannabis has long been connected with THC (the psychoactive ingredient in the plant that causes a euphoric 'high' when consumed) (Burstein 2015).

7.5 Benefits of Hemp Oil for Skin and Hair

7.5.1 Anti-inflammatory

All skin types, including normal, oily, and dry, can benefit from hemp seed oil products. It deep cleans by removing dirt and grime from all types of skin and dissolving excess sebum. It also aids in the control of sebum production (frequent in oily skin) (Prociuk et al. 2008).

7.5.2 Nourishing

Hemp seeds are one of the most well-balanced and diverse natural sources of essential oils. High fatty acid composition gives skin greater suppleness and makes hair more lustrous and robust. Hemp seed oil, when used topically, strengthens the skin and makes it more resistant to infection. (Anwar and Kunz 2011).

7.5.3 Moisturizing

Hemp oil is a natural humectant, meaning it absorbs moisture into the skin and penetrates deeply. It also absorbs quickly into the hair roots, strengthening the scalp and reducing dandruff. In terms of moisturizing properties, the hemp seed oil is similar to argan oil (Shahzad 2012).

7.5.4 Anti-aging

Hemp Oil aids in the anti-aging process by smoothing fine lines and wrinkles. Hemp seeds have high linoleic and oleic acids, which contribute to this. These important fatty acids are required to keep the skin healthy (Ranalli and Venturi 2004).

7.5.5 Antimicrobial Effects

Antibacterial properties have also been reported for hemp seed oil. These boost the extract's anti-acne and anti-inflammatory properties even more. Hemp oil contains numerous antioxidants that protect the skin from free radical damage (Anwar et al. 2010).

7.5.6 Suitable for Sensitive Skin

Hemp seed oil's fatty acids may aid in balancing the skin and prevent acne-causing irritation. The addition of CBD oil derived from plant matter may also help treat acne. CBD may affect the sebaceous glands in those with persistent acne, causing them to produce less sebum (Freeman et al. 2019).

7.6 Examples of Hemp Oil-Based Products

As a result of these advantages, hemp oil is being used in a growing number of goods. The following are some examples:

7.6.1 Carun Active Hemp Soap

Hemp oil and buckthorn, aloe Vera, and Curcuma are among the bio components used in this cosmetic soap. Preservatives and colorants are not used in this vegan product. It comes in a 100 g jar suitable for all skin types, including sensitive skin.

7.6.2 Patchouli Hemp Bar Soap by Society

All-natural bar soap is made with organic Patchouli Oil and hemp to gently and organically clean all skin types. It's made entirely of natural bacteria, enzymes, and ingredients and has no synthetic chemicals.

7.6.3 Hemp Body Butter by Body Shop

For optimum hydration and defense, this moisturizing blend is mixed with rich hemp seed oil, which is abundant in important fatty acids, leaving your skin soft and supple.

7.7 RADICAL Skincare Rejuvafirm CBD Facial Oil

It's been hailed as a superfood detox and anti-aging skin oil, with the calming and antioxidant qualities of CBD oil being highlighted. It also contains essential fatty acids.

7.8 Industrial Applications of Hemp

7.8.1 Furniture, Textiles, and Fabrics

Hemp fiber can be spun, woven, or knitted into a wide range of long-lasting and pleasant clothes. Hemp fiber was a popular fabric for clothes in the 19^{th} and early twentieth centuries, as well as the mid-twentieth century, due to its resilience and versatility (Prakash et al. 2018). Hemp fiber has traditionally been utilized to manufacture ropes, rigging, nets, and sails. In comparison to other natural fibers like flax and nettle, hemp fiber is extremely robust. Hemp can generate a range of fabrics comparable to cotton but are more durable. Numerous consumer brands and commercial channels, such as Adidas and Patagonia, have incorporated hemp goods into their offerings, helping to popularize hemp as a garment fiber or accessory (Uluata and Özdemir 2012). Textiles made from hemp fibers can be used in a variety of ways, and hemp materials offer unlimited potential. Bracelets, necklaces, anklets, rings, rings and rings, watches, and other adornments can be made from hemp fibers (Matthäus and Brühl 2008). Hemp fabrics are simple to manufacture, long-lasting, breathable, multifunctional, and biodegradable. Fabrics have the highest capacity ratio of any fabric, keeping you cool in the summer and warm in the winter. Hemp fabrics are frequently preferred in the summer due to their outstanding sanitary characteristics. Hemp clothing is more robust and resistant to deformation than cotton clothes. Cotton and silk are less resistant to weather and UV radiation than fibers. Antimicrobial, hypoallergenic, and mold-resistant textiles are also available (Ditrói et al. 2013).

Hemp is a great material for rugs, hemp carpets, and other textiles. Clothing, shoes, and caps are manufactured entirely of hemp or blend natural and synthetic fibers. Hemp can also be used as an upholstery and furnishing environmentally beneficial fabric. Hemp rope tends to bond to itself, which might be beneficial in some situations. Because hemp yarn is smooth, homogeneous, durable, and comfortable to wear, it is used in jewelry. Crafts, gardening, and landscaping can all benefit from hemp twine. The same crushed hemp seeds used to manufacture edible oils are utilized to make hemp oil (Kaushal et al. 2020). Hemp oil can be used to clean and maintain finished wood as well as bring out the richness of unfinished wood grain. The oil smells like walnuts. Hemp is used as a raw material in clothing, furniture, luxury, and fashion (Baron 2018). Several European enterprises, on the other hand, are conducting research and development to bring European hemp back into the industrial textile industry by substituting it for synthetic fibers.

7.8.2 Paper

Hemp fiber was commonly used to make paper scrolls in ancient China. It was more resistant to degradation and more decisive than tree-based paper, especially when wet (Malomo and Aluko 2015). Because of the good physical features of its pulp and its tensile strength, hemp is an important raw material for creating paper. Hemp fibers were mostly utilized to manufacture special pulp and paper until recently, after its "rediscovery" in Europe in the 1990s (Nichols and Kaplan 2020). Hemp paper is made with less chemicals than tree-based paper. Hemp pulp is three to six times more expensive than wood pulp. It's high-quality and long-lasting, suitable for storing forms, money paper, and cigarettes. Teabag paper, coffee filters, non-woven sheets, and carbon tissues are examples of specialty papers (Yang et al. 2017). Hemp fibers can be mixed with other pulp fibers such as wheat straw or flax to create high-quality papers. Due to the cyclical nature of the sector, industrial hemp is not competitive in the paper market for traditional papers (Frassinetti et al. 2018). Hemp paper was found to have greater oil and air filtration capacities when compared to cotton paper used in automotive engines. Hemp paper was thinner, lighter, and smaller in terms of mean pore diameter, porosity, oil penetration, and penetration. Hemp paper was successfully used in a pilot study for an engine oil filter (Schwab et al. 2006).

7.8.3 Insulation and Building Materials

Hemp-based constituents can be turned into various profitable products, including concrete, wood, and even plastic. Hemp fibers' mechanical strength is useful in these materials. Traditional mineral and oil-based biomaterials have certain significant benefits over hemp-based ones. Hemp-based building materials are also said to absorb carbon dioxide, making them environmentally friendly. The biggest downside, however, is the lack of durability assurances (Leizer et al. 2000). Hemp fibers are mostly utilized for insulation and construction, such as insulating material and insulation wool. These fibers can also be employed for soundproofing and acoustic purposes. This is a field of study that is now undergoing rapid growth. Because of its unique properties, hemp straw can be utilized to build various construction and insulation materials. Because of its narrow pores, hemp fiber works well in thermal insulation composites. The woody hemp core of the stem is crushed to produce it. When coupled with mud for an old-style cob building, hemp strands can be used similarly to straw in bale construction (Montserrat-De La Paz et al. 2014). Mixing a binder, such as lime, with non-fibrous hurds particles yields high-quality building blocks. Hemp concrete, hempcrete, and hemp-lime are biocomposites. Construction is seeing an increase in hemp shives combined with lime. Horts and shives are used to make light concretes and mortars for various applications, including wall building, insulation, and underflooring. Hemp can also manufacture various construction materials, including roofing tiles and insulation (Callaway 2004). Hemp-based products can be used to build foundations, beneath floors, walls, roofs, paneling, pipes, and paint, as well as to replace wood and other materials in the construction of homes and other structures. Walls can be made of hemp wallboard or hemp cement, and hemp insulation, such as hemp cement, can be used to insulate beneath the floorboards. In Europe, hemp concrete/hempcrete is increasingly commonly used as a versatile and environmentally beneficial building material. Hemp-lime is a low-embodied energy, long-lasting, carbon–neutral building material. As a result, it's a low-cost, low-density material with poor heat transmission. The density and moisture content of a substance influence heat conductivity (Timilsena et al. 2016).

7.9 Composites and Plastic Alternatives

Hemp is a versatile fiber that can be used in a variety of applications, including automotive, furniture, and fashion composite manufacturing. Industrial hemp can be used as a source of plasticizing material that is both sustainable and carbon positive. Bast fibers are great for composite/biocomposite manufacture due to their length and strength, whereas hurds are suitable for particleboard and biodegradable plastic manufacturing. Hemp may be processed into a variety of products utilized in the interior and exterior of automobiles. Door and boot trims, rear shelf and roof liner panels, dashboards, pillar trimmings, seat shells, underbodies, and other applications make up the interior press molding market (Petrović et al. 2015). Hemp fibers compete for high-quality interior materials alongside flax, jute, and kenaf fibers. They are less costly and have better mechanical qualities than fiberglass counterparts. Plastics bonded with hemp fiber are supposed to save energy and minimize greenhouse gas emissions (Belščak-Cvitanovic et al. 2016). Hemp fiber-reinforced plastics are used to make furniture and other consumer goods. Bio composites are expected to be used in yachts, eyeglasses, and ski goggles. Alternatives to fossil-based polymers include poly (3-hydroxybutyrate), which is biodegradable and biocompatible. (Wang and Xiong 2019).

7.10 Hemp's Uses in Domestic Animals

Hemp hurds is used in horse bedding, chicken bedding, and pet litter. Hurds absorb more liquid than straw and need to be replaced less frequently. They are less allergic and have more excellent odour-suppressing properties than wood shavings and hay (Russo 2007).

7.11 Uses of Hemp in Energy Production

Hemp is a flexible biomass with the ability to generate energy via bioplastics. Industrial hemp can be burned directly or processed into bioethanol or other liquid fuels. Hemp biomass has been suggested as a solid fuel or feedstock for the generation of biogas and bioethanol (Vasantha Rupasinghe et al. 2020). Hemp oil can be used to make biodiesel and bioethanol, two fuels/biofuels. Hemp oil is valuable because it produces a lot of biomass and energy per hectare. Bioethanol is easy to incorporate into existing fuel systems and can partially replace fossil fuels in transportation (Vonapartis et al. 2015). The biggest question is whether industrial hemp can produce as much ethanol as other biomass feedstocks. Another problem is the creation of effective pretreatment processes that remove lignin and allow enzymes to reach cellulose for sugar release.

7.12 Conclusion

With outstanding productivity and quality, China is the world's leading hemp grower and exporter. Hemp is a versatile crop that produces stalks, seeds, and leaves for a variety of uses. The economics of hemp use are a hot topic of discussion.

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Chapter 8
Hemp Usage as a Green Building Material, Plastic, and Fuel

N. Rajak, N. Pandey, Y. B. Tripathi, and N. Garg

Abstract The growing apprehensions about increasing carbon emissions have made global leaders take robust action to prevent catastrophic climate change and global warming. Building construction is one of the many factors responsible for the increase in global pollution. Therefore, in this area, green construction is the most important step to reduce carbon emissions and other factors that cause the increased global pollution level. Hence, the revival of eco-friendly green materials could be a steppingstone in this way. Vegetal concrete construction materials based on biomass will be able to offer the beneficial solution of carbon sequestration in addition to the low embodied. These vegetal-based concretes are composed of an organic or inorganic binder and biomass derived from agroforestry industries such as rice husk, straw bale, hemp, kenaf, cork, and others. One of the vegetal concretes is hemp concrete, which has been extensively explored and researched, making it one of the best green materials for other purposes, such as an alternative to plastics and fuel in the form of biofuel. This chapter provides an overview of hemp-based concrete research, which is rapidly increasing in the green building sector, as well as plastic and fuel.

Keywords Hemp concrete · Lime · Green building application · Fuel · Plastic · Polymers · Biodegradable · Carbon dioxide (CO_2)

8.1 Introduction

Cannabis sativa L(Hemp) has been studied as an industrial hemp. It is developed primarily for industrial and therapeutic use. It may be utilized to produce a broad variety of items. Hemp has been reported as the fastest cultivating plant worldwide. It is a substantial herbaceous plant native to Asia and Central Asia and is used as traditional medicine, whereas it has also been a source of textile fibre since ancient times (Tourangeau 2015).

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Cannabis sativa L. has three subspecies-

- *Cannabis sativa L.*
- *Cannabis ruderalis*
- *Cannabis indica L.* (elevated amount of Tetra- hydro cannabinol, is the main class ofcannabinoids that creates the narcotic effects).

The stem of hemp comprises two cellular zones i.e. a core wooden part and the outer bark (Bocsa and Karus 1998; Bouloc and Werf 2013; Fernandez-Tendero et al. 2017). Epidermis and phloem are the most commonly usable part of hemp stalks.

Hemp crop is ready for harvesting in two to three months and due to its rapid growth rate, it could be a well alternative to other raw materials. It contains bundles of important phytochemicals as well as an important cradle of cellulose and Wooden fibres. Hemp seeds are rich in oils and other phytonutrients that are generally used in human food or animal feedstuff. The main chemical constituent of hemp fibre is lignin cellulose and hemicellulose (Jankauskiene et al. 2015). Both the construction and the pharmaceutical industries have shown a keen interest in this valuable plant due to its significant metabolites and important bioactive components. Its secondary metabolites have been used in manufacturing biodegradable plastics, therapeutic drugs, biofuels, and concrete (Andre et al. 2016).

Humans have been utilizing hemp from 8000BCE for a variety of purposes. According to reports, the plant has around 25,000 applications. Some of the applications of hemp are discussed below.

8.2 Use of Hemp

From ancient times, hemp has been utilized in textiles and is used to treat numerous illnesses in traditional Indian and Chinese medicine systems (Hartsel et al. 2016).

In modern times its application hasn't been restricted to textiles or in medicine only but also used in padding and furnishings, construction, food industries, automobile industries, biodegradable plastics, paper formation, jewellery, oil, soap, food supplements, protein flour, and biofuel production (Csakvari et al. 2021).

Hemp applications have also been reported in the beverages sector and nutraceutical products (Crini et al. 2020). Some of the usages of hemp are listed in Fig. 8.1.

8.2.1 Hemp Usage as a Green Building Material

As per the reports published by the United Nations Environment Programme, emissions from the construction company have reached the highest ever level till date in 2019. This has created the problem of achieving the ambitious climate change targets, as 50% of all the materials extracted from the earth's crust are used in construction,

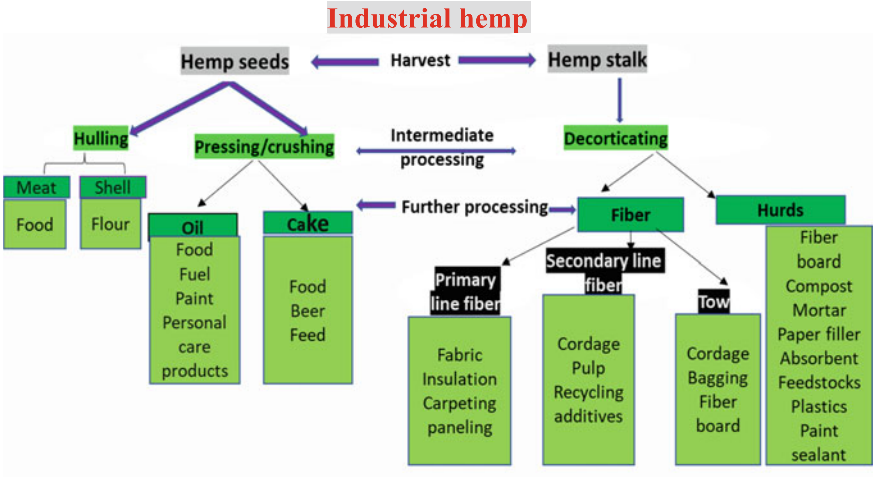

Fig. 8.1 Hemp products and their uses

and making these uses of materials add up a significant amount of greenhouse gases (Folina et al. 2020).The pushing of buildings and construction sectors into a low carbon pathway would help in slowing down climate change and can recreate the stronger economic recovery benefits. Therefore, a necessary consideration of green building material uses and associated technology implementation is needed (Ingrao et al. 2015).

Hemp is known as a fast-growing plant, so it could be considered as a better solution against carbon addition-based materials. Hemp concrete or lime hemp concrete (LHC) is a type of aggregated form of cellulose concrete, made with hemp hurd or wood (shivs) and lime, which is used as a lime-based binder. Hemp concrete is a subset of cellulose aggregate concrete (CAC), which is a larger group of construction materials that include bio-based particles as aggregate and a mineral binder. Building materials such as a bio-aggregated form (Amziane et al. 2017), or vegetal concretes (Amziane and Sonebi 2016) uses biomass, which added low embodied energy and renewability, and provides the additional benefit of carbon sequestration. Vegetal concrete is lightweight concrete made up of crops such as hemp, jute, flax, ricehusk, cork, etc., and is composed of an organic or inorganic binder and biomass. Among the vegetal concrete, Hemp concrete is one of the most documented building materials in the present time (Karam et al. 2021).

Hemp concrete operates differently from traditional construction like cement blocks, regular bricks, cinder blocks, cellular concretes, etc. Hemp concrete can naturally regulate the temperature of the buildings by diffusion of the accumulated heat. Hemp concrete is a good humidity regulator, lightweight, hasless density, buffering qualities, low embodied energy, and excellent acoustic insulation (Abdellatef et al. 2020).

The binding property of hemp

Binder is the most crucial component of a concrete-like substance, because of its availability and minimal emissions during manufacturing. Because of the high amount of silica contents present in the woody parts of the hemp plant, it can bond easily with lime (Kinnane et al. 2016).

Hemp shives are a renewable organic raw material. Due to the cellular structure and hydrophilic nature, an affinity for water substantially interferes with the setup procedure of hydraulic binders, thereby, impeding the structural cohesion of hemp concrete units. The hydraulic binder is a mixer with three ingredients: CEM I32.R, Ca $(OH)_2$, and cement bypass dust (CBPD). Microscopic analysis (SEM) indicates that cement and slag react to form CS-H, which increases the mechanical performance of hydraulic binders. As a result, it is critical to design binders/additives that will enhance the setting qualities of hemp concrete (Terpáková et al. 2012).

Hempcrete is a durable and carbon-negative material. It absorbs carbon dioxide (CO2) from the atmosphere and creates calcium carbonate or limestone, which increases the physical strength of hemp-derived concrete. While one research reveals that pulverized fuel-ash isn't extremely adjusted with lime, its widespread ease of use allows it to be the most preferred binder as compared to lime pozzolana binders. However, due to its strong reactivity with lime and plentiful availability, ground granulated blast furnace slag (GGBS) and metakaolin are excellent alternatives for creating a lime-pozzolana binder (Walker and Pavia 2014).

8.2.1.1 Thermal Property

Hempcrete density depends upon the quality and quantity of shivs size and porosity, Because hemp shivs are less dense than aggregates derived from rocks, they significantly reduce the density of the resulting concrete. (Stevulova et al. 2012). Hemp-based concrete is considered to have a high thermal capacity, low thermal conductivity, strong thermal mass which provides building comfort and regulates sudden heat change than traditional cement concrete. In one of the research, hemp concrete was shown to have an exclusive heat capacity of around 1500 J/kg K in arid conditions and may reach over 2900 J/kg K (Collet et al. 2017; Louvain 2008). In comparison, the exclusive heat capacity of traditional cement concrete ranges from 800 to 1200 J/kg K (Pan et al. 2018).

8.2.1.2 Hygro-Thermal Behaviour

Hemp-based concrete is used as a green building material. Because of the hygrothermal property, it reduces the use of heating systems by 7–8% and cooling systems by 10–30%. Hempcrete shows a high-water vapour permeability and a high moisture diffusion coefficient of 2.3×10^{-11} kg/(Pa.ms) and low to medium relative humidity. Moisture buffer value (MBV) denotes a material's capacity to absorb or release moisture, (Latif, Lawrence et al. 2015a, b). Higher moisture buffer value indicates better material's capacity to manage the surrounding humidity of the environment (Shea et al. 2012). Hempcrete has been reported for its great moisture buffer value as compared to traditional concrete's moisture buffer value (Hamzaoui et al. 2019; Latif, Ciupala, et al. 2015a, b).

8.2.1.3 Acoustic Insulation Properties of Hemp-Based Concrete

Hemp-based concrete has been proven to provide high permeability and acoustic insulation (Kinnane et al. 2016). The researchers argued that walls of the concrete made of hemp have greater sound absorption capacities as compared to conventional concrete walls. It has also been reported that hemp shivs composed of lime-pozzolana binders have superior sound absorption properties as compared to binders with more hydraulic components, and un-rendered hemp-concrete walls may absorb 40–50 of the incident signal (Nguyen et al. 2011).

8.2.2 Applications of Hemp-Based Concrete

Investigation of hempcrete began around the 1980s. Utilizing the various kinds of binders in ratio with hemp shivs can form broad application materials to be used in load-bearing, thermal insulation, and sound absorption (Magwood 2016).

Hemp-based concrete has beenvisualized as a well justifiable alternative to traditional insulating materials like fibreglass, dense-packed cellulose, etc. (Modi et al. 2018). Some of the uses of hempcrete are listed below:

8.2.2.1 Hemp Concrete Walls

Hemp concrete is not toxic and has numerous applications. It can be used as a roof, slab, and wall material. Magwood 2016 et al. defines the hempcrete walls as vapour permeable, and it can minimize moisture-related issues in any climate (storms and rain) (Colinart et al. 2016).

8.2.2.2 Hemp Concrete Insulation Panels

In most low-rise projects, hempcrete with a density of 250–350 kg per metric cube could be utilized to provide insulation to the external-facing wall. Hempcrete insulation panel is suitable for cladding, floor covering rafters panel (Modi et al. 2018). For insulation of the roof, the use of hempcrete provides advantages, like stopping the pests. Due to its robust mechanical strength, it doesn't blow over for many years. It is also very good in providing resistance to moisture, mildew, decay, and pest than the conventional insulations. Hempcrete is credible insulation for massive outer walls and facades, which provides superb thermal and sound insulation. It produces an airtight seal in windows, without the use of petrochemical-based materials (Sonebi et al. 2015).

8.2.2.3 Building Application

Hempcrete-based blocks are known for walling application, which is the most popular and investigated application of hemp concrete. The product has strong strength and rigidity or stiffness for use in multi-story construction and high-rise buildings. Hempcrete is a sustainable building material, fire-resistant, and provides safe buildings. Hemp-based concrete renders can be used to reduce the heat conductance of traditional walls (Sassoni et al. 2014).

8.3 Hemp usage as Plastic

Plastic is now one of the most used materials on the planet. Plastics are made of long chains of carbon polymers, and these polymers provide flexibility and plasticity to plastic, which allows them to be moulded into various shapes. Traditional plastics are non-biodegradable and provide a negative effect on our land, water, and wildlife, on the other hand, bioplastics are made from Plant Oil, Cellulose, Corn, Starch, Potato, Sugarcane, Hemp, etc. (Www et al. 2008). Hemp plastic is the only type of plastic that is completely biodegradable and recyclable. Hemp plant consumes four times more CO2 from the atmosphere as compared to other plants. Hemp fibre is stronger than traditional fibres (Angulo et al. 2021). Compounds like Bisphenol-A (BPA), benzene, and toluene present in traditional plastics, that release hydrocarbon, are absent in hemp plastic (Murali and Mohan 2014). Most of the plastics in the present time are made from petroleum-based compounds, which release toxic gases into the environment. Hemp plastic is merely generated using cellulose-based extraction from the hemp plant and therefore it does not create toxicity during production and help to reduce the greenhouse effect (McVicker et al. 2021).

Plastics, that are completely made from the hemp plant, are 100% biodegradable and recyclable. We often consider the recycling of bio-based plastic as the conversion of garbage into useable material. If we increase the utilization of more hemp plastic, then we will be far more ecologically friendly because hemp plastics take around six months for decomposition and its derivatives are not toxic for the environment. Plants are gathered and processed down into essential components for manufacturing, and a product is created. After use, it is disposed of in a landfill, where nature will take its course and separate it into essential nutrients for plant growth, and the cycle is completed (Shahzad 2011). This process is shown in Fig. 8.2.

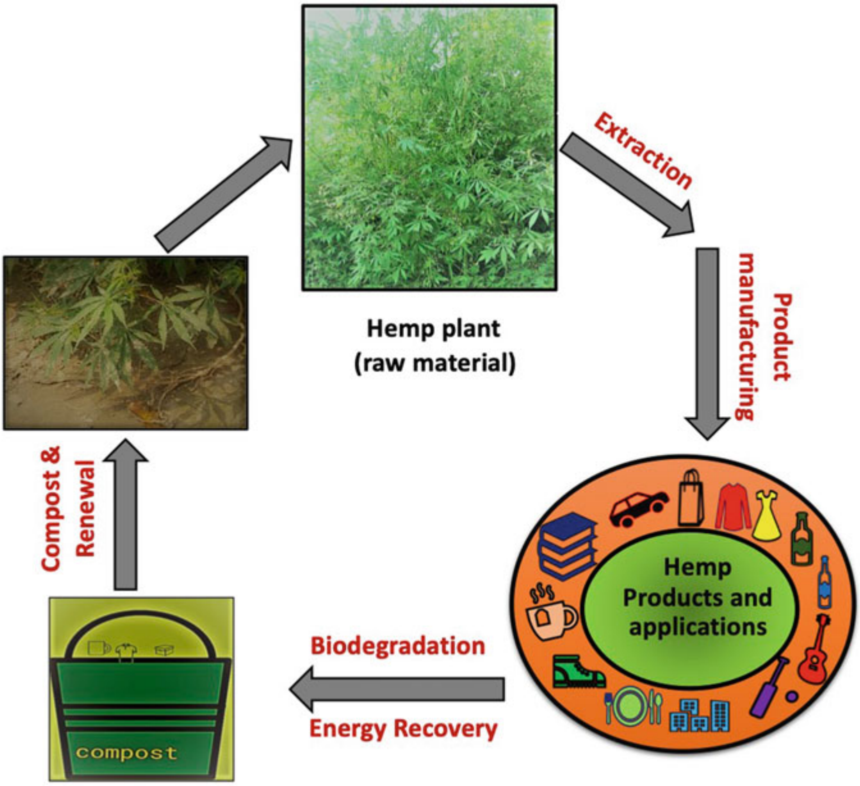

Fig. 8.2 Hemp cycle

8.3.1 Application of Hemp Plastic

Hemp plastics resilience makes it desirable in a variety of sectors. Hemp plastic is versatile and valuable to use in several industries such as construction, automotive, transport, and packaging industries. Hemp-based plastics are stronger and safer as compared to petroleum-based plastics. Hemp-based plastics are lightweight and have a high density-to-weight ratio. This enables it to be utilized in aircraft to control weight on large structures. Because of its adaptability, hemp plastic may be utilized to replace traditional polymers in a variety of applications such as electronics, containers, toys, cosmetics, bags, car parts, boats, furniture (Singh et al. 2021).

Hemp-based plastics do not produce wear and tear on the screw and mould as glass fibres do, and it does not offer the same safety and health hazards as glass fibres do. Hemp-based plastics can help to save endangered wildlife. One of the primary reasons for its advantage over traditional polymers is its flexibility.

8.4 Hemp as Fuel

Reducing reliance on fossil fuels has recently emerged as a key problem. With the increased demand for coal, gas, and oil-based energy, fossil fuels may run out for the upcoming half-century (Singh et al. 2021). Hemp's low feedstock cost combined with greater biomass that is high in carbs and comparatively low in lignin forms it an environment-friendly and sustainable alternative for bioenergy output (Rehman et al. 2021; Van Der Werf 2004). This renewable feedstock may assist any country in lowering its energy import expenses while also ensuring a sustainable energy supply (Rehman et al. 2021). Hence hemp-based biofuel has the potential to help us lessen our reliance on fossil fuels. Hemp may be utilized to produce bioethanol, biogas, solid fuel, biohydrogen, and biodiesel. The Western nations such as Finland, Ireland, Poland, Latvia, Spain, and the United States produce hemp for bio-energy generation.

For millennia, hemp seed oil has been used as lamp fuel. According to research, hemp can be used to make two forms of biofuel: biodiesel and ethanol. Hemp seeds are pressed to extract their oils and fats, which are then used to make biodiesel (Burczyk et al. 2008; Casas and Rieradevall I Pons 2005; Petker et al. 2020; Rice 2008). The substance is subsequently converted into biofuel for use in vehicles cars through a series of procedures. Hemp biodiesel fulfils the required criteria, and it is also a superior fuel, beating regular diesel in all aspects remaining oxidation stability. Nevertheless, its oxidation efficiency can be increased by adding antioxidants. It is projected that hemp-based biodiesel output could exceed 800 L/ha/year, outperforming other crops such as sunflower, soybean, peanut, and rapeseed (Jankauskienė and Gruzdevienė 2015). Hemp-derived ethanol is formed by a variety of fermentation processes and it can provide distinct benefits in transportation (Sipos et al. 2010).

8.5 Conclusion

Increase in the global warming has let many countries and people modify many daily practices, which could help in reducing global burden. Due to explosion in the population, an increase in the demand for housing infrastructure and fuel has emerged. Housing industry is one of the major factors that has led to an increase in carbon emission through the production of raw materials like cement, gypsum, and other derivatives, which contribute to localized pollution. Concrete is a vital component in the building industry and cutting off the dependency on traditional materials could help in regulating pollution. Therefore, creating an alternative hemp-based concrete might be a potential solution to the problem. As hemp has been used in a variety of industrial goods, such as medications, building materials, biofuels, insulation, textiles, paper products, it provides additional industrial benefits. Further research into cannabis and its industrial applications might unleash a massive force for global change to environment friendly life style. Removing official restrictions on hemp consumption and manufacturing may help a boost in commercial production of hemp based products. Apart from its utilization as a building material, hemp-based biofuel is another option to create green fuel. Since biodiesel provides automobile industry with an alternative to traditional resources, hemp based biodiesel or ethanol would cause less carbon emission. Therefore, to bring the hemp as a robust plant of industrial value in the future requires further research and a pragmatic approach to establish it as one of the sources for multimodal use.

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Conflict of Interest The authors declare no conflict of interest.

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Chapter 9
Demand and Supply Gaps: Seeds and Raw Material

Priyanka Mishra, Praveen Kumar, Yamini B. Tripathi, and Neha Garg

Abstract Hemp is one of the oldest known crops with huge industrial and pharmaceutical applications. Most parts of the hemp plant are used in industry: stem for fibre production, leaves for animal bedding and construction, roots in phytoremediation and flowers for essential oils and pharmaceuticals. Seeds of the Hemp plant are a rich source of various nutrients that can be used to produce oil, flour for bread supplementation, as feed for organic farming. Realizing Hemp as a multifaceted and sustainable crop, recently there is a renewed interest in Hemp production. In this chapter, we are discussing Hemp global market, demand and supply and factors affecting industrial hemp production.

Keywords Cannabis · THC · Demand · Supply · Hemp seeds · Industrial hemp cultivation

9.1 Introduction

Hemp is an anciently grown crop used for its fibre and medicinal properties. Interest in the cultivation of industrial Hemp decreased due to the control of cannabinoids for recreational purposes and the introduction of synthetic fibres. However, with the advancement in plant sciences, new hemp varieties with lower THC content (0.2–0.3%) have sparked a new founded interest in industrial hemp production. Most of the hemp plant parts are used in industry: stem for fibre production, which can be utilized in textile, paper and fabric industry and leaves for animal bedding and construction, roots in phytoremediation and flowers for essential oils and pharmaceuticals (Farinon et al. 2020).

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9.2 Hemp: A Multifaceted Crop

"Cannabinoids" are natural compounds isolated from *Cannabis sativa* that has the distinctive C21 terpene phenolic structure. The derivatives and transformation products of this family of chemicals are likewise classified as cannabinoids. The research focused on *C. sativa* has led to the isolation of a total of 120 cannabinoids, which can be segregated into several classes: delta-9-trans-tetrahydrocannabinol (9-THC), delta-8-trans-tetrahydrocannabinol (8-THC), cannabichromene (CBC), cannabigerol (CBG), cannabinodiol (CBND), cannabitriol cannabielsoin (CBE), cannabicyclol (CBL), cannabibinol (CBN) and others as 'miscellaneous type' (ElSohly et al. 2017).

Hemp, sometimes known as 'industrial hemp', constitutes different cultivars of *Cannabis sativa* used for industrial or therapeutic purposes. Hemp is used to producing a variety of items and exhibits very fast growth (Small 2015). It is also known to be one of one the first plants to be utilized for useable fibre around 50,000 years ago. Some of the commercial applications of hemp products include hemp seed oil, paper, rope, textile products, clothes, biodegradable plastic products, paint, insulation material, biofuel, food, and also as animal feed. However, over the twentieth century, industrial hemp production declined due to the increased use of cotton and synthetic fibres, as well as the restriction of hemp cultivation in many countries due to the psychoactive chemical 9-tetrahydrocannabinol (THC). The European Union has resumed the legal production of industrial hemp with THC concentrations of less than 0.2%, which has reignited interest in hemp farming (Sayer and Brands 2014).

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida (dicotyledons)
Subclass	Hamamelididae
Order	Urticales
Family	Cannabaceae
Genus	Cannabis
Species	sativa

United States Farm Bill 2014 defines industrial hemp as "the plant *Cannabis sativa L.* and any component of such plant, whether growing or not, with a delta-9 tetrahydrocannabinol (THC) concentration of not more than 0.3% on a dry weight basis" (United States Department of Agriculture). The market for industrial hemp is expected to be driven by rising consumer awareness of the benefits of industrial hemp, increased legalization of industrial hemp cultivation in various countries, and increased utilization of hemp in diverse industries such as textiles, pharmaceuticals, food, construction materials, beverages, personal care products, furniture, and paper.

The industrial hemp market (USD 4.6 billion in 2019) is expected to rise to USD 26.6 billion in 2025, achieving 34% CAGR (Compound Annual Growth Rate) (Oskaroochi and Byun 2020). Before that, the global market for Hemp production was estimated to double between 2016 and 2020 (Schluttenhofer and Yuan 2017). Globally, about 25,000 Hemp products might be present in the market and the largest importer of Hemp in the USA (Johnson 2011). The rising demand for industrial hemp products due to its number of health advantages and higher occurrences of ailments like various sleep disorders and epilepsy have contributed to the market's growth. However, the market expansion of industrial hemp is projected to be hampered by the complex regulatory structure for its use in many nations. In terms of value, hemp fibre influenced the industrial Hemp market in 2018 (Musio et al. 2018). Due to its higher durability than cotton, hemp fibre is mostly employed in the paper, textile and pulp industries. Furthermore, because it is a renewable resource, its use is growing in a variety of industries, including building, animal bedding, agriculture, furniture, and automobiles. In addition, its demand is predicted to rise in the coming years as it is used to make biofuels and bioplastics. Because of its importance in avoiding illnesses including anxiety, sadness, pain, and acne; CBD hemp oil is expected to be the fastest-developing variety. Furthermore, the increased use of CBD hemp oil in eatables, personal care products and health supplements is likely to ignite the market. The food category dominated the industrial hemp market by application in 2018, because of the widespread use of hemp seed oil along with hemp seeds owing to its high nutrient content such as proteins, vitamins, and omega-3 fatty acids (Leonard et al. 2020). Hemp seeds are eaten raw or added to cereals, smoothies, and yoghurt as a topping. The market for hemp-based food is being driven by increased consumer recognition of the benefits of consuming hemp-derived goods. In 2018, the Asia Pacific market had the biggest share of the industrial Hemp market (Crini et al. 2020). This dominance can be traced to the textile and paper industries' substantial production and use of hemp fibre. Furthermore, market growth is expected to be fueled by the rising consumption of hemp-based personal care products and cosmetics products in the Asia Pacific region, as well as the legalization of industrial hemp in dietary supplements. Due to a surge in hemp seed consumption as well as their utilization in various eatables for example smoothies, yoghurt, energy bars and cereals; the European market is expected to develop at the fastest CAGR, particularly in Germany and the Netherlands. Furthermore, with increased awareness of the nutritional benefits of hemp consumption, demand for hemp-derived pharmaceuticals, food and personal care products are likely to rise. Furthermore, increasing industrial hemp legalization in the European region is likely to fuel the industrial hemp market in the approaching years.

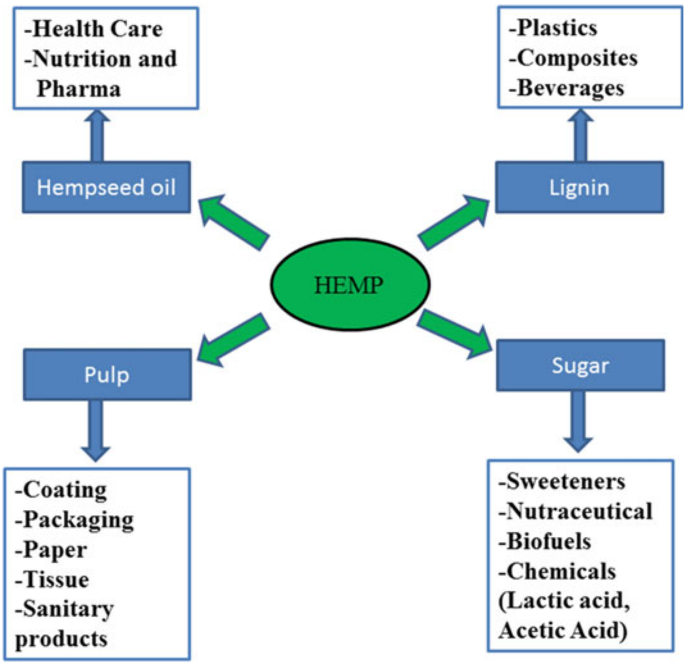

Fig. 9.1 Multiple roles of industrial hemp in different sectors

9.3 Application of Industrial Hemp (Fig. 9.1)

9.3.1 Utilization in the Textile Industry

Hemp has traditionally been utilized for textiles since the dawn of time—hemp fabric samples dating back as old as 8000 BC have been discovered in China—but it has recently seen a rebirth. Hemp has shed its slightly harsh and difficult image, and has been blended with silk for use in lingerie, and is also being employed in more apparent situations where its resilient property is best utilized supplying raw material for jeans, shoes, and other rugged sportswear.

9.4 Utilization in the Food Industry

Hemp oil is edible as well as highly nutritious, containing important fatty acids and accounts for almost a third of the weight of hemp seeds. Hemp's whole seed has around 25% protein, is a rich source of iron and calcium, and has more omega-3 fatty acids in comparison to walnuts. The presence of all these nutrients points to its potential in the food industry and dietary supplements industry. Production of beer, wine and various other alcoholic beverages production as well as iced tea is also possible using Hemp.

9.4.1 Utilization in Paper Making Industry

While the hemp-based paper industry accounts for only approximately 0.05% of the global paper industry, it has been in use for at least 2000 years. Although hemp is a readily renewable and tenable source for paper pulp paper, hemp-based paper pulp is several times more expensive than wood pulp due to the lesser number and relatively older equipment for pulp processing in the hemp paper industry.

9.4.2 Utilization in the Construction Material Industry

Hemp may be used to make a variety of building materials. It can be turned into insulator materials like it is used in the Netherlands and Ireland. Additionally, hemp is also used to produce engineered building materials such as fiberboard, pressboard, as well as 'hempcrete', which is a stronger, lighter, and more eco-friendly concrete alternative.

9.4.3 Utilization in the Plastic and Fuel Industry

Hemp is also a promising feedstock for the manufacturing of polymers. Indeed, during the early 1940s, Ford famously manufactured a prototype car from hemp and soy-based plastics. Hemp was recently used to make curtain liners for the shower, CD and DVD covers, and a variety of other items. Hemp can also be used to generate biofuel. Hemp oil may be converted to biodiesel in the same way that any other vegetable oil can. Although there are still concerns about converting the food-producing land into land that is used to unquestionably sound power vehicles. There's no reason why hemp stalks or other leftovers couldn't be used as a feedstock for cellulosic ethanol technology as it becomes more commercially viable, which has been on the horizon for a few years now. Given this, it's reasonable to assume that hemp may be used to create fuels, which would be chemically similar to petroleum-derived gasoline or diesel.

9.4.4 Utilization in Chemical Cleanup

Hemp's usage in soil contamination cleanup is one of the most intriguing. Industrial hemp was tested to help heal the soil at the Chernobyl nuclear catastrophe site in Ukraine in the late 1990s. Hemp has good promise in aiding cleaning up of the land contaminated with various contaminants like sewage, fly ash, and other heavy metals due to its rapid growth which can be up to 250–400 plants/m^2, attaining up to 15 feet length. Despite this, hemp's usage in the phytoremediation process is still in its early stages and needs more exploration.

9.5 Manufacturing of Industrial Hemp (Fig. 9.2)

9.5.1 Compatible Condition for Industrial Hemp Manufacturing

On average, hemp farming equipment may yield 700 pounds of hemp grain or 5300 pounds of straw from a single acre of hemp. The same straw can be turned into 1300 pounds of fibres. Growth conditions on hemp farms must remain constant, pest

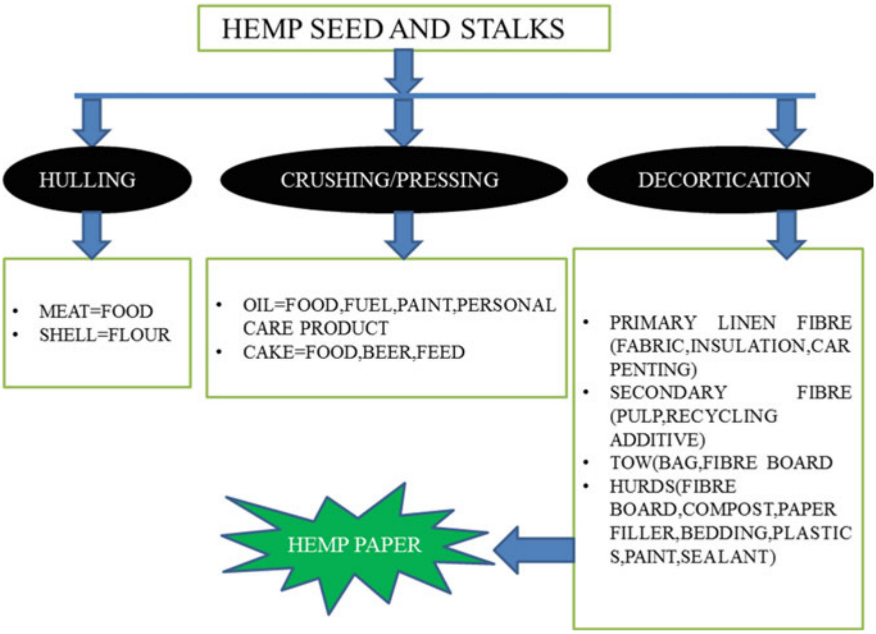

Fig. 9.2 Processing of industrial hemp

and other diseases free for a hemp farming cycle to operate as planned and deliver an optimal crop. Although hemp is capable to grow in a wide soil range, it prefers nitrogen-rich, non-acidic ground, which is also perfect for growing maize. As a result, soil testing is required for hemp growing to assess soil fertility and decide fertilizer management. Hemp likewise prefers a humid environment and gentler climatic conditions. Hemp, on the other hand, requires a minimum of 20–30 inches of rain over its life cycle, and its water requirement grows until flowering.

While appropriate moisture is necessary for hemp growth, humid conditions during crop harvesting and processing are detrimental, and they can quickly degrade the crop's quality. The processing environment should be stable since thorough cleaning and drying are essential aspects of the process. Direct sunshine, harsh temperatures and high oxygen levels must all be avoided when working with raw materials. Plants for Hemp processing ought to be climate-controlled, well-ventilated, and humidity-controlled to achieve optimal conditions. The processing equipment should be constructed to minimize dust and other pollutants introduced by exposure to the elements. Each part of the hemp plant, from the roots to the leaves, could be processed and converted to an industrial hemp product. As a result, the methods for harvesting and processing are determined by the desired application.

The stalk of the hemp plant is a very adaptable plant part, which can be used in the manufacturing of rope, paper, animal bedding, and insulation and building materials. Hemp textiles are made from the stalk's bast fibres, which can be combined with other fibres. Extracts of CBD can also be obtained by isolating CBD from the plant's stalks and stems. Seed oil can be extracted from hemp flowers and buds. Seeds isolated from the flowers can be used in the production of Hemp oil. Utilization of Hemp seeds can be done in various ways. Hemp seeds are considered a superfood and can now be purchased in most health food stores. The remaining stalks and leaves are usually considered trash if a hemp product company is only interested in the harvesting of flowers and seeds from the hemp plant. This hemp biomass, on the other hand, can be utilized to generate textiles, clothing, or cables by another company. Hemp ethanol or biofuel can be made from the stalks if they are fermented. The type of processing equipment required will be determined by the final product. All of the components of the hemp plant will be cleaned and dried. Decortication and retting are two processes that the plant's stalks will go through. For the seeds, other plant parts such as its leaves, flowers and buds are typically bucked and de-hulled. Bucking or de-budding also termed as de-stemming, is the removal of flowers and leaves from the stem of the hemp plant.

The efficiency and safety with which the hemp materials are handled across production process facility determine the margin between profit and loss in the industrial hemp sector. That is the reason that the best tube conveyor system to be used in the facility of hemp processing should have a modular design and should be custom optimized for specific needs, ensuring that every system is adapted with the right size of various parts, tube diameter, and material for the unique design of the hemp processing facility, space availability, and downstream applications.

9.5.2 Hemp Seed Production

Hemp seeds are very nutritious and a rich source of protein and sulphur. Hemp seeds can be used to make seed cakes, protein flour and can also be used as animal feed (https://extension.psu.edu/industrial-hemp-production). Hemp seeds have several bioactive molecules such as cannabinoid, cannabidiol. Cannabidol exhibits antibacterial and immunomodulatory effects (Straus 2000) which could be useful to be used as a feed for organic farming of hens (Eriksson and Wall 2012).

Generally, Hemp varieties with medium (6–7 feet) and small size (3–5 feet) are preferred for seed production. Further, varieties with low levels (0.3%) of THC should be selected. Hemp is generally grown in rows for seed production as it might be easier to remove the other weeds mechanically. The depth of the planting should be between ½ and ¾ inches. Usually, Nitrogen phosphate and potash are used as fertilizers depending on the soil type (Kaiser et al. 2014).

9.6 Disease of Hemp

Hemp crops can suffer the loss of yield because of several diseases. The hemp plant is prone to various fungal and viral pathogens; abiotic diseases, pests like insects and nematodes and others. (Hazelrigg et al. 2020; Wang 2018). Tackling the diseases associated with the plant, the loss of yield can be significantly improved. It is estimated about 90 fungal species can cause diseases on hemp (Balthazar et al. 2020).

9.6.1 Hemp Blight

Grey mould or *Botrytis cinerea* cause grey lesions by infecting seeds inflorescence, stalks and leaves, progressing to a fast rotting of the entire plant (Balthazar et al. 2020). According to an estimate, the grey fungal infections can decline the production of outdoor hemp crops by 32% during the damp season (Werf et al. 1995).

9.6.2 Hemp Leaf Spot

Scattered leaf spots are observed on both young and mature leaves. Another type of leaf spot called Septoria leaf spots are grey spots throughout the plant and are caused by Septoria sp. (Rahnama et al. 2021). Other species that cause leaf spots include Cercospora and Anthracnose.

9.6.3 Hemp Powdery Mildew

Hemp Powdery mildew was observed as small white powdery patches on the leaves which eventually form colonies on plant including leaves, stem and buds. The fungal pathogen identified is Golovinomycesambrosiae (Wiseman et al. 2021).

9.6.4 Abiotic Diseases

The abiotic disease includes nutrient deficiency, draughts and mineral deficiency. These stresses build up quickly and cause an immediate effect on the crop and yield (Hazelrigg Ann).

9.6.5 White Mold Infection

White mold infection is caused by Sclerotinia and causes wilt and white fluffy fungal growth on the stem. Sclerotinia has a wide host range (Wang 2018).

9.6.6 Viral Infections

Viral infections cause mottling, stunting, leaf roll twisting and spotting over the entire plant. Many viruses have been known to infect hemp crops including hemp streak virus, Arabis mosaic virus, beet curly top virus, hemp mosaic virus and tobacco mosaic virus have been isolated from the hemp plant (ŞEVİK 2020).

9.6.7 Nematode Infections

Hemp plants with nematode infections show stunted growth, impaired development of the roots. The root-knot nematode, Meloidogyne incognita has been found in the soil samples of hemp crops and is known to cause infection in the crop (Lawaju et al. 2021).

9.7 Management of the Hemp Diseases

Make sure the plant start material is free of infections. The field should have good fertility and a proper soil drainage system. Using drip irrigation rather than the splash will help prevent many water-borne diseases. Proper use of fungicides and pesticides to remove the causative organism is required. Utilization of fertilizers to overcome nutrient deficiencies should be done. Fields must be cleaned up after harvesting the crop (Wang 2018).

More recently, hemp crop yield using the phytomicrobiome of the plant is being explored. The usage of plant growth-promoting rhizobia has been implicated in improved yield and quality and biological control of the pathogens (Lyu et al. 2019).

9.8 Conclusion

Industrial hemp provides a large variety of products to the global market. A renewed interest in the cultivation of Hemp has increased a concomitant demand for its propagation at an industrial scale. Traditional methods of seed production and other foliage products require hemp to be lower in THC content, to uplift the supply of hemp, certain parameters such as disease-free seeds, proper cultivation, getting rid of various insects and other bugs like nematodes, preventing various fungal and viral diseases and abiotic factors like nutrition, water and light should be optimized.

Relieving restrictions on hemp production has also promoted hemp-related research and the field is expecting to witness new varieties with increased resistance to pathogens and increased. However, more research in this field is required. Proper treatments for fungal infections and suitable pesticides for hemp need to be developed.

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Conflict of Interest Authors declare no conflict of interest.

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Chapter 10
Selective Breeding for *Cannabis* Variety

Shanmugam Aravindan, Mohanapriya Balamurugan, Manivelan Kalaiarasan, and Pushpa Raman

Abstract Cannabis is the most versatile species. Hemp and marijuana have been used for fibre, oil, medicinal and recreational purposes from millennia. Throughout the last century, the plant has been generally outlawed because of its psychotropic effects in many nations. In recent past, the studies on cannabis revealed the evidence of its high medicinal properties and its uses in treating life threatening diseases, which leads to the relaxation of legislation in many counties. Now, the genetic and genomics as well as the cannabis derived products enjoys renewed attention. In this chapter, the discussion was made on the advent of genomics and breeding strategies to improve various traits of cannabis. This will bring insights on future direction of cannabis breeding**.**

Keywords Cannabis · Breeding · Hemp · Sex-determination · Flowering · Cannabinoid

10.1 Introduction

Cannabis species gained great attention today because of its numerous uses in medicinal, industrial and recreational purposes (Backer et al. 2020; Kovalchuk et al. 2020; Russo 2019). The plant is cultivated mainly for its fibre, seed and cannabinoids. It constitutes about 500 phytochemicals with various therapeutic uses to treat life threatening diseases, most notably Parkinson's disease, multiple sclerosis, epilepsy, Alzheimer's disease, cancer and diabetes (Erzen et al. 2021; Gibbard et al. 2021;

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Murnion 2015; Namdar et al. 2018). In cannabis, the major psychoactive component is THC (tetrahydrocannabinol), the THC content of 0.3% or less is considered as the non-psychoactive and grown for hemp (fibre type) and in contrast, marijuana (drug type) contains up to 30% of THC (Barcaccia et al. 2020; Clarke and Watson 2007; Mudge et al. 2019). Apart, hemp varieties have great potential to sequestrate carbon due to its rapid growth. Hence, it can be utilized as biofuel or as carbon repository in construction materials (Finnan and Styles 2013). Beyond that, hemp seed oil also has high nutrition value as it the rich reserve of omega-6 and omega-3 PUFA (3:1) (Leizer et al. 2000; Schultz et al. 2020). Despite, marijuana cultivation is criminalized and prohibited around globe because of its psychoactive essence of THC. The "United Nation convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988" recognized cannabis as the narcotic drug and prohibited its use and cultivation, still it posing the major issue in legitimization of cannabis with high THC content (Aguilar et al. 2018). At present, the studies over the decades revealed the potential of cannabis on treating various diseases. Thus, many countries slowly releasing their legalization on cannabis grown for medicinal and scientific objectives in regulated region. This opens up the avenue to study the genetic and genomics of cannabis and paves way for the breeding of new varieties of this versatile for various purposes. Thus, the comprehensive review was made in this chapter on its botanical classification, advent of genomics and breeding strategies to improve various traits of cannabis.

10.2 Botany of Cannabis

Cannabis (2n = 2x = 20) is a dioecious plant originated in central Asia about 5000 BC and distributed around Asia and Africa (Table 10.1). The genus cannabis comprises majorly of three species viz., (a) *C. sativa* (hemp type) (b) *C.*

Table 10.1 The current scientific classification of Cannabis

Taxon	Scientific name and common name
Kingdom	Plantae (plants)
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Equisetopsida
Subclass	Magnoliidae
Order	Rosales
Family	Cannabaceae
Genus	*Cannabis*
Species	*Cannabis sativa* L.

Source USDA-ARS 2020

indica (drug-type) contains remarkable amount of the psychoactive compound Δ^9-tetrahydrocannabinol (9-THC) and (c) *C. ruderalis* (intermediate). *C. sativa* is an annual with erect stems and robust taproot. The stems are woody, branched (opposite or alternate), furrowed and angular in shape and height varies from 1 to 6 m. They have a strong taproot system, usually goes upto 30–60 cm depth but 2.5 m in loose soils and shows more branching in wet soils. Leaves are arranged in the orientation of either alternate, opposite or spiral, green in color with seven lobes and have serrated margins. Nevertheless, the shape and size of the leaflets alters in accordance to their origin. The leaflets have the length of 6–11 cm and breadth of 2–15 mm. The both upper and lower surfaces have dispersed resinous trichomes. Inflorescences contains several flower heads found on leafy stems from each leaf axil. The staminate flowers (2.5–4 mm) possess five pale-green sepals and pendant stamens with lanky filaments. The sessile pistillate flower are found in pairs (Fig. 10.1). The type of fruit is achene (single seed) have hard shell securely covers with ovary's thin wall. It is about 2–5 mm long, ellipsoid in shape, bit compressed, smooth, widely have brown colour and mottled.

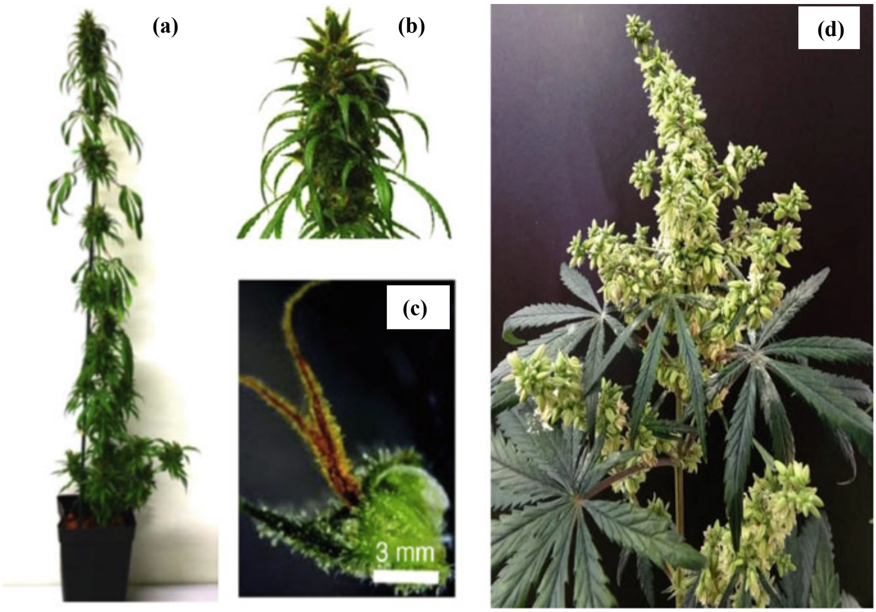

Fig. 10.1 **a** Female flower of cannabis. **b** Part of the pistillate flower. **c** Female flower. **d** Male flower (*Source* Farag and Kayser 2017)

10.3 Breeding of Cannabis

Traditionally cannabis breeding is based on "mass selection", "cross-breeding", "inbreeding" and "hybrid breeding". For decades, both medicinal (drug type) and hemp (fibre type) varieties were produced by mass selection. For traits with a high heritability, mass selection is being used. Effortlessly, Cannabis cultivars can be multiplied and maintained through vegetative propagation. Cannabis is usually a dioecious crop pollinated by wind. Thus, the genetic structure of both natural population and mass selected breeds shows high heterogeneity, whilst this high genetic diversity favoured selective breeding. Inbreeding can also be possibly achieved by producing monoecious plants artificially i.e., by alter the flowers sex from pistillate to staminate on few branches to promote autogamy. Several efforts were made to induce monoeciousness using chemicals have revolutionized the cannabis breeding. Nevertheless, sexual reproduction shows genetic instability and phenotypic variability, the optimistic way to use cannabis seed varieties are the development of true F_1 hybrids. At present, numerous hybrids and some pure lines were brought into commercial cultivation by many private sectors (Table 10.2). Heterosis can be exploited in present-day fibre (hemp) varieties, but it has yet to be investigated or documented in recreation (drug) types. The first publication on the genome sequence of *C. sativa* in 2011 aided the transition from conventional breeding to molecular approaches (Van Bakel et al. 2011). Thus, the advent of genomics and in silico tools will create a new avenue for targeted cannabis breeding (Fig. 10.2).

10.3.1 Breeding for Fibre Quality

Fibre quality depends strongly on fibre bundles morphology and cell wall chemical composition of the elementary fibre (Rowell 2000). The fibre quality and yield changes over a period during plant development viz., cellulose content rises up to 56–65% till late flowering. Besides, the fibre quality is affected by various factors like cultural practices such as density of plants, application of nitrogen fertilizer and time of harvest (Amaducci et al. 2008b). High quality fibre and suitable for mechanical extraction are the important traits appreciated by the hemp industry. High quality trait includes high and fine bast fibre, high cellulose, lower degree of lignification, minimized cross links between pectin and other structural cell wall components and efficient decortication properties (Ranalli 2004). However, the relationship between lignin content and fibre quality relies on its purpose. In concise, lower level of lignin is preferable for textile purpose, because lignin polymer impede decortication process and intensifies the rigidity of fibres (Ranalli 2004). Contrarily, antioxidant and adhesion properties of lignin are related to increase in composites stability and encourage the attention of lignified fibres in novel application (Pickering et al. 2016). Recently, an association panel with 123 hemp cultivars from varied parts around the globe were reported with the extensive phenotypic variations for 28 traits associated with

Table 10.2 Origin of Cannabis varieties

Variety	Country
Finola	Finland
Glukhov 33, Kuban, USO 11, Zenica, USO 13, USO 15, USO 31, YUSO 14, YUSO 16	Ukraine
Asso, Carmagnola, CS (Carmagnola Selezionata), Carmono, Carma, Codimono, Eletta Campana, Ferrara, Ermes, Fibrimor Fibranova	Italy
Fasamo, Ferimon	Germany
Santhica 27, Epsilon 68, Fedora 17, Fedora 19, Fedrina 74, Felina 32, Felina 34, Fibrimon 21, Fibrimon 24, Fibrimon 56, Futura, Futura 77, Futura 75, Santhica 23, Dioica 88	France
Kompolti Sargaszaru, Kinai unisexualis, Kompolti, Kompolti Hybrid TC, Kompolti Hyper, Elite, Fibriko	Hungary
Fibramulta 151, Irene, Lovrin 110, Moldovan, Secuieni 1	Romania
Beniko, Bialobrzeskie, LKCSD, Dolnoslaskie	Poland
Chamaeleon, Dutch "Yellow" line	Netherlands
Ermakovskaya Mestnaya	Russia
Delta 405, Delta-llosa	Spain
Kenvir	Turkey
Swissmix	Swiss
Ratslaviska	Czech
Silistrensi, Mecnaja copt	Bulgaria
Pesnica	Slovenia
Flajsmanova, Novosadksa, Novosadska plus, Novosadska konoplja	Former Yugoslavia
Kinai Egylaki, Kinai Ketlaki	China
Kozuhura Zairai	Japan

Source Farag and Kayser 2017

fibre quality (Petit et al. 2020c). The content of cellulose, hemicellulose, lignin and bast fibre were determined largely by the genetic components with high heritability and low $G \times E$ interactions, suggesting that this panel is promising for maximizing the genetic gain and further studies of genetics underlying the fibre quality traits. On contrary, the variability in pectin, bast fibre fineness and decortication efficiency are highly influenced by environment. Despite the large variability, the genetic means of these traits remains mysterious. Salentijn et al. (2019) reviewed the candidate genes for quality fibre traits and majority of them are involved in lignin metabolism or encode for plant hormones engaged in development with a feasible impact on lignin. More recently (Petit et al. 2020b) used the same panel for genome-wide association (GWAS) approach and genotyped using a large set (>600,000) of SNPs to unravel the quantitative trait loci (QTLs) linked with quality fibre. In this study, 16 QTLs among six were stable over environments were identified for various fibre quality traits like

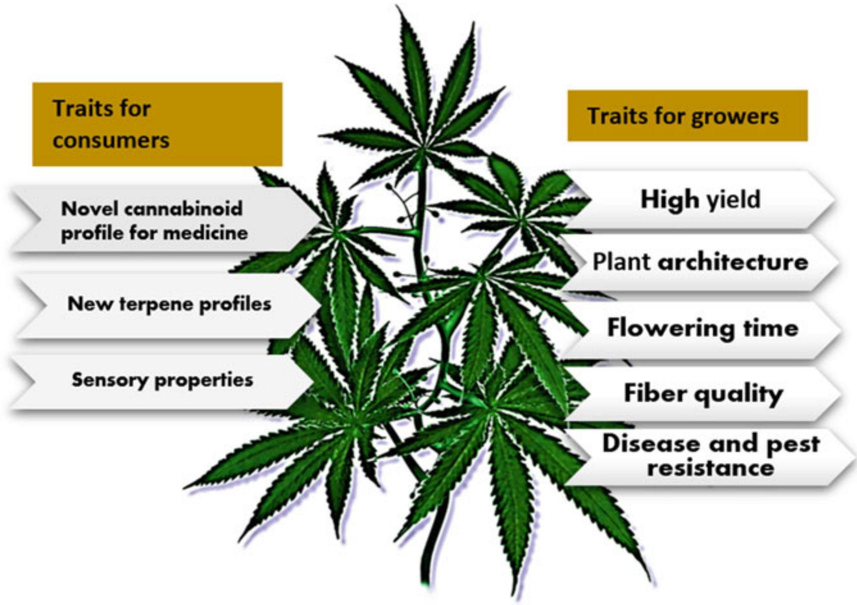

Fig. 10.2 Traits targeted in cannabis improvement

mannose, glucose, xylose, lignin, glucuronic acid, and bast fibre content. In addition, 12 candidate genes are reported to have a function in biogenesis and alteration of lignin, mono and polysaccharides. Still, breeding for this trait is bounded, largely due to the inadequate understanding on its genetic architecture.

10.3.2 Breeding for Flowering Behaviour and Sex Determination

Cannabis is extremely influenced by photoperiod and temperature, the short-day condition with uninterrupted darkness of ∼10–12 h is given which induces the flowering instantaneously (Amaducci et al. 2008a; Salentijn et al. 2019)). However, cannabis cultivated in 24 h light also flowered, but dry matter content in the floral parts are largely reduced (Schaffner 1926). A few cannabis cultivars grown predominantly for cannabinoid production are day-neutral plants viz., *C. sativa* var. spontanea (McPartland 2018). On the basis of flowering time, the genotypes can be categorized into early (40–60 days); medium (60–90 days) and late (90–120 days) types (Zatta et al. 2012). In diecious cannabis, Sex determination system has been understood well. Males possess the heterogametic chromosome (XY) whereas feminine plants have homogametic sex (XX). Diecious plants occurs extensively in nature, whereas monecious species are the result of mutants selected in the course of domestication. Monecious plants usually have diverse sex ratios may gradually turn back to natural dioecy after few generations (Faux and Bertin 2014). Therefore, to conserve monoeciousness careful regular selection for monecious phenotypes are required at the time of seed multiplication (Mediavilla et al. 2001). The quantitative variation and inconsistency of the phenotype over generations proposed that the sex expression is quiet polygenic in nature (Faux and Bertin 2014). Besides the genetic control, sex determination is also regulated by epigenetic factors (Soldatova and Khryanin 2010). Apart from that, ions and phytohormones also alters the sex expression. Zeatin promotes femaleness by accumulating copper (Cu++) and zinc (Zn++) ions, on the other hand Pb^{++} ions favours masculinity effect (Galoch 1978). Generally, auxins and ethylene induce female flower, whereas cytokinins and gibberellins induce male flowers. The use of chemicals such as silver thiosulfate also induce masculine effect on female (XX) plants and is widely used in seed production (Kaushal 2012). Flowering time and sex determination have strong influence on fibre quality and seed yield of cannabis. The progression from juvenile to the reproductive phases is most crucial in hemp breeding, because maximal quality fibre occurs immediately after flowering (Amaducci et al. 2008b). Later, the fibre quality declines as the transit of allocated nutrition and carbon from vegetative parts towards developing floral parts and seeds. In addition, the flowering synchronizes with the phase of secondary bast fibre production, is marked by profound lignification and may results in poor fibre quality (Liu et al. 2015). Another crucial factor directing those traits is plant sex. Large difference in the fibre quality and seed yield was observed between the monecious and diecious cultivars. Recently, a study reported that monecious breeds contains more average bast fibres with elevated cellulose and mannan level, nevertheless diecious genotypes are late flowering with higher xylans and lignin content (Petit et al. 2020c). The lignification gets intense on the commencement of flowering and proceeds till seed maturation. Male plants are less lignified and develop fine fibres in compared to female, but they are highly susceptible to pest (Amaducci et al. 2015; Liu et al. 2015). Moreover, the higher proportion of males resulted in the reduction of seed output (Faux and Bertin 2014). The targeted breeding for the regulation of blooming time and sex expression or determination offers the possibility for long term gains in seed yield and fibres quality. Attempts were made to map the sex-linked marker and QTLs associated with the sex expression (Faux et al. 2016). An hemp association panel with 123 genotypes was found to have a wide variation in blooming time and sex determination traits (Petit et al. 2020c). This study shows that the traits have high heritability and are controlled by the genetic elements. Additionally, significant GxE interactions were observed for the flowering time. Genome-Wide Association Studies (GWAS) was on performed on same 123 accession panel using 600 k SNP markers. Across the environment, eight QTLS among six for blooming time attributes and two for sex determination covering the genic regions of 33 predicted transcripts involving microRNA, miR156 were identified. In flowering time QTLs, the gene involved in perception and transduction of lights and transcription factors that regulates flowering were reported whereas in QTLs for sex determination, the phytohormones especially auxins and gibberellic acid were discovered (Petit et al. 2020a). However, knowledge on genetic and molecular basis on sex determination, sexual dimorphism and blooming time is limited. The markers associated with the selection for monoecy or specific flowering time phenotypes are still in its infancy.

10.3.3 Breeding for Cannabinoid Content

For the past two decades, the genetics means of the various chemotypes has been well studied. However, the complexity of Cannabis genome with numerous transposable elements and large heterozygosity made it more challenging to derive conclusive results on loci controlling cannabinoid production (Laverty et al. 2019). Distinct loci had been hypothesized for determining plant chemotypes. The locus B possesses two codominant allele, "BT codes for the THCA/THC synthase, BD for the CBDA/CBA synthase" (De Meijer et al. 2003). Based on the existence of one or both alleles, they are classified as chemotype I (BT/BT), chemotype II (BT/BD) or chemotype III (BD/BD). In addition, null alleles (B0) of synthase gene were proposed to be linked to chemotype IV where no production of CBDA and THCA thus, the metabolic precursor cannabigerol (CBGA/CBG) accumulates. Further, two independent locus O and C encoding for CBCA/CBC synthase is associated with chemotype V and VI, respectively (Fig. 10.3) (Table 10.3). The chemotype I (high THC) was crossed with chemotype III (low THC) to study the genetic basis. The resulted F1 plants are primarily of type II, yields THCA as well as CBDA. In F2, it follows the Mendelian segregation pattern 1:2:1 ratio of chemotype I, II and III plants respectively (De Meijer et al. 2003; Weiblen et al. 2015). Accordingly, the results support the concept of codominant alleles at single locus and evident that these traits are further complex. The new draft genome analysis postulated that THC and CBD synthases are not coded by the alleles in same gene, instead rather by the different locus in drug and fibre type cannabis respectively (Grassa et al. 2018; Laverty et al. 2019). The CBD and THC synthase genes are embedded between the multiplex tandem duplications of non-functional synthase genes and interspersed with long terminal repeat (LTR) at regular intervals which limits the genome assembly and analysis at these loci (Grassa et al. 2018; Laverty et al. 2019). In addition, copy number variation in CBD and THC synthase genes may also influenced the level and constituents of cannabinoid (Vergara et al. 2019). High throughput analysis of BT and BD markers shows that numerous plants in fact have both locus (Toth et al. 2020). In addition, numerous plants with BD/BD genotypes, particularly those produce high CBD, have THCA content above 0.3%, despite the lack of function of BT allele (Toth et al. 2020). This remnant THC was a by-product of the CBD synthase. The CBDA synthase encodes for both CBDA and THCA in a 20:1 ratio, according to reports from in vitro studies (Zirpel et al. 2018) and also, in *In planta*, the similar ratios was observed with high CBD hemp cultivars (Toth et al., 2020). This shows that increase in CBDA production will also increase the THCA as a by-product. Then, the Cannabis genotypes with higher level of CBD might be at the risk of surpassing the legal thresholds limit of THC. Gaining

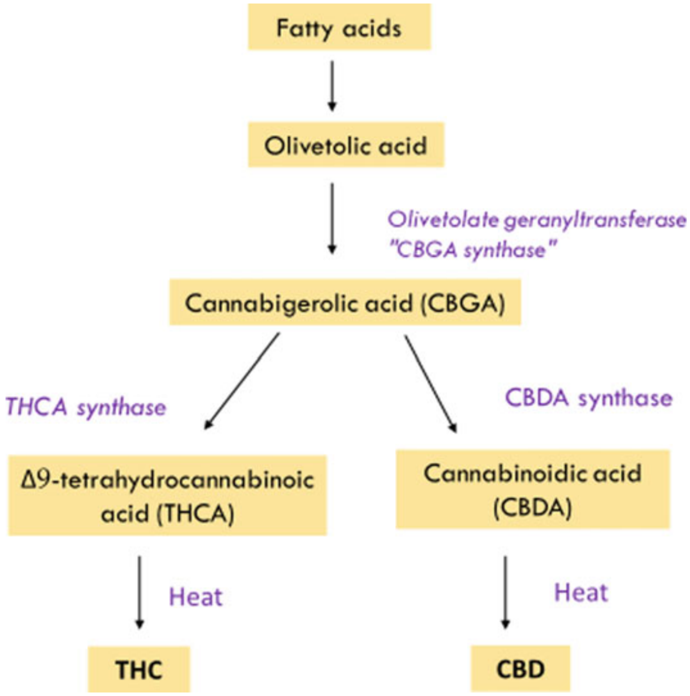

Fig. 10.3 Biosynthesis pathway of tetrahydrocannabinol (THC) and cannabidiol (CBD)

Table 10.3 Different chemotypes of Cannabis

Chemotype	Content (dry weight basis)	Locus	References
Chemotype I	THC prevalent (Drug type) THC >0.3%; CBD <0.5%	B locus (BT and BT)	De Meijer et al. (2003)
Chemotype II	Intermediated THC ≥0.3%; CBD >0.5%	B locus (BT and BD)	De Meijer et al. (2003)
Cemotype III	CBD prevalent (Fibre type) THC <0.3%; CBD >0.5%	B locus (BD and BD)	De Meijer et al. (2003)
Chemotype IV	Cannabigerol (CBG) prevalent CBG >0.3%; CBD <0.5%	B0 allele, a mutant form of the B_D locus	De Meijer and Hammond (2005)
Chemotype V	Zero cannabinoids Total cannabinoids content <0.2%	Locus (O) located upstream of the B locus	De Meijer et al. (2009)
Chemotype VI	Prolonged juvenile chemotype cannabichromene (CBC)	C	De Meijer et al. (2009)

knowledge on the genetics underneath the various chemotypes will be potent for the targeted breeding programme in future. Strict legal regulations around the globe, made it hard for the farmers to cultivate chemotype III, IV and V cultivars due to their residual THCA which arises legislative difficulties. In particular, type III often has slightly high THC content than the permissible limit (Schilling et al. 2020; Toth et al. 2020). Thus, the most significant goal of the breeder is to develop zero-THC lines with high CBD content of about 15–20%. The point mutation may alters the levels of derivatives (Zirpel et al. 2018). Hence, natural variation prevails for the CBDA synthase gene associated with altered cannabinoid composition i.e., very low or lack of THC has to be identified. Other cannabinoids like CBG, CBC and terpenes variants are highly gaining attention in medical fields (Booth and Bohlmann 2019). Hence developing cultivars with specified cannabinoid profiles might be a fortune interest of researcher.

10.3.4 Breeding for Stress Tolerance

The effect of biotic and abiotic stress on crop depends on the crop stage, degree and duration of stress. The disease affecting the cannabis are “damping off”, “fusarium and crown rot”, “pythium rot”, “powdery mildew”, “bud rot” and “post-harvest mold” (Punja 2021). The corn earworm is the key pest of cannabis in particular it damages the flower bud. Other pest viz., Eurasian hemp borer and Hemp russet mite also had the greater potential to cause crop injury (Cranshaw et al. 2019). The cannabinoid levels are not only involves genetic components and also influenced by various factors. The exposure of hemp plants to insects spikes up the cannabinoid production and exceeds the legal limit of THC. Moreover, feeding of CBD and THC spiked plants to corn earworm found to have significant reduction of body weight (Jackson et al. 2021). Among the diseases, powdery mildew has been common for both hemp and drug type cannabis. The economic loss caused by powdery mildew in cannabis production is unknown. This will not cause the total crop loss but affects the end use quality. The use of fungicide to control powdery mildew accommodates with controversies in regard to its efficacy and consumer response (Scott and Punja 2021). Other management strategies like usage of strong UV lights (Scott and Punja 2021) and growth-promoting rhizobacteria (Lyu et al. 2019) are also limited, because it yet becomes most prominent disease in both field and green house condition. Thus, the genetic resistance will provide greater potential for the growth and sustainability of cannabis industry. The genetics of Powdery mildew resistance was depends on the R-genes, present in various crops (Ning et al. 2014). The resistance mechanism against powdery mildew is complex which involves abundant alterations in gene expression and production of various biochemical substances (Qiu et al. 2015).The sequencing and annotation of 42 Cannabis genomes was done and identified copy number variations (CNVs) and SNPs governing cannabinoid synthesis and powdery mildew resistance and found that 82 genes were associated with powdery mildew resistance (McKernan et al. 2020). He also reported that breeding cultivars less than 0.3% THC might ameliorate pathogen susceptibility. More recently, linkage mapping with 10 k SNPs identified first "powdery mildew" resistant gene *PM1* in the *cannabis sativa* which is the single-dominant locus endows total resistance to powdery mildew (Mihalyov and Garfinkel 2021). The research investigating the stress tolerance of hemp is limited. The transcriptome study revealed the genes differentially expressed between the drought tolerant and susceptible cultivars. The most notable candidates are NAC, peroxidases, inositol oxygenase, expansin and genes involved in ABA signaling pathways contribute to the drought tolerance in hemp (Gao et al. 2018). Additionally, Caplan et al. (2019) reported that under controlled drought stress condition the concentration of major compounds viz., CBDA, THC and CBD were increased. However, the duration and timing of the drought stress is the major manipulating factor. Likewise, the differential expression of proteins (Cheng et al. 2016) and genes (Cao et al. 2021; Guerriero et al. 2017) in response to salinity tolerance has also been reported. Hence, further detailed studies are required to understand the interaction of cannabinoid with various stresses.

10.4 Genomics of Cannabis

The Cannabis is diploid (2n = 20) posses 9 somatic chromosome and a pair of allosomes. The size of haploid male (XY) genome is reported as 843 Mb and 818 Mb for female (XX), the presence of largest Y chromosome causes the difference among sex in their genome size (Sakamoto et al. 1998). In addition, it is predicted that ~ 70% of the Cannabis genome accounts for repetitive sequences (Gao et al.2020). The multiple repeats misassemble in one contig creates assembly collapse. This is the challenging feature while using short read sequencing technology. In 2011, the first draft Cannabis genome of drug type cultivar, Purple Kush (PK) was sequenced using short read sequencing technology, which does not resolved the repeat rich and low complexity region of the genome (Van Bakel et al. 2011). Recently, long-read or third generation sequencing, concurrent with linkage and physical mapping allowed genome assembly at chromosome-level from Finola (FN), CBDRx, PK and wild Cannabis (CR) cultivar (Gao et al. 2020; Grassa et al. 2018). Sequencing with the Oxford Nanopore technology, the female genome of CBDRx genotype results in the assembly size of 876.148 Mb (Grassa et al. 2018). And the first genome-wide annotation was made and displayed it as a reference genome (Jenkins and Orsburn 2019). Using PacBio single-molecule sequencing, the genomes of PK (female), FN (male) and CR genomes are sequenced and assembled, have their sizes of about 891.96 Mb, 1009.67 Mb and 812.52 Mb, respectively (Gao et al. 2020; Laverty et al. 2019). The genetic maps were constructed for genomes of CBDRx, PK and FN varieties (Grassa et al. 2018; Laverty et al. 2019) and physical map for CR genome (Gao et al. 2020). Moreover, sequence of 40 diverse genotypes were generated with Illumina as a part of "Cannabis Pan-Genome Project" (McKernan et al. 2020). This genomic information will serve as a valuable reservoir for understanding the genetics underlying the extensive phenotypic diversity resides across Cannabis. In addition, bisulfite sequencing, genotyping by sequencing (GBS) and amplicon sequencing are available for both hemp and drug type cultivars. Based on GBS data representing 400 samples, shows that hemp and drug type cannabis form different populations, segregating not only at BT or BD locus, but at the locus throughout the genome (Lynch et al. 2016; Sawler et al. 2015; Soorni et al. 2017). The Bisulfite sequencing discloses methylation in DNA which takes to the next level perception on gene regulation by epigenetic mechanisms (Li et al. 2020; Schilling et al. 2020). The characters like sex expression and flowering time are strongly influenced by environment, and it will help to investigate on which extent they are epigenetically regulated. This might create the pavement for 'climate resilient' breeding of cannabis. Further, several studies have been focused on transcriptomics of cannabis. Most notably, the transcriptome profiling on the bast fibre formation (Behr et al. 2016) and transcriptome sequencing of trichomes, for the purpose of depicting the expression of genes encoding for terpene and cannabinoid biogenesis (Livingston et al. 2020; Zager et al. 2019). In addition, the expression of sex-linked genes has been studied in two recent research. (McKernan et al. 2020; Prentout et al. 2020). Thus, the abundant data are available on the genome structure and it will pave way for the breeding advancement in cannabis.

10.5 Constrains in Cannabis Breeding

A "consultative group on international agricultural research (CGIAR)" has facilitated the easy exchange of knowledge and materials of numerous crops among research communities which helps in germplasm utilization, but by this the cannabis crop is not benefited. Genetic diversity is prime most important for any successful breeding program. But the germplasm diversity in cannabis is under recession due to the legal prohibition on cultivation and exchange of seeds, replacement of landraces across the world which forbids ex-situ conservation, preference of clonal propagation and limited seed viability. The public acceptance of cannabis for medicinal purpose is established in very few countries but only in indoors cultivation which also leads to narrow gene pool. Preservation of diversity requires seed banks not only just seed companies, sustained funding and research efforts.

10.6 Conclusion and Future Prospects

In debates, the cannabis crop has always heated up the controversy from ethics to scientific pharmacological and therapeutic applications and even in taxonomical classification. Apart, the studies over the years have witnessed the significant progress in cannabis research and unraveled the exciting opportunities and challenges forward. The manipulation of cannabinoid synthases as well as the genetic and environmental control of flowering and sex determination has been ratified as the complex field of research in cannabis. The major challenge in cannabis breeding is developing crop ideotypes that harmonize all traits, currently it is not possible thus the genetic control of the traits are remained ambiguous. This would be speed up by molecular tools. Despite the enormous potential, utilization of molecular markers in cannabis breeding is surprisingly limited hitherto. Another constraint is the legal restriction for growing the drug type cannabis all over the globe except Canada. Unequivocally, the tremendous advent in the genomics of cannabis will dissect out the underlying genetic architecture and hasten the progress in all those areas. Although, morphological and phenotyping studies are also inevitable for understanding the developmental phenology intricates in cannabis.

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Chapter 11
Pre- and Post-harvest Processing and Quality Standardization

Cindy S. Orser

Abstract The rapid acceptance of hemp farming has created tremendous opportunities across many industries, including research, agriculture, manufacturing, production, fabrication, construction, and pharmaceuticals. We are seeing the re-emergence of hemp fiber applications as a highly regenerative and synergistic building material from centuries past and creating new approaches with carbon farming to reduce greenhouse emissions. While the USDA specifically legalized industrial hemp having a THC limit of 0.3%, the consequence by default seemingly made resin-type CBD hemp also legal, and the preferred crop since it can comply with the definition. The evidence is readily apparent by the cornucopia of CBD-laden products in the marketplace despite the lack of any FDA opinion to date on their regulatory status. Quality standards should require hemp-derived ingredients destined for human consumption to meet the same standards as any other food product, witth minimum testing for biological, chemical, and physical contaminants. The impact of weeds and plant pathogens, including insects, often tempts growers to apply pesticides currently unregistered for use on hemp or other crops destined for human consumption. The use of unregistered pesticides on hemp creates a route for human exposure to inconsistently regulated chemicals. Without question, regulation lays ahead for the resin hemp CBD industry. Additional pressure from fermentation-derived cannabinoids produced at a fraction of the cost, combined with strained relations from the state-regulated, yet federally illegal, drug-type THC industry, adds to the challenge for hemp farmers. The success of the legal hemp industry will hopefully serve as persuasion for the federal rescheduling of drug-type THC cannabis as well.

Keywords Hemp pre-harvest · Hemp post-harvest · Hemp biomass · Quality standards · Smokable hemp

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11.1 Introduction

There are three distinct phenotypes of *Cannabis sativa L.*: fiber hemp, resin CBD hemp (Fig. 11.1), and drug-type THC cannabis, each grown for a different purpose as indicated by their names. After 80 years of covert breeding, the dioecious outcrossing nature of cannabis has contributed to its extensive genetic heterogeneity and associated phenotypic variability (Sawler et al. 2015). Most genetic analyses have centered on cannabinoid production and content of drug-type THC cannabis, particularly for the predominant cannabinoids: Δ9- tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) (Meijer et al. 1992; Meijer and Keizer 1996). The heritability of phenotypic diversity in the morphology of fiber traits such as cell wall composition, stem decortication, bast fiber content, or quality of fiber bundles across genotypes of fiber type hemp was unexplored until recently (Petit et al. 2020).

With the signing of the 2018 Agricultural Improvement Act, better known as the 2018 Farm Bill, on December 20, 2018, hemp became legal to cultivate and sell across US state borders. Before this date, all cannabis was considered a Schedule I substance at the federal level. The legalization of hemp led to heightened interest in the cultivation of hemp and the inevitable fall in hemp prices across the U.S. The oversupply of hemp forces even large growers to scale back production or move from resin CBD hemp cultivation to fiber hemp production. The fiber market is very robust and in its infancy. In 2019, 80% of the hemp grown in Montana was for CBD extraction and today those growers have switched over to grain and fiber production (Helmer 2021).

Fig. 11.1 Resin CBD Hemp *Cannabis sativa L. Source* https://www.coloradocbdseed.com/abacus-early-bird

Many challenges have been associated with this ramp-up in hemp cultivation, starting with the USDA's narrow definition of hemp as *Cannabis sativa L.* plants with a Δ9-THC concentration of not more than 0.3%. Some initially interpreted 0.3% to mean the Δ9-THC content only, without accounting for the contribution of decarboxylated tetrahydrocannabinolic acid (THCA) content or other THC isomers such as Δ8-THC. The 2021 final adoption of the 2018 Farm Bill guidelines has clarified the sum of both Δ9-THC and potential Δ9-THC from THCA decarboxylation is used to determine the 0.3% cutoff.

11.1.1 Hemp Diversity

The rapid growth in the hemp industry within the U.S. created confusion for state regulators and hemp farmers. While some hemp was grown for fiber and seed, most of the 2019 and 2020 hemp harvest was extracted for cannabidiol (CBD). Therein lies the problem since resinous hemp is often above the 0.3% THC threshold. Distinguishing the categories of fiber hemp, resin hemp, and drug-type THC cannabis based on genetics is the alternative approach to THC content. I have previously published an initial field evaluation of our molecular DNA-based assay called Tru-Hemp ID™, which correctly identified 420 out of 420 individual seed, leaf, and flower cannabis samples (Hilyard et al. 2019). Tru-Hemp ID™ used only two single nucleotide polymorphisms (SNPs) identified by Henry (2018) in the cannabis genome; Mito 318′683 in the mitochondrial genome and 8′374 in the THCA synthase gene (Table 11.1). Together, these two SNPs present an inexpensive molecular-based means to differentiate fiber hemp, resin hemp, and drug-type THC cannabis (Hilyard et al. 2019).

The previously published logit graphical representation of the distribution of THC content across 157 hemp samples tested with Tru-Hemp ID™ demonstrated distinct separation of resin-type hemp samples shown in green dots from drug-type THC cannabis shown in red dots (Hilyard et al. 2019). Note that a cutoff of 0.3% THC eliminated 72% of the hemp samples. However, moving the THC cutoff to 1% THC is inclusive of all but two outliers (see Fig. 11.2) (Hilyard et al. 2019).

Table 11.1 The distinction of single nucleotide polymorphisms*

Category	Mito_318′683	THCAS_8′374
Industrial hemp fiber and seed	A/A	A/A
Resin hemp oil production—CBD	C/C	A/A
THC cannabis oil production—THC	C/C	G/G or A/G

* *Source* (Hilyard et al. 2019)

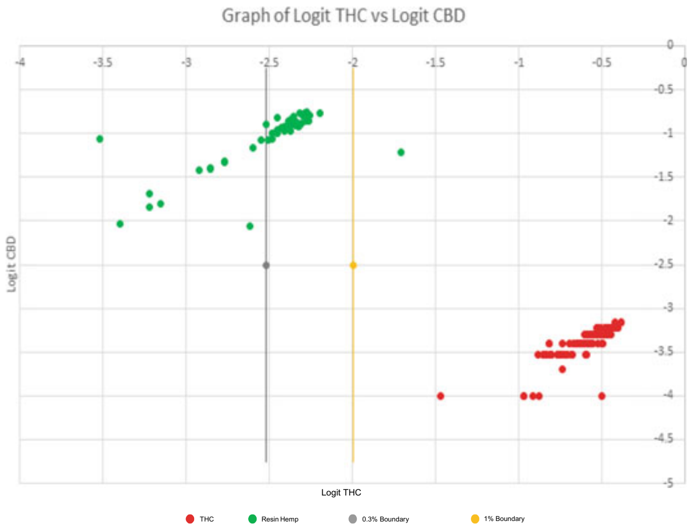

Fig. 11.2 Logit graphical representation A logit graph depicts the log of the odds ratio = log[percent/(1-percent)]. *Source* (Hilyard et al. 2019)

11.2 Hemp Pre-processing

11.2.1 Hemp Phenotype

Hemp, like most plants other than auto-flowering varieties, is influenced by the length of daylight. Changes in the photoperiod regulate the time of flowering (Amaducci et al. 2012). Hemp grown where the photoperiod transitions from long-day to short-day early in the season, will flower early, and vice versa; if the photoperiod transition occurs later in the season, then the flowering is also later (Salentijn et al. 2019). Plants accumulate the majority of their biomass before flowering when nutrients shift to make flowers and seeds. In the case of fiber type hemp, lignification of cell walls and bast fiber formation increases after flowering (Van Der Werf and Turunen 2008; Liu et al. 2015). The fiber phenotype is influenced by plant density, irrigation, and harvesting time, influencing plant height and stem diameter (Amaducci et al. 2015).

De Meijer et al. (1992) described extreme diversity in hemp plant height, stem diameter, and stem yield among 206 genotypes with accessions up to 4 m high to dwarf phenotypes of only 1 m height (Meijer et al. 1992; Meijer 1994; Meijer and Keizer 1996). A recent study evaluated the genetic variability and heritability of 28 traits relevant to hemp's fiber quality (Petit et al. 2020). Five agronomic traits, four different flowering traits, including sex determination, nine fiber measurements (morphological and processing-related properties), and ten parameters of cell wall composition, identified which traits are worth further investigations from mapping

Fig. 11.3 Fiber-type hemp field. *Source* https://textileschool.com

studies (Petit et al. 2020). The quality of hemp fiber is a complex trait worthy of further research (Fig. 11.3).

11.2.2 Cultivation of Fiber-type Hemp

Cultivating fiber-type hemp favors close spacing, 4 inches between plants or even closer, to encourage straight stems and abundant seed production where male plants are desirable for seed production. While cultivating resin-type CBD hemp and drug-type THC cannabis, plants are spaced 4 to 8 feet apart, and great efforts are taken to eliminate all-male plants to avoid seed formation. A fiber hemp field resembles a corn or sugarcane crop more than typical cannabis, Christmas tree-esque plot.

As with any other agronomic crop, cultivation style and choice of hemp variety should match the environmental conditions. Industrial hemp can be harvested by specially modified harvesting equipment such as combine harvesters. These machines cut down the hemp plant at the base, cut off the flowering head for flower or seed processing, and sort the stalk for fiber processing.

Weeds can impact the resulting yield of a hemp crop through sheer competition for resources, both nutrients, and water. Understanding the source of weeds and the type of weed is crucial to controlling the weeds. Since there are no approved pesticides for weed control in hemp, other than two EPA-approved products containing capric acid or acetic acid, cultural practices such as cover crops, mowing, and hand weeding are current best strategies. Once the hemp crop is established, weed control becomes less of a concern as the hemp plant tends to outcompete most weeds.

Hemp can suffer from bacterial pathogens. Biotic hemp diseases include bacterial blight, crown gall, and leaf spot, as well as fungal diseases including anthracnose, black dot disease, black mildew, stem canker, charcoal rot, downy mildew, fusarium root rot and wilt, gray mold, and verticillium wilt to list a few. Further blight can occur from nematodes and viral diseases. Moreover, because there are no fungicides or insecticides approved for hemp, the best strategy is to avoid introducing these pathogens through clean horticultural practices.

Use of any EPA-registered pesticide on hemp must list on the label directions for use on hemp. Alternatively, the active ingredient(s) are listed as exempt from a tolerance on unspecified food crops; or exempt from federal regulations under Section 25b of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In addition, any pesticide product used on hemp must also be registered within the individual state where the hemp is being grown.

11.2.3 Hemp Drying

The most critical step for all types of hemp post-harvest is the drying/curing phase that determines the ultimate quality of the resulting hemp flower, food, fuel, or biomass for subsequent extraction. Hemp harvested too wet or dried too slowly will allow microorganisms to take up residency and spoil the crop, making it unusable for food or medicinal use. The goal of optimizing the drying/curing step is to preserve the terpenoid and cannabinoid profile of the harvest. Drying can be carried out by hanging individual hemp branches upside down in a large, well-ventilated shed with controlled 60% humidity and temperature between 60–70°F or outdoors in an open-sided drying barn if weather conditions cooperate.

Planning for drying requirements is critical. If a large harvest is expected, auxiliary drying equipment can be used to accelerate the process, even taking the plants directly from the field via conveyor belts to a dryer with automated airflow, temperature, and humidity controls to maximize efficiency and retain terpene content. Alternatively, the hemp can be cut and left to dry in the field like a hay crop based on the growing location.

11.3 Hemp Post-processing

The next critical pre-processing step is grinding of the dried or cured resin-CBD type hemp. The effect of grinding the hemp is to increase the surface area for solvent extraction, whether using supercritical carbon dioxide (SCFE), ethanol, or butane to increase the extraction yield of cannabinoids by allowing higher packing density into extractors. The main concern with grinding is not to heat the dried hemp and unknowingly volatilize terpenes and thereby change the chemical profile of the crop. One practical approach to reducing potential heating is to lower the temperature of the matrix, even freezing the dried hemp to prevent any volatile waste.

With the revival of hemp as an agronomic crop, quality standards are slowly being adopted from other industries embracing good agricultural practices (GAP), including organic certification and good manufacturing practices (GMP).

11.3.1 Harvest

Fiber-type hemp. Harvesting for fiber occurs after flowering but before seed set and can be carried out with modified machinery. If the flower is extracted for CBD, the flower heads need to be removed from the stalks. Then the constituent parts of the hemp stalk, the fiber, and the inner core or bast need to be separated using a different machine called a decorticator. Decortication is easier if the stalks are softened by wetting or "retted." The retting process affects the quality of the resulting fiber (Green Sky Labs 2021). After the decortication is complete, the fiber is then dried to around 10% moisture content.

Hemp seed production. Harvest hemp seed using commercially available harvesters around six weeks after the plants flower or when ripe. Working with hemp is notoriously tricky due to its high resin content that accumulates on harvesting equipment. Hemp seed requires careful handling to avoid damage, and each seed batch should be kept separate for uniform quality and moisture content during storage. After seed harvest, the seeds are hulled, and the remaining plant material can either be dried, shredded, and extracted or formed into pellets for different purposes.

Resin-CBD hemp. After harvest, high CBD hemp is dried to prevent deterioration and ensure maximum preservation of the extractable CBD and terpene content. Drying typically takes place indoors in well-ventilated spaces of appropriate standards for a product intended for human consumption. Such measures include clean and dry floors, proper insect and animal control. The plants themselves are typically hung upside down. After drying, either the entire plant is processed, or the flowers are removed from the leaves and stalk for a higher quality CBD-content extract. CBD flowers are hand-harvested to ensure quality and no damage if the CBD is for medicinal use.

Pelletized hemp biomass. The hemp biomass leftover from seed and fiber products can be formed into pellets for animal feed, bedding, or absorbent. The leftover hemp biomass usually is not appropriate for CBD extraction since it is not grown for human consumption and can often become contaminated with microbes, heavy metals, pesticides, and other farming chemicals.

Hemp storage. Hemp intended for food or medicine is stored in controlled facilities for temperature, humidity, light, and hygiene. Individual batches labeled with their quarantine or storage location prevent confusion later.

11.3.2 Hemp Toll Processing

The number of toll processing services for hemp is growing, with some offering mobile capabilities for on-site extraction and distillation. As the regulatory oversight for the use of CBD in finished products evolves, it will be essential to work with those companies that follow GMP principles including GMP certified, and are at a minimum operating at food grade Hazard Analysis Critical Control Points (HACCP) principles (HACCP 1997). Some producers are using the term organic but without any legal justification., Organic certification of a finished product requires that all constituents, including the hemp and additives, are certified organic. A few organically certified hemp toll processors exist in North America, e.g., Rhizo Sciences based in Seattle, Washington.

11.4 Hemp Testing

11.4.1 Sampling

Every lot or batch of hemp that is destined for human or animal consumption should be tested for biological, chemical, and physical contaminants. Testing should occur after the final step in the production process. The residues of any contaminants, whether through pest control or manufacturing, could have been introduced and perhaps even concentrated.

Hemp product lots or batches must be sampled for testing in a representative manner. The purpose of testing is to determine whether safety and quality requirements are met. After that, the remaining sample should be retained for one year after the sale of products originating from that particular lot or batch. The retention should be stored under controlled environmental conditions to ensure it meets the requirements to prevent biological and chemical contaminants from being introduced and minimize loss of cannabinoid content.

Hemp grown under any State, Tribal, or USDA-approved plan must be sampled by a trained sampling agent and compliance tested for total delta-9 tetrahydrocannabinol (THC) content on a dry weight basis (USDA 2021a). The sampling protocol must ensure a confidence level of 95% that the plants will not test above the acceptable THC level of 0.3% on a dry weight basis. The flower samples are cut from the top 5 to 8 inches from the main stem. For plots of less than one acre, a minimum of one plant is sampled. If the hemp crop is more than 10 acres, the number of plants to be sampled to create a composited sample follows the Codex Alimentarius Commission (Codex Alimentarius 2018) but also adheres to the USDA sampling guidelines (USDA 2021b).

11.4.2 Analytical Testing

Analytical testing of a randomly taken representative sample of hemp biomass is recommended to provide an accurate accounting of the cannabinoid and terpene content and determine any contaminant issue with pesticides, heavy metals, or microbes. Most cannabis complicit states have strict laws about which pesticides are

Table 11.2 Heavy metal limits for cannabis

Heavy metal limits	Arsenic ppb	Cadmium ppb	Lead ppb	Mercury ppb
American herbal pharmacopeia	2000	820	1200	400
U.S.P Pharmacopeia	200	200	500	100

screened for and what action limits trigger a failure. It is always best to avoid using all pesticides for the biomass's resulting quality, the environment, and neighbors.

In most regions of the U.S. where hemp is grown, it is sampled and harvested before maturity to ensure the crop meets the limit of 0.3% THC. A valid test result includes the total available THC derived from the THC plus THCA, multiplied by 0.877%, and also the delta-8-THC content for a total sum. Testing methodologies that meet these stipulations include gas chromatography and liquid chromatography; however, new instrumentation, such as Big Sur Scientific's unvalidated device using mid-Infrared (IR), offers an appealing alternative requiring limited processing time and delivering potency results minutes for growers and processors (Big Sur Scientific 2018).

Testing requirements for hemp beyond cannabinoids have evolved to include contaminant screening for heavy metals in addition to pesticide residues. Heavy metals can be problematic as *Cannabis sativa L.*, when grown outdoors, will accumulate inorganic elements depending on the soil conditions. While State-based drug-type THC heavy metal standards were originally adopted from the American Herbal Pharmacopeia recommendations for herbs (Upton et al. 2014; AHP 2014). The AHP standards have been superseded by U.S. Pharmacopeia (USP) inhalation limits, which are more stringent (Table 11.2) (USP 2017).

Not every state imposes microbial limits for cannabis. Still, outdoor-grown cannabis, depending on the environmental conditions, may have higher bioburdens for fungi coming out of the field. Those numbers can become worrisome if the crop is not properly cured and dried, leading to mycotoxin concerns.

Hemp testing laboratories are required to calculate the Measurement Uncertainty (MU) and take it into account when reporting THC concentration test results. Applying the ISO-17025:2017 MU requirement is a big step forward in demonstrating the inherent heterogeneity of cannabinoid content in cannabis and hemp flower. Laboratories must use appropriate, validated methods written in standard operating procedure (SOP) format for all sampling, testing, and retesting activities and are encouraged to be ISO-17025 certified. After December 31, 2022, testing laboratories must be registered with the DEA to handle controlled substances, given the possibility that a hemp sample is greater than 0.3% THC.

It is the responsibility of the producer to pay for any fees associated with compliance testing and retesting. Test results from compliance testing are shared with the licensed cultivator and appropriate regulatory bodies, including State Departments of Agriculture, Tribal authorities, and the USDA. If a hemp sample is found to be above the 0.3% THC limit, the licensee can remediate the hemp by shredding the plant material into biomass and having it retested.

If a grower's hemp crop tests above the allowed 0.3% THC, it is destroyed on the same site where it was grown. If the entire crop is deemed in violation, the options for destruction include plowing the crop under, composting it into green manure for use on the same land, or burning. If the entire harvest is not over the 0.3% THC limit, then remediation is allowed, whereby only the non-compliant plants are pulled for destruction.

11.5 Hemp Biomass

Biomass can have different meanings depending on the grower. Biomass can refer to everything harvested from the cannabis or hemp plant, including the flower, fan leaves, stalks, seeds, trim, and anything else from the living plant. This approach allows for conventional growing and harvesting equipment because the entire plant is harvested and homogenized instead of separating the flower to process separately. This method of harvesting yields hemp biomass with a higher cannabinoid content due to the incorporation of the mature flower. Alternatively, the high-cannabinoid flowers are removed, and the resulting hemp biomass will have lower cannabinoid content. Biomass can also refer to a hemp fiber crop where the resulting fiber is used in making paper, fabric, insulation, particleboard, hempcrete, hemp wrappers, and many other innovative products. The taller the stalks, the longer the fibers.

The quality, smell, and color of hemp biomass depend on the hemp plants' environment and any toxic pesticides used during the growth cycle. The color of the biomass should be deep green and not yellow or brown, with no visible signs of mold or insects. When the grower's only goal is to extract CBD and or THC, the quality and aroma of the cannabis flowers dictate the timing of harvest to maximize the concentration of cannabinoids and terpenes. Because terpenes are volatile, they are subject to loss during the drying and curing process. It is now widely accepted that terpene content constitutes the aroma and the taste and physiological potential of the biomass. With markets becoming competitive and profit margins thinning, producers look to reduce costs by extracting the biomass that is a by-product of the smokable cannabis flower industry.

11.5.1 Hemp Seed

In addition to hemp being a sustainable and low environmental impact biomass crop for use in building materials and extraction in the biopharmaceutical and cosmetic industries, hemp also produces edible fruit. *Cannabis sativa L.* hempseeds were once thought to be a by-product of the hemp fiber industry and not recognized for their high nutritional value (Farinon et al. 2020; Vonapartis et al. 2015; Kriese et al.

2004). The cultivation of hemp for fiber was curtailed for the past 80 years; its edible fruit was no longer available and fell out of favor even for animal feed in the U.S. Hempseed's acceptability has just recently been introduced on a state-by-state basis for its exceptional nutritional and functional features into a growing market (Karus et al. 2004; Irakli et al. 2019). Hempseed contains 25–35% lipids with a perfectly balanced ratio of fatty acids, 20–25% protein that is easily digestible, and high fiber content. Beyond the remarkable nutrition of hemp seed, it also contains a wide array of beneficial secondary metabolites, including antioxidants, flavonoids, tocopherols, carotenoids, and phytosterols. The actual quantity of secondary metabolites is affected by environmental and agronomic growing conditions.

11.5.2 Hemp Building Materials

Hemp fiber is not only stronger than conventional wood building material for structural framing but also less expensive to process than wood and a genuinely renewable crop. At the same time, hemp acts as a carbon sink. Remarkably, acre for acre, hemp is the most efficient biomass source in the world (Ziner 2021). Hemp represents a proven recourse from limited timber harvesting for structural building materials where the cellulosic strength contributing content is critical. Hemp has the highest cellulose concentration of any plant material at 72% compared with 42% for wood. The higher the cellulose content, the easier the conversion into paper and particle board with lower input costs and a 90-day turnaround from seed to harvest for paper production (Ziner 2021).

Many hemp-based building materials, including insulating panels, acoustic damping particle boards, and hempcrete blocks, are now widely available. Hemp was historically used for centuries, including by the Romans in building the aqueducts over 500 years from 312 BC to AD 226, some of which are still standing (Fig. 11.4) (USGS).

As a growing substitute for wood products, hemp has many advantages: a new crop can be ready to harvest within six months, sequestering four times as much carbon from the air as a forest acre for acre. Hempcrete is the most popular hemp-based building material, made with a refinement of the traditional lime-based binder. Because hempcrete is not as dense as concrete, it will float in water. It makes good insulating material due to the trapped air inside and its breathability, natural resistance to mold, and mildew. On top of that, it is fire resistant.

Primary building materials such as pressed particle board and plywood are continually in high demand despite growing regulations to reduce their emission of toxic formaldehyde. Plywood's properties are based on the quality of the wood materials and the adhesives used to fuse them into sheets. When creating wood-based materials, a high cellulosic filling material, typically rye flour, is incorporated to help the adhesive mixture, a melamine-urea–formaldehyde (MUF), form a binding gel with the wood particles. A Polish group recently published a study showing that the substitution of standard rye flour with hemp flour had a significant effect on the

Fig. 11.4 Roman aqueduct at pont du gard, crossing the gard river in southern France**.** (*Source* Wikimedia: Creative Commons License)

viscosity of the resin, reducing the setup time and resultant strength and amount of emitted formaldehyde (Kawalerczyk et al. 2020). This is a welcome outcome since formaldehyde is toxic, causing eye irritation, sleepiness, and lack of concentration, and is probably carcinogenic to humans. Hemp flour acts as a scavenger of formaldehyde without any decrease in the mechanical properties of the plywood (Kawalerczyk et al. 2020).

11.6 The Economics of Hemp

The hemp flower is the most popular commodity. Cured flower can be used for smoking directly, rolling into joints or blunts, or high-yielding extraction and distillation. Biomass used to make extracts can be turned into several subsequent products, including a crude ethanol extract characterized by its full spectrum rich in cannabinoids, terpenes, and flavonoids, and the less desired plant waxes and chlorophyll. Ethanol extracts are used to make tinctures and edibles. Distillation of the crude ethanol extract will remove the waxes and chlorophyll. Solventless extractions will yield resin suitable for vaping or dabbing.

11.6.1 Marketing Hemp

After a successful growing season, hemp farmers have many options for selling their biomass. The first determining factor is whether the biomass was grown as resin type hemp for its extraction of CBD or fiber type hemp to be processed into usable products from hempcrete to hemp fabric. Whether a hemp grower is looking for a buyer or a buyer is looking for biomass, the first step is to test the biomass at a qualified cannabis testing lab.

The traditional avenue to selling biomass is direct sales through building a network to find an interested buyer. Other options now exist, including future contracts to have a guaranteed buyer before the hemp crop is in the ground or the use of a broker whose job is to connect buyers with growers. Brokers take a commission from the sale but can be worth being freed up from the negotiations. Lastly, a share-cropping option can be struck with a willing hemp farmer and a buyer willing to cover the upfront costs of getting the crop in the ground and harvested. Following the footsteps of other established crop commodity markets with a critical mass, individuals become more inventive with their offloading efforts.

11.6.2 Hemp Crop Yield

Hemp biomass per acre is highly variable, given starting seed stock and ensuing environmental conditions. If the crop is not intended to set seed, an acre of land can yield from 1200 to 3500 pounds of hemp biomass typically intended for cannabinoid extraction, where biomass is often sold based on the CBD content. The average flower yield across 152 distinct cultivars in the Midwest was 1.22 lbs. per plant (Alberti 2021). If the crop is intentionally let to set seed, those biomass numbers can easily double, potentially providing two sources of revenue: hempseed and hemp fiber.

Currently, two cannabinoids, CBD and cannabigerol (CBG), determine a crop's profitability while the THC content determines its compliance. Data suggest a linear relationship between total CBD and THC with a preferable ratio of 25:1 for a maximum of 8% CBD to stay within compliance at 0.3% THC. For CBG cultivars, the average total THC tends to be lower, but there is no linear correlation to CBD content, reflecting the biochemical pathway of getting from CBG to THC and/or CBD (Alberti 2021).

11.6.3 Extraction Efficiency

The extractable amount of CBD depends on the percentage of CBD in the biomass and the efficiency of the extraction method of choice, ranging from 50–85% efficiency. If biomass tests at 4% CBD, a 70% extraction efficiency yields 13 to 14 g of CBD per lb. Testing before and after extraction to estimate potential yields and stay within USDA compliance is essential. The absolute 0.3% cutoff for THC shows some weakness, with at least three states upping the compliance cutoff to 1.0% THC in Wisconsin, Minnesota, and Texas.

The theoretical maximum yield of CBD and THC can be estimated based on the percentages of CBD and THC found on the Certificate of Analysis (COA): (CBD%) x 454 g = g of CBD in a pound of dried hemp biomass. Keep in mind that extraction efficiencies are not 100%, but between 50–85%. A compliant crop coming in at 0.3% THC would yield 1.3 g of THC per pound of dried hemp biomass.

11.6.4 Competition

Growing hemp engineered to produce other novel cannabinoids or interesting secondary metabolites could help hemp farmers capture a unique market share and potentially avoid holding an unsold harvest. However, bioengineering companies are growing competition, such as Demetrix, Twist Biosciences, and Ginkgo Bioworks. They can quickly produce vast quantities of individual cannabinoids inexpensively using genetically modified organisms, most notably yeast in large fermenters.

11.7 Quality Standardization

The dietary supplement and food manufacturing industries are informative to the cannabis industry through the adoption of the internationally recognized management of food safety-related risk, called Hazard Analysis Critical Control points (HACCP 1997). The principles are well established: performing hazard analyses, identifying, monitoring critical control points (CCP), establishing corrective actions, verification procedures, and record-keeping, including adhering to specifications, testing results, buyer approval, distribution, and shipping orders. Adopting HACCP would reduce product loss, increase product consistency and quality, provide inventory control, and increase profits by being ready for federal legalization.

Hemp-based ingredients destined for human consumption should be produced, packaged, labeled, stored, distributed, sampled, and tested following validated SOPs. All necessary steps to achieve specific outcomes while avoiding adverse out-of-specification events such as contamination with an unknown substance should be taken. The tenets of HACCP from the food industry, including building and equipment sanitation and employee hygiene, become critical (HACCP 1997). Ensuring that all personnel who carry out SOPs are adequately trained and have documented demonstration of competency (DOC) for a given task.

11.7.1 Facilities

The facility must maintain records describing the sanitation program, including the building and equipment and maintenance records for the equipment, employee training records, routine swab testing, or another form of environmental monitoring. All records shall be retained for a defined time, taking legal or customer requirements into consideration for the shelf life of the product.

Security. Prevent unauthorized entry by establishing a security program to monitor critical systems such as operations and storage areas that meet the regulatory authority's requirements. The security system should include video monitoring to prevent theft and product loss.

Pest control measures. Only approved pest control products are permitted when products are sold for human consumption and use. Any sanitizers or non-food chemical agents on site must be properly and clearly labeled and handled to avoid contamination of hemp-based products.

Storage. Hemp-based products must be clearly labeled and stored under conditions that maintain their quality and authenticity to prevent cross-contamination from occurring. Labeling specifies storage conditions, including temperature and humidity, which should be checked daily with calibrated recording devices. Any deviations from storage specifications must be noted, with appropriate actions taken when required. Adherence to storage conditions is periodically audited as determined by inherent risk.

11.7.2 Registration and Authentication

Most individual states with approved USDA hemp programs maintain hemp cultivar registration programs, as does the USDA. A very select group currently offers both hemp cultivar registration and product authentication through the PurityIQ platform service, one of the first to bring authentication to the cannabis and hemp market through a combination of both genotyping and metabolomic fingerprinting via NMR analyses under the Cannabis Authenticity and Purity Standards (CAPS) (Purity IQ 2021). Following the initial registration, the propagated materials can be verified using genomic and metabolomic authentication (Purity IQ 2021).

Unfortunately, there is no global consistency concerning the regulations (i.e., quality, authenticity, and identity) that control legal access to cannabis and/or its production, distribution, and sale. However, there can be a private standard, such as CAPS, that evolves from a consensus among stakeholders and includes the attributes or requirements demanded by regulatory authorities. It is also a voluntary standard not required by legislation. The knowledge and science of cannabis/hemp and the relevant testing requirements are advancing rapidly. The services rendered by Purity-IQ are intended to meet the needs of all stakeholders in the cannabis/hemp industry. CAPS is not intended to duplicate regulators' testing needs but to complement them as a prerequisite for establishing product authenticity and purity through the adoption of GMP standards (Purity IQ 2021).

11.7.3 Cannabis Standard Reference Materials

The National Institutes of Standards and Technology (NIST) creates standard reference materials (SRMs) of defined composition for many industries. SRMs are time-consuming to create but are essential for any industry for use in round-robin studies to compare how accurate testing laboratories perform using their standard operating procedures and instrumentation. NIST creates SRMs for many ingredients found in foodstuffs as well as crops. It is encouraging to see NIST finally creating hemp SRMs in an acknowledgment of the legal hemp cannabis industry. However, this may take some time as NIST is still conducting blinded studies across participating cannabis labs across the country under a program called CannaQAP which stands for Cannabis Quality Assurance Program (NIST 2021). CannaQAP was created to help forensic and independent cannabis testing laboratories improve their test methods through large-scale interlaboratory comparisons as moderated by NIST.

In the meantime, as NIST completes its studies, the University of Kentucky (UKY) has advanced standard reference materials as part of its Hemp Proficiency Program (UKY HPP 2021). The UKY hemp reference standards include four hemp samples, under 0.3% THC and analytically tested by at least 50 cannabis testing laboratories. The published certificates of analysis for the reference standard test samples contain the average total THC, total CBD, and other cannabinoid weight percentages. Until any NIST cannabis SRMs are introduced, the UKY samples are the best alternative reference standards in the hemp industry. We recommend that all cannabis analysis laboratories currently analyzing hemp samples use the UKY reference samples to validate their methods through participation in the HPP.

11.8 Smokable Hemp

While states exercise their independent authority over accepting smokable hemp, the federal USDA remains supportive of it as an agricultural commodity, making the barrier to entry lower. However, confusion surrounding hemp-derived CBD abounds, which ironically started the whole hemp craze. A long-awaited FDA ruling for how CBD should and can be included in consumer products would solve part of the dilemma that states face. The other confounding issue is that hemp is cannabis, *Cannabis sativa L.* Therefore, it looks and can smell like the other highly regulated and federally illegal variant, drug-type THC cannabis, making differentiation difficult for law enforcement and commercial enterprises (Fig. 11.5).

Fig. 11.5 Smokable hemp
Source hoban.law

11.8.1 Smokable Hemp Market

The 2020 smokable hemp market is estimated to be in the $80 M range compared to the total resin hemp CBD product market of around $2 billion and the drug-type THC cannabis market of around $20 billion (Hemp Industry Daily 2020). However, smokable hemp is emerging with a 5X growth prediction anticipated by 2025 due to several contributing factors, notably improved genetics. Improved genetics reliably result in compliant harvests under 0.3% THC by dry weight with higher yields, elimination of rogue male plants, auto-flowering varieties that eliminate the growing season variabilities, and the promise of increased novel cannabinoids and enhanced sensory perception from terpene compounds.

Several factors contribute to the attractiveness of the smokable hemp market. Foremost, while the USDA regulates how hemp is cultivated and every state is required to have a USDA-approved hemp cultivation plan, there are no federal regulations on smokable hemp product labeling or packaging. It is not marijuana; it is not tobacco, so whose jurisdiction does smokable hemp reside. If bulk hemp is compliant with the USDA definition of hemp as being under 0.3% THC by dry weight, it is doubtful that the DEA will take further notice of this commodity. Presumably, after the bulk hemp flower transitions to a smokable product for human consumption, it would fall under FDA oversight; however, that has not happened. The FDA is more focused on studying inhaled vaping products, including e-nicotine devices, rather than smokables. CBD vapes could be regulated as tobacco products or drug products depending on the pending regulatory approach at the FDA. Smokable hemp flower has a long runway, albeit at the mercy of State mandates and restrictions.

There is the option for smokable hemp companies to pursue FDA approval as a smoking cessation product. This approach would require human clinical studies and FDA approval to market. An FDA-approved smokable hemp product would be an attractive option for the current 34 million tobacco cigarette smokers in the U.S., with a sizable fraction looking to decrease their nicotine intake.

The primary market for smokable hemp flower is quite large and can be marketed by demographics and geography. The highest demand for smokable hemp flower is currently in the South, followed by the West and those under 35 (Hemp Industry Daily

2020). These two markets represent the cannabis-oppressed and cannabis-starved South and the satiated drug-type THC cannabis market in the West. Nevertheless, both are attracted to this new product category of smokable hemp.

Another attractiveness of hemp is the cornucopia of secondary metabolites, terpenes, and flavonoids, many of which have known physiological activity with beneficial outcomes for mental and physical health (Russo 2011). Today we do not even know the extent of their favorable contributing effect when combined with inherent CBD or now CBG levels.

Moreover, one can imbue hemp flower with the perception of any favorite drug-type THC cannabis strain through widely available terpene mixes that mimic the chemical profile of favorites such as Blue Dream or OG Kush. Branding and marketing this version of smokable hemp to devoted marijuana smokers who would like to experience the sensory perception of their favorite strain but without the intoxication of THC. The benefit of what terpenes or other cannabis secondary metabolites contribute combined with CBD's analgesic and anti-inflammatory attributes is quite appealing.

Seven states, including Texas, Iowa, Indiana, Kentucky, Louisiana, Hawaii, and New York, ban smokable hemp products and a handful of other states are on the legislative fence. The lack of regulations over hemp products beyond the 0.3% THC cutoff combined with a lack of clarity on CBD in foodstuffs keeps the hemp industry in limbo. Hemp is also not aggressively taxed as a commodity at the wholesale or retail levels like drug-type THC cannabis. California appears to be blocking its legality until such legislation and taxation schedules are in place (California Legislature 2021). There is also the state-level influence of the profitable, albeit regulatorily shackled, drug-type THC industry that has not warmly embraced the fully emerged resin hemp CBD industry. With a lower barrier to purchase, smokable hemp flower products represent an inroad into the drug-type THC market share.

11.8.2 Regulatory Matters

Regulation lays ahead for the whole hemp CBD industry including smokable hemp. One expectation is that the FDA may regulate smokable hemp much like traditional tobacco products, with a minimum requirement of a consistent product traceable back to the hemp farm. At the same time, the FDA's definition of tobacco as "any product made or derived from tobacco intended for human consumption" would not apply to unadulterated smokable hemp (21 CFR§1140.3). For hemp-derived CBD products specifically made for vaping, the situation is not as simple. Vaping products could fall within the definition of a tobacco accessory as any tobacco product "intended or reasonably expected to be used with or for the human consumption of a tobacco product" (21 CFR§1140.3). When a CBD cartridge can be switched out for an e-liquid nicotine cartridge, it is "reasonably expected" to be used in the same manner, which does require an application for premarket authorization (Drotleff 2020).

Recent state level actions in Colorado have increased the level of contaminant screening that will be required for hemp and hemp-derived products starting in October 2021 (CDPHE 2021). And California's Governor just signed into law AB45, which will legalize the retail sale of hemp-derived CBD products in the state and require them to comply with the same drug-type THC cannabis regs, including licensing of facilities and expanded testing requirements (California legislature 2021). In addition, the new California law will place smokable hemp on the sidelines until the legislature works out taxation in 2022, a major setback for hemp farmers (Hempsupporter 2021). Finally a ruling by the Minnesota Court of Appeals (PR Newswire 2021) states that THC from hemp is the same as THC from drug-type cannabis and just because it is under 0.3% doesn't give it shelter from Minnesota's Controlled Substances Act.

11.8.3 Hemp Recon

Applying the FDA's tobacco product requirements to smokable hemp creates barriers for producers looking for quality and consistency in CBD. Smokable hemp companies can look to the experience from the tobacco industry to overcome these challenges. For example, reconstituting hemp for a consistent filler product for scaled production of individual sticks that will meet potential regulatory requirements.

A limited number of botanical-based companies are capable of paper manufacturing to produce hemp-based filler to assemble various products such as hemp wrappers and traditional roll-your-own (RYO) applications for its customers.

Like tobacco, a hemp-based filler can use distinct blends to create consistency in products year after year to blend from one crop to the next while retaining flavor and active ingredients. Reconstitution of hemp is also used in smokable hemp wrappers, a rapidly growing market that brings innovation to hemp cigarettes, cigars, and hemp cones.

11.9 Conclusions

Oversupply of hemp is an issue in the U.S. Growers have recognized the glut and scaled back acreage. A hemp surplus exists due to the lack of a consistent national legal framework and a lack of definitive guidance from the FDA. In addition, state and local jurisdictions often determine where hemp can be sold and consumed, further blocking access to the market. Moreover, access to processors has also been a chokepoint for growers to reach the market.

A small number of hemp industry players have intentionally augmented hemp-derived products with delta-8 THC thinking it to be a loophole to increase total THC content and yet remain within the delta-9 THC limit restrictions for hemp (Helmer 2021). However, this strategy has backfired with at least twelve states, including

Alaska, Arizona, Arkansas, Colorado, Delaware, Kentucky, Idaho, Iowa, Mississippi, Montana, Rhode Island, and Utah, banning the addition of delta-8 THC in hemp-based products. Similar legislation is moving through several other states. The U.S. Hemp Authority has also declined to certify delta-8 products. These actions have limited growers' opportunities to sell biomass into the delta-8 THC market (Helmer 2021).

11.9.1 Need for Regulatory Oversight

Given the popularity of cannabis use and the expansion of outdoor hemp cultivation, cannabis can act as a potential route of human exposure to harmful environmental contaminants, including pesticides, metals, solvents, microbes, and mycotoxins. Currently, 682 cannabis contaminants are regulated by different state-level agencies in the U.S. (Leung et al. 2021 unpublished data). Nevertheless, these regulations are primarily inconsistent and result in potential health hazards of susceptible populations among cannabis users with medical conditions. An increase in cannabis production and use is expected to lead to a surge in the discharge of neuroactive substances and metabolites into the wastewater stream and, ultimately, freshwater habitats. These neuroactive chemicals include THC and metabolites such as THC-COOH and THC-OH, collectively referred to as environmental cannabinoids. The levels of acute and chronic aquatic toxicity towards bioindicator species of ecosystem health, including sediment invertebrates and fish species, and the effective range of pollution are poorly understood (Leung et al. 2019).

Without a federal regulatory approach to outdoor hemp cultivation, individual States are issuing requests for proposals (RFP) to gather crucial information on how urban hemp cultivation impacts water quality. Regulation is crucial, particularly in marginal arid landscapes with limited, scarce water resources. Specifically, when illegal pesticides are used, it is essential to characterize their runoff and gather baseline data and predictive toxicological outcomes to advance precision farming methods for hemp in the U.S.

11.9.2 Carbon Farming

Carbon farming is rapidly becoming an obvious strategy to reduce greenhouse gas emissions through capturing carbon dioxide in vegetation and soils. Hemp row crops can provide a carbon sink when sustainably-grown due to the versatility of the by-products extracted after growth. Carbon farming can create an additional income stream for farmers by connecting them to companies willing to purchase carbon offset credits to restore landscapes, advance climate change, and improve food security.

Europeans were early adopters of carbon farming in the transition to a sustainable food system, minimizing agriculture's environmental impact and reversing biodiversity. One early non-profit to scale carbon cycle solutions in the U.S. is the Carbon Cycle Institute in Marin County through collaborations with local, state, university, and federal policymakers (CCI 2021). Carbon farming is a promising option for hemp farmers.

11.9.3 Future Outlook

Active collaboration between land-grant universities, non-profit organizations, and grower-cooperators is rapidly changing the trajectory of hemp farming. University participation has provided much-needed data analytics on planting methods to agronomic performance indicators for hemp farmers. Hemp is typically grown in small acreages of under 5 acres, making it a specialty crop requiring high inputs, e.g., genotyped clones and early weed and pest control, and benefiting from such scholarly studies.

> Hemp fiber can play a pivotal role in commerce and economic development. However, the most important thing governments need to understand is hemp's potential for healing the planet and advancing human health. As hemp fiber gains momentum, it is not a question of phasing out other fibers and completely replacing them with hemp. The interesting feature of the "hemp business model" is that the synergies with existing industrial capacities are virtually unlimited. (Ziner, 2021).

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Chapter 12
Scientific Testing, Forensic Identification, Evidences, and Differences in Policy Frameworks of Hemp

Amarnath Mishra, Shrutika Singla, and Dipayan Deb Barman

Abstract Cannabis, also known as hemp plant, is a part of the *Cannabaceae* family. It contains many alkaloids, including T.H.C. and cannabidiol. The use of cannabis has been a considerable debate for centuries. It has many advantages and disadvantages to using cannabis. All parts of the plant are abusable, and people even abuse cannabis. That's why some part of the plant has been taken under control of the Controlled Substances Act. The hemp plant is not only abused, but it is an essential part of various Indian ceremonies. Even it is also a part of many Ayurvedic medicines. In many countries, including India, the government has restricted the growth and development of the plant. It can be grown in specific areas for specific purposes like research and development and medical care. But many authorities are working to sanction the use of weed in India for various purposes.

Keywords Cannabis · Hemp · Controlled substances · Marijuana · C.S.A

12.1 Introduction

Cannabis belongs to the *Cannabaceae* family, and it consists of about 80 naturally dynamic synthetic mixtures in excess. The most generally realized fusions are delta-9-tetrahydrocannabinol (T.H.C.) and cannabidiol (CBD). Some portion of the plant has been controlled under the Controlled Substances Act (C.S.A.), which came into play around 1970 under the medication class "Marihuana" (usually alluded to as "weed") [21 U.S.C. 802(16)]. "Marihuana" has been recorded in Schedule I of the C.S.A. for a long time because it has higher chances to be abused, which is deducible in enormous part to the psychoactive impacts of T.H.C., and the space now conceded clinical application of the factory in the United States (F.D.A.).

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In India's old Vedas texts, strict researchers depicted weed as "one of five most holy plants." Cannabis has always been a piece of various ceremonies and merriments in India for centuries. Antiquated Indian Ayurvedic rehearses the utilization of this plant as a prescription for absorption and circulatory strain. Almost 191 plans and above 15 measurements structures have remembered weed as a critical element in the Ayurvedic texts written by Ayurvedic professionals. The plant can be seen and grown all through Himalayan lower regions in India and the adjacent fields, which have been expanded from Kashmir to Assam. This availability and the bounty of Marijuana are an exceptional chance for India to tackle the plant for economic development.

The government has restricted the plant's growth to government-approved premises and research fields. Only these can grow and sell the parts of the plant and products formed from the plant such as bhang (a beverage formed by mixing cannabis in milk), irrespective of the fact that India has a long history with the plant (India's Cannabis and Market).

12.2 Regulation of Cannabis in India Today

Cannabis has been misjudged lawfully as well as economically in India. As per the NDPS Act of 1985, if any person is found to be doing the exchange and utilization of both marijuana tar (charas) and the bud (cannabis), they will be taken under detainment for as long as 20 years. Due to this, there is severe restriction on marijuana (counting hemp) creation in our country. However, the state government has some rights to keep in check on the plant's growth and provide license for the development of the plant in some particular situations, such as for research work. If we talk about reality, some of Uttar Pradesh and Uttarakhand districts have licenses to grow the hemp plant in their surroundings.

The Indian Cannabis market has assembled critical considerations as of late regarding the court petitions to sanction the growth of weed with the help of many non-governmental organizations. According to the Indian Cannabis market, the therapeutic advantage of Marijuana should not be ignored. The Great Legitimization Movement, an N.G.O. in India, is consistently authorizing weed usage for clinical and query purposes. In the mid-year of 2019, the Delhi High Court surrendered a writ fascination recorded by G.L.M. looking for the decriminalization of Marijuana underneath the NDPS. According to the NDPS Act, the get-together of Marijuana with other compound drugs was found to be "abstract, easygoing as appropriately as ludicrous." Although needed to be heard in February 2020, the gathering has been pushed back to May 1, 2020.

Many administration authorities are maintaining the validation of weed. Authorities including Maneka Gandhi and Tathagata Satpathy have supported marijuana decriminalization. Madhya Pradesh was chosen for the legal growth of Marijuana for restorative and modern causes in November 2019. As perhaps the most unfortunate state in the country, it is trusted that the legitimization will draw new organizations to the front. In February 2020, in Manipur, it was announced that the B.J.P. government is contemplating the approval of weed for clinical and present-day purposes (India's Cannabis and Market).

12.3 Cannabis in Indian Market

As per research done through Grand View Research Inc., the world market level of unlawful Marijuana will reach $146.4 billion with the guide of the quit of 2025. In the event that we talk about India, a us of a with a general population of around 1.4 billion and a developing working gathering, the suitable market for Cannabis things is liberal.

Various promising Indian Cannabis new businesses have emerged late, some of whom are teaming up to fill in the homegrown market. These new businesses are by and large zeroing in on drugs, beauty care products, materials, extras, and food sources. Boheco, the Bombay Hemp Company, is one of the most encouraging businesses in the market.

This enterprise is upheld with the guide of the most notable financial benefactors, alongside Google India's Managing Director Rajan Anandan and Ratan Tata of Tata Sons. The business is chipping away at a rural premise, and it intends to reexamine the upkeep of hemp in Indian cultivation. Also, it gives natural substances to individual new organizations, Hempster and B.E. Hemp.

In February 2020, much medical care, based in India, supported the HempStreet, which mainly focuses on the use of hemp in the Ayurvedic medicines, which results in the brought up of $1 million pre-series A subsidizing. In addition, the organization will help in innovation development, research advancement, and dispatching another arrangement of Marijuana-based items by financing in it. According to Abhishek Mohan, one of the prime supporters of HempStreet, they have set new achievements for the therapeutic weed area in India. They are likewise fabricating blockchain innovation to follow the weed from seed to deal, taking out the danger that the Marijuana they develop will add to the substance misuse issue.

As per HempStreet's originator Mohan, universally, around one of every five, or 1.5 billion individuals experience the ill effects of persistent agony. India is anticipated to be positioned most elevated as far as constant torment cases by 2025, introducing a tremendous market for the organizations working to make therapies for ongoing agony with the help of cannabis (India's Cannabis and Market).

12.4 Hemp

Hemp, a fibrous plant which is always valued for its easy development and adaptability for the atmosphere (Fortenbery and supra). Traditionally, hemp strands have been helpful in making papers and rugs (Garland 1946). Even though rope and apparel keep on being produced using the same, and the fiber discovers its direction into such obscure items as composite boards found in cars, numerous cutting edge utilizes spin around biofuel and elective proteins from the more customary creature and soy sources (Fortenbery, supra note). Regardless of such reiteration of employments, the plant stays illicit for its growth and development in the U.S. (Monson 2009), even though it is lawful to import, have, and burn-through, in as much as the hemp material doesn't consider T.H.C. to enter the body (C.F.R. 2011).

12.5 History

Throughout the long haul, weed has been used for severe, current, helpful, and various purposes (Crowther et al. 2010; Potter 2014). Regardless, throughout the previous 150 years, significant social and political conflicts, including weed, had emerged all through the planet. Moreover, specialists extensively suggested weed focuses and colors in Europe and North America for a grouping of diseases from the 1850s through the underlying very few years of the twentieth century (Russo 2004). Regardless, in the U.S. during the mid-1900s, smoked weed (alluded to by different work-related conversation term Cannabis or marihuana) relates with explicit reproached ethnic and racial minorities, and different pieces of the country pre-incorporate its purposes (Bonnie and Whitebread 1999; Schlosser 1994). This, finally, achieved the foundation of the public authority Marihuana Tax Act of 1937 (Musto 1972), which constrained obligations and other administrative loads on the Cannabis "s clinical and non-clinical jobs.

VIn the U.S. not long after the arrival of the Act, and as the specialist's gear stretched out with numerous other medication decisions, interest in the gainful effects of weed and cannabinoids slowed down until pot use extended during the 1960s, accidental, and beyond question bound, with antiwar and other social difference improvements (Crowther et al. 2010). Young people around the United States attempted various things with Marijuana and various drugs, and different of them observed that weed was advantageous for explicit infirmities (Joy et al. 1999). Additionally, research in Israel by Dr. Raphael Mechoulam showed that tetrahydrocannabinol (T.H.C.) is a fundamental psychoactive piece of the Cannabis plant (Mechoulam et al. 1970).

These improvements had a few results. From one viewpoint, cultural caution over this expanded utilization of weed reignited worries about its negative impacts and incited examination into its psychoactive and possibly habit-forming properties (The Medicalization of Cannabis 2009). On the other, the idea of "clinical Cannabis" was conceived, and recharged interest in weed's clinical properties started to arise (Randall and O'Leary 1998) gradually.

In any case, steady bad attitudes about weed in explicit countries, including the U.S., completed the Single Convention on Narcotic Drugs (1961) (Mead 2014). As indicated by this Convention, weed and Cannabis tar were set in the most restrictive class 1. The gathering included was effectively anticipated (subject to some versatility for a party's "OK certainty" decisions) to deny their creation movement, bargain, etc.

The United States was associated with the Single Convention, and, after the Marihuana Tax Act was struck someplace close to the U.S. High court in Leary v. U.S. [395 U.S. 6 (1969)], Congress authorized the Controlled Substances Act of 1970 (C.S.A.), which joined past government acts and regulations managing the treatment of narcotics, energizers, hallucinogenic, and medications etc.

12.6 The classification of Marijuana Under the C.S.A.

The C.S.A. was authorized to a limited extent to execute the United States commitments under the Single Convention. Its motivations are given in Fig. 12.1.

Under the C.S.A., substances are ordered into five timetables, contingent upon their remedial advantage and capability to bring about misuse, redirection, reliance, and habit (Yeh 2012). Timetable I is the greatest prohibitive. Maryjane and T.H.C.s are already included in Schedule I, alongside other drugs such as mescaline, peyote, psilocybin, MDMA, and L.S.D. Opium and, for all intents and purposes, all narcotics, cocaine, amphetamines, and various substances are in Schedule II.

If all else fails, all substances and the items from those substances are organized in a comparable schedule. Regardless, there is a confined perspective for unmistakable preparation. For case, T.H.C. what is more, its isomers are in Schedule I, yet F.D.A.-supported plans of a T.H.C. isomer (delta-9) are in lower plans.

Under the C.S.A., Cannabis is characterized as:

Assuming we discuss the expression "marihuana," it alludes to all pieces of the plant Cannabis sativa L. if creating; its seeds; the pitch eliminated from any piece of such plant; and every one of the items shaped from it, salt, subordinate, mix, the availability of such plant, its seeds or tar. The bar mature stalks of such plant, fiber made from such stalks, oil or cake delivered utilizing the seeds of such plant, another compound, create, salt, subordinate, mix, or arranging of such mature stalks, fiber, oil, or cake, or the cleaned seed of such plant which is unequipped for germination.

As the definition shows, Cannabis fuses its combinations and auxiliaries, similarly to engineered structures. Like this, more than 100 cannabinoids that are available in the Cannabis plant are furthermore portrayed in Schedule I by the action of definition and not as a result of a thoughtful examination of their abuse potential. Just T.H.C. is autonomously and unequivocally recorded in the C.S.A. as a Schedule I substance (Brenneisen 2007).

Neither the C.S.A. nor the Code of Federal Regulations (the executing rules) portrays involving the substance for clinical use; be that as it may, the U.S. Drug Enforcement Administration (D.E.A.) has many guidelines that ought to be gotten to fabricate together recognized clinical use (Fig. 12.2):

- The medication’s science should be familiar, and it can be easily duplicated,
- There should be satisfactory wellbeing contemplates,
- There should be satisfactory and all around controlled investigations demonstrating viability,

- Qualified specialists should acknowledge the medication, and
- The logical proof should be generally accessible (Drug Enforcement Administration 1992).

So far, the government courts have maintained D.E.A.'s utilization of these models (D.E.A. 1994). The presence of episodic reports of clinical use (regardless of the number of) and the presence of state "clinical marijuana" laws (regardless of the number of) are not adequate to meet these standards. Be that as it may, F.D.A. endorsement of an item as a doctor prescribed medicine is adequate (yet not essential) to exhibit its acknowledged clinical use.

The plan I substances can be managed particularly in legislatively endorsed investigation programs [Investigational New Drug (IND) supported by F.D.A. also, D.E.A. Plan I research registration]. The situation with Timetable I includes restrictive essentials for security, recordkeeping, limit, and transport. The substances essential for Timetable I should not be taken out from the U.S. whether or not the patient is chosen a clinical primer.

12.7 An Escape from Schedule I

Rearranging in government law is, for the most part, directed through a managerial interaction (D.E.A. 2010, 2016; Hoffman et al. 2018). Under this interaction, the F.D.A. at first leads a complete appraisal of the substance's ability for maltreatment, also known as "eight-factor investigation" (8FA), because there are eight legal elements that bear on misuse potential. F.D.A.'s clinical and logical judgments limit D.E.A.; however, they may think about extra information, like the degree of misuse and redirection. Then, D.E.A. disseminates a proposed rule in the Federal Register, which allows the public warning and an opportunity to comment, item, or solicitation a final regulation appointed authority hearing. The D.E.A. responds to the public's comments and fights and a short time later, assuming that no strong requesting for a gathering is made, disperses a Final Rule rescheduling the thing or substance. Assuming that an interview request is made and permitted, the last rescheduling action can be delayed for a long while or more.

This revamping framework was begun by the Department of Health and Human Services/F.D.A. as another prescription underwriting measure or by a captivated person. 21 CFR 1308.44. Congress has every one of the privileges and capacity to pass another regulation for arranging, rescheduling, or interpreting the substance. There is no compelling reason to break down any abuse connected with the data or the results of a 8FA by Congress to go on with things like this.

12.8 The Status of Hemp Under Federal Law

Cannabis is an umbrella term, and various assortments containing different cannabinoid proportions and other substances, for example, terpene profiles—exist in nature due to rearing. Casually, one might say that Cannabis assortments might be delegated by the same token "drug-type" or hemp. In Europe, there are vigorous and grounded hemp manufacturing units (Vantreese 2002; Commission of the European Communities 2004). Notwithstanding, "hemp" is not characterized under European law. Maybe, specific pedigreed seed assortments might have been developed, which are used to generally rear for their fiber or seedthose containing a deficient level of T.H.C. (not over 0.2% by dry weight) (Commission of the European Communities 1989).

In the U.S., the hemp plant is not categorized and taken under C.S.A. Irrespective of this, it characterizes Maryjane, yet few proportions of the plant and their parts, including tail or fiber, cleaned seeds, and their arrangements —are not the part of the above said definition. Overall, the seeds which have been disinfected and the fibers obtained from the plant are not considered weeds, due to which these are mainly utilized for business purposes. Notwithstanding, there is a particular case for the exclusion. If "tar" is removed from any of the portions of the plant, then that would still be known as cannabis as we all know that all the cannabinoids are situated in resinous trichomes, which are situated on the inflorescences and upper leaves of the plant. Therefore, in principle, all extracts of cannabinoids from weed are characterized as marijuana (Potter 2014).

Notwithstanding, in December 2018, the 2018 "Homestead Bill" [The Agriculture Improvement Act of 2018 (Gottlieb 2018) was endorsed into law. According to the Farm Bill of 2018, hemp and its parts, considering the extracts and various cannabinoids obtained from the plant containing not more than 0.3% T.H.C. on dry weight, will be characterized as Cannabis plant. According to C.S.A. Act, the term "Hemp," which is so popular, is derived from the meaning of cannabis and is presently not considered as a controlled substance under government acts. The bill does not approve impedance with highway business (even though it does not certifiably approve such trade); probably, such trade is legitimate, essentially between states that permit such trade.

According to the Farm Bill of 2018, the development of hemp needs to be authorized. Its compliance must be directed with "state plans" as declared by a state that should include, in addition to other things, necessary arrangements for T.H.C. testing. On the off chance that a state does not wish to give an arrangement, the United States Department of Agriculture has all the rights to do as such. Likewise, the USDA has all the rights to provide the instructions and guidelines; however, the law expressly saves the current ward of the F.D.A.

12.9 The Development of State Cannabis Laws

In 1996, during the AIDS emergency in California, many electors endorsed a drive to decriminalize specific Marijuana-related exercises by explicit classifications of people. Suggestion 215, the Compassionate Use Act of 1996, permitted a passing tolerant and their respective guardian to develop and have weed for clinical purposes. C.A. Health and Safety Code, Article 2 (Cannabis). Oregon and Washington followed presently. The use of the substance for clinical purpose was restricted in the years that quickly followed since numerous patients and parental figures could not develop their Marijuana. Numerous doctors were reluctant to give the "proposals" essential to qualify the patient for lawful assurance.

Nonetheless, starting in around 2004, retail dispensaries started to show up, just as larger quantities of doctors could give proposals. In 2012, Colorado turned into a primary state that supports, by drive, the sporting or "grown-up use" of cannabis. Revision 64 (Use and Regulation of Marijuana); Article 18, §16 of the Colorado Constitution.

Many states and the District of Columbia have now released acts for the utilization of weed for treatment and remedial purposes (NCSL). Eleven states and the District of Columbia license sports and "grown-up use" weed (ProCon 2018a). Seventeen states just license items with high cannabidiol content and less THC5 content.

The laws made for the clinical use of weed have been accepted in various states with different terms and conditions (ProCon 2018b). In many states, the clinical use of the substance to the patient might be suggested by doctors, and some of the time different sorts of medical services suppliers, only in the cases when its use profit the (since cannabis is a Schedule I substance, doctors cannot endorse it). Doctors are frequently excluded from proficiency and other obligation that is prefaced exclusively on giving such a suggestion or exhortation. In any case, doctors can be at risk for giving suggestions that would harm the patient or the person taking it (Medical Board of California 2018) or that guides and abets an infringement of government law (Conant v. Walters 2002). For the most part, the clinical use laws incorporate a rundown of "qualifying" ailments with which a patient should be analyzed. These rundowns might be gotten from distributed logical investigations or case reports, from a declaration of people, support gatherings, and different sources. While they shift, these rundowns frequently contain conditions like epilepsy and malignancy.

The laws made by the state for the grown-up use of Marijuana fluctuate more or less as the clinical laws (ProCon 2018a, b). Aside from Vermont and D.C., which do not permit business deals—the other ten states permitting business action set up administrative frameworks that consider ownership and individual development just as business development and deals. All sporting states require people of 21 or above to have or develop cannabis. The amount of weed an individual can have ranges according to the area and state.Thus, the number of plants one can consume (for the most part, up to six). Across the sporting states, clinical cannabis laws are generally more lenient regarding individual belonging and development. They frequently grant patients to buy and develop more significant amounts as they access more intense items and partake in a lower charge rate.

As far as business frameworks, the ten expresses that grants highlight varying administrative frameworks; however, for the most part, they take into account state-authorized organizations to participate in business creation, dissemination, and deals of cannabis and cannabis items. Also, various states have various strategies for controlling their clinical and sporting frameworks. California, for example, includes a solitary, fit administrative system—the Medicinal and Adult-Use Cannabis Regulation and Safety Act (S.B. 94) (Business et al. 2016) [need a complete legal reference in the code]—however, partitions clinical with sporting in the isolated market influx and efflux. To some degree, unexpectedly, Colorado has separate protected changes for every framework while additionally isolating clinical and grown-up use in the discrete market flux.

Last, the quality control (counting testing) labs and name prerequisites for clinical and sporting are very lopsided, and there are chances that it might be non-existent in certain states (Klieger et al. 2017). A few states—like California—needs research facility for the testing of Marijuana as well as weed items to ensure that they satisfy quality and wellbeing guidelines, while different states—like Arizona (simply clinical)—do not have state-commanded testing (Milley 2018). Since, for doctor prescribed meds, these prerequisites are by and large controlled by F.D.A., it could be trying for states to foster such necessities and to discover sufficient assets to authorize them. Be that as it may, various worldwide standard-setting associations, like ASTM and AOAC, are occupied with creating principles for testing, quality control, and so on, of marijuana and cannabis items. A few marijuana quality control direction records are accessible from the American Herbal Products Association and the American for Safe Access, which are being utilized by various states for building up quality principles.

12.10 State and Federal Law Conflict

As per the Supremacy Clause of the U.S. Constitution, the government appropriates rather than overrides conflicting state laws, or in struggle, with administrative law in some ways (Mead 2014; Todd 2012). Nonetheless, the arrangement has been made in the government C.S.A., which mainly focusses on the drugs laws and acts that have been seized in the state as well as in case there would be a "positive clash" with the C.S.A. Without a doubt, laws, and acts related to the state are essential authorization expert relating to the drug-related offenses.

The state laws related to the weed that has been portrayed above- especially the early laws—are mainly known to decriminalize exercises and activities related to Marijuana under state criminal laws. They do not need a specific group of people or organizations to direct weed-related exercises. On the off chance that an individual/business wishes to keep away from an infringement of the government C.S.A., that individual or element can stay away from weed-related exercises out and out.

Therefore, most state and government courts that have considered this issue have noted that these state laws are not discredited by the C.S.A. (Brilmayer 2017; Guenthner 2017).

People and substances who decide to take part in cannabis-related exercises would abuse the government C.S.A. Notwithstanding, the national government, by and large, do not arraign people who have (or share) modest quantities of Marijuana, instead zeroing in their requirement needs on more significant weed business elements or medication dealing associations, especially those engaged with highway transport or unfamiliar importation (see the area "Purposes behind Limited Federal Enforcement of the Controlled Substances Act").

12.11 Reasons for Limited Federal Enforcement of the Controlled Substances Act

The Department of Justice (D.O.J.) validated a much less forceful role toward weed-related exercises than the past organizations which worked underneath Obama. In 2013, D.O.J. gave an update planned to direct United States lawyers in implementing circumspection (Cole 2013). The update expressed that it was anything but a D.O.J. need to make a requirement move against people or elements engaged with marijuana exercises if best the exercises were legitimate beneath state cannabis laws (regardless of whether clinical or sporting). Notwithstanding, D.O.J. would take into account authorization activity if the exercises contrarily affected eight explicit government interests6. This reminder was likewise implemented to the development and production of farther from the authority of the Farm Bill (US Attorney Marshall Letter to Rep 2018).

Past Attorney General Jeff Sessions dropped this notification (Sessions, 2018). Regardless, no extraordinary execution move has been made. This may be a result of various factors. A rectification to the Consolidated Appropriations Act of 2018 confines the D.O.J. from using any resources to hold states back from completing their clinical (not adult-use) Cannabis regulations. It thwarts DOJ/DEA and other power's work environments from using resources for forestall hemp-related brandishing exercises, which may be real under the Farm Bill. 115th Congress, Pub. L. No. 115–141. This Appropriations Act is accurate through September 2018 yet will presumably be loosened up by somewhere around one Continuing Resolutions. Additionally, there are Members of Congress who, for various reasons, would likely conflict with tremendous DOJ/DEA prerequisites against state-endorsed Cannabis works out. Finally, the country is defying a doctor-supported ongoing medication use crisis by and extensive, including opiates and DOJ/DEA have other execution needs. These parts could explain the shortfall of a decisive prerequisite of the C.S.A. towards weed-related works out. The present-day Attorney General William Barr has demonstrated that he will consent to the spirit of the Cole update (Hampson et al. 2003).

12.12 The Emergence of Cannabidiol

Individuals' anxiety about cannabidiol (CBD) has exploded in past a few years. CBD can be purchased on the web, in ganja dispensaries, and, dynamically, in staple and customary suppers assets shops and different shops. So how did CBD emerge into the public eye?

In contrast to T.H.C., CBD doesn't have euphoriant attributes (Jones et al. 2010). But the person and development of CBD have been known for a seriously prolonged stretch of time, the nearby assessment had been coordinated to examine its useful weed. Preclinical assessments proposed an expansive extent of potential applications (Jones et al. 2010), yet clinical examinations in a couple of signs, including epilepsy, had conveyed unbalanced and unconvincing results. At long last, in 2003, researchers at the National Institutes of Health (N.I.H.) got a patent attesting a technique for restoring infirmities added about by means of oxidative pressure, as neurodegenerative or ischemic contamination, with the organization's guide non-psychoactive cannabinoids (Jones et al. 2012).

In 2007, the lab of Professor Ben Whalley coordinated a movement of preclinical examinations that generously displayed that CBD had against seizure properties (Project 2018; Vogelstein et al. 2015). Once dissipated at coherent social occasions and appropriated, these examinations caused much income in the United States. Project CBD was molded by a bit of non-benefit, which publicized the results (Maa and Figi 2014). Cannabis cultivators, who had inadvertently discarded CBD-rich varieties in work to bring groupings affluent up in T.H.C., noticed. An as of late settled legitimate testing office assessed a plant not permanently set up that a couple of CBD-well off combinations remained, and different concentrates have been made. The Discovery Channel in 2011 shot one perceive dealing with a CBD focus on his youngster who had a disastrous kind of epilepsy (Discovery Channel, "Weed fight records"), and word went locally of gatekeepers with kids with correspondingly resolute epilepsies.

A California family, learning about CBD from their clinical guardian, endeavored a couple of sorts of things with their kid who had unmanageable epilepsy. Amazingly, he had an incredibly unbalanced response to those things. In any case, after scrutinizing the new preclinical investigation, they got that G.W. Drugs, the supporter of the assessment, had a standardized sort of CBD. Consequently, they attempted to interface the association to call for induction to the item (Potter 2013).

A Colorado family, who had seen the Discovery Channel segment on YouTube, similarly searched for CBD for their daughter, who furthermore had a stunning sort of epilepsy. They observed a wellspring of CBD close by, which diminished their daughter's seizures (European Hemp Industries Association 2018). Her exciting response was trapped in August 2013 in an account named "Weed," made by Dr. Sanjay Gupta of CNN. The program delivered a tidal wave of interest among families with similarly plagued kids. Families moved to Colorado looking for admittance to the item that came to be known as "Charlotte's Web"; states passed laws allowing ownership and at times assembling of high-CBD, low-THC items, and inside a couple of years, a wide assortment of CBD items were accessible, indicating to treat a large number of ailments.

Sources of Cannabidiol: As mentioned above, more noteworthy than 100 cannabinoids are found inside the plant. The Cannabis plant (counting hemp varieties) produces cannabinoids in glandular trichomes, which seem like little golf balls, now and again on a piece tail. These trichomes are assembled in the inflorescences and inside the top passes on to a more confined degree (ProCon 2018b; Lee 2016). The tail and seeds have no cannabinoids. In this way, even though hemp seed oil offers a respectable wellspring of Omega 3 and 6 unsaturated fats, it is obliged effectively no cannabinoids.

T.H.C. furthermore, CBD are the most extreme cannabinoid. During the 1970s, weed makers began to raise weed collections that conveyed consistently growing centralizations of T.H.C., since by far most acknowledged that every one of the effects of weed-each psychoactive and medicinal lay in the T.H.C. At the point, while CBD became "rediscovered" in the United States, as depicted over, the "CBD-well off" groupings that had been reachable to be taken out were "drug-type" varieties, rather than excellent hemp arrangements. Along these strains, directly following the 2014 Farm Bill, hemp groupings turned into the essential wellspring of CBD.

The quality hemp, i.e., those beginning in Europe, are not successful wellsprings of CBD. The main combinations contained 0.5–4.0% CBD by dry weight (Cascardi 2018), although, as a result of recreating, more current groupings could contain as much as 7–8% CBD (Hanus et al. 2005). Without a doubt, even at that more critical level, a colossal measure of hemp ought to be created to isolate a considerable proportion of CBD. Moreover, hemp is a "phytoremediator," i.e., it acclimatizes significant metals from the residue (F.D.A. 2018b). Therefore, it is miles principal that the improvement conditions be meticulously made due.

Cannabidiol may, regardless, be sired from drug-type arrangements of weed and a while later cleaned to wipe out a couple or the total of the T.H.C. Then again, CBD may be made utilizing a designed connection. Regardless, taking everything into account, it is vast that the maker chooses a designed fitting measure that conveys a comparable CBD isomer as that made by the plant. A substitute isomer could have a unique medicinal and toxicological profile by and large (Bonn-Miller 2017).

12.13 Legal Status of Cannabidiol Under the Controlled Substances Act

CBD is described in Schedule I of the C.S.A. since it's far viewed as a compound or subordinate of weed. 21 USC 802. In any case, as approved, the 2018 Farm Bill has debooked hemp as it is described under that regulation. In like manner, business venture movement with hemp (counting its concentrates and cannabinoids) is substantial. A DEA selection is not expected to expand hemp or lead studies with hemp. In any case, assume logical investigation, i.e., human subjects, is concerned. An investigational new therapeutic medication prohibition (IND) needs to, regardless, be opened with F.D.A., and the investigational thing should be created in a work environment that consents to colossal collecting practice (G.M.P.) prerequisites.

12.14 Cannabidiol and the FDA

FDCA drops any article from being presented in expressway business assuming it has far wanted to be used to cure, solace, commitment, or fix of an ailment or inconvenience—other than if that item has been pushed via F.D.A. as a specialist recommended drug. 21 U.S.C. stage 321(g)(1). In choosing "anticipated use," F.D.A. will break down a wide variety of sources—marks, notices, destinations, web essentially based media—to figure out an item's intentional use (F.D.A. 2018a). For instance, in 2015–2018, F.D.A. dispatched advice letters to creators of CBD things (presented on the web and in various shops), enlightening them that their items were misbranded and at last unlawful because of logical cases (F.D.A., Warning Letters, and Test Results for Cannabidiol-Related Products; (F.D.A. 2018a)).

Moreover, in 2015 and 2016, F.D.A. attempted countless CBD not permanently set up that north of a lot of them contained considerably less CBD than the many aggregates. Some had no CBD using any means, and some had more conspicuous proportions T.H.C. This quality-control concern has been declared by researching CBD things sold in dispensaries (Mister 2019).

In 2018, F.D.A. gave the essential CBD Warning Letter that depended somewhat on deficiencies in Good Manufacturing Practices (for drug things, not planned for dietary upgrades) (F.D.A. 2018a). F.D.A. moreover assigned, strangely, powerful things for which clinical cases have been being made.

Also, beginning in 2016, F.D.A. communicated in its Warning Letters that CBD is an answer in wholesome improvement or food. F.D.A. relied upon regions 21 USC 201(ff)(3)(B)(ii) and 21 USC 321(ff)(3)(B)(ii) of the FDCA. Which give that, assuming a substance is being thought about in enormous clinical starters, i.e., as an element of another drug application (N.D.A.) process], a change maker can't attempt to do a "smooth course" across the sizable and lavish N.D.A. degree through merging the substance into a feast or dietary improvement. The primary exclusion for this limitation is for a substance that was then advanced as a food or dietary upgrade before the clinical fundamentals began. The substance has certainly been publicized, or at least, not just present as unlabelled contamination. Moreover, a conflict can be made that the advancing should not have been violating an administration regulation like the C.S.A.

Different producers are trying to avoid F.D.A's. Statement concerning region 321(ff)(3)(B)(ii) by advancing their things as "hemp removes" (University of Mississippi 2018). In any case, many of these things give the CBD content on the name, site, or verification of examination (C.O.A.). It stays indistinct whether F.D.A. will lay out that these things are violative of the FDCA.

12.15 Cannabis-derived product going through the F.D.A. Approval Process

Broad communications research Marijuana much of the time fuse the contention that, as it is a Schedule I substance, weed cannot be investigated in the United States, extensively less move successfully employing the torments of the F.D.A. support measure. This declaration is, for the most part, fake. Schedule I status indeed grows the level of complexity for any investigation study. For example, all experts, whether or not clinical or preclinical-ought to get Schedule 1research enlistments. 21 C.F.R. region 1301.18. Then again, experts having D.E.A. Expert enlistments in Schedules 2–5 (which most specialists would have) may coordinate exploration in Schedules II-V as an "accidental development" to their Practitioner selections and do not ought to get additional enlistments or licenses. 21 C.F.R. area 1301.Thirteen. Since Marijuana is a controlled substance, an investigator cannot get weed from dispensaries or victims to test the beneficial effects of arrangements that victims may utilize. The Marijuana should come from an enlisted cultivator with D.E.A. as a Schedule I producer. An investigator with a Schedule I concentrates on enlistment should get Marijuana from some other D.E.A. registrant

Despite the D.E.A. Plan I enlistment, researchers ought to, all things considered, moreover get Schedule concentrates on licenses from the nation-controlled drugs authority. However, unfortunately, the product association for that Schedule I enrollments/licenses, including research site examinations, for the most significant part, do not emerge simultaneously, yet as an option are sequential, with the country, by and large, going first.

Additionally, the University of Mississippi is, at this point, the principal legislatively lawful United States wellspring of assessment grade Cannabis. The United States' "single source" position has commonly been established on its evident responsibilities under the Single Convention on Narcotic Drugs, 1961. Under the Single Convention, assuming that a signatory country emphatically endorses the local advancement of weed, the cannabis stocks ought to be exclusively moved by obliged by a public association. The United States public working environment is the National Institute on Drug Abuse (NIDA), a piece of N.I.H. NIDA contracts with the University of Mississippi to review grade Marijuana. For sure, even academic experts coordinating inspectors who began starters (I.I.T.s) need to get studies to Cannabis through NIDA.

This single-source essential is a particular issue for creators since individuals who wish to coordinate United States research on a weed surmised thing that will incite a N.D.A. ought to have the choice to foster a lot of a specific grouping of weed under comparative dependably controlled conditions. The investigational material used in the Phase 3 assessments should be identical to that used in the toxicology examines or interfacing studies ought to be coordinated. The Phase 3 material should be comparable to that used in the promoted thing (Wang et al. 2016). The average yearly outdoors yield from the University of Mississippi 12 segment of land "farm" is 500 kg of plant material (Ng 2015, Cannabis Research). Using assessment to convey adequate material for Phase 3 clinical primers and commercialization of its CBD object Epidiolex®, GW Pharmaceuticals fosters a risen-CBD imparting chemovar in a 45 segment of a land glasshouse.

The drug approval association announced in 2016 that it would select additional cultivators to convey research-grade weed, similarly as Marijuana to be used in the gathering of FDA-supported, weed-deduced things; in any case, as yet, no enrollments have been given (Vantreese 2002).

Regardless, this public office need applies just to Marijuana that is created inside that country's limit. Investigational weed things may be delivered Out of entryways the country and, inside the United States, imported underneath an IND for inspirations at the rear of the exploration. Two Marijuana-derived things (Sativex®and Epidiolex®) were explored inside the United States along these lines, and United States researchers have as of past due been permitted to utilize D.E.A. to import Cannabis cases from Canada for inspiration driving examinations.

Any weed deduced investigational thing should show quality, security, and sufficiency to achieve F.D.A. underwriting. Setting to the side the obstructions depicted north of, an incredible Cannabis thing, i.e., included major and minor cannabinoids, similarly, as terpenes and flavonoids, faces enormous standardization and quality control issues-join quality into the homegrown starting materials. Outside improvement can introduce the risk of debasement from adjoining pesticide and produced fertilizer use, bird droppings, etc. To ensure consistency in maryjane content, plants should be incited by clones or some near cycle rather than seeds. The improvement medium should be without profound metals. Ideally, no pesticides or fungicides would be used. Subtleties for the ordinary, natural substance (B.R.M.), plant drug substance (B.D.S.) (the arranged or removed material), and the finished natural medicine thing (B.D.P.) ought to be set and settled upon by the F.D.A. Since cannabinoids are accessible just in the plant's destructive construction (THCA and CBDA), the material should go through decarboxylation to dispense with a carboxyl social event if the impartial design (T.H.C. furthermore, CBD) is needed. This decarboxylation step can lead fittingly without leaving damaged decarboxylated material or corrupting the cannabinoids-particularly on a gigantic business scale (Wang et al. 2016). Assuming the estimation design requires extraction of the cannabinoids, the extraction cycle must not achieve a B.D.S. with staying hazardous solvents. An astounding crystallization measure is required if the finished thing is made from a detached cannabinoid (Wang et al. 2016). Robustness considers on both the B.D.S. furthermore, B.D.P. ought to maintain the end date, by and large, 2–3 years (Ng 2015).

F.D.A. has provided a guide to develop typically complex doctor-supported prescriptions (U.S. Dep't of Health and Human Services and US FDA 2016). While this course allows some versatility in the first place periods of investigation, when the thing shows up at Phase 3, the essentials are comparable to anything made from a singular produced molecule. Assuming that the thing is made only out of a cleansed cannabinoid, it relies upon every such essential.

Likewise, similarly as with any investigational thing, the F.D.A. will survey all collecting areas and cycles to ensure that a Quality Management System is set up and that all current incredible gathering practices (cGMP) for drug things are followed (Ng 2015). Again, this examination is thorough and can take 5–7 regular working days.

B.D.P. also, a cleaned cannabinoid thing should go through a total extent of preclinical and clinical security and feasibility testing, including drug/medicine and food/drug joint effort inspects. Additionally, on the grounds that a cannabinoid thing is gotten from the weed plant and is subsequently generally considered dynamic in the central tangible framework, the thing should go through a battery of tests to choose the degree (or not) of its abuse potential: receptor confining and preclinical assessments, similarly as an uncommon human abuse commitment review.N.D.A. has made it mandatory that producers/allies explore the assessments and make another Schedule accessible to F.D.A. F.D.A. then, at that point, explores the data given and, immediately on the help of the thing or substance, and after this, F.D.A. will ad-lib the idea and give it to D.E.A. Under the new Improving Regulatory Transparency in New Medical Therapies Act, 21 U.S.C. region 811(j), D.E.A. incorporates 90 days inside to evaluate all data and make a rescheduling decision, which is circulated in the Federal Register as a stretch last norm (IFR). This is because, under the IFR, there is plausible that a thing could be sold.

The prescription prerequisite association would coordinate the full definitive rescheduling measure portrayed previously, with public warning and the opportunity to comment, article, or request an administrative regulation-appointed authority hearing. It is unrealistic (but possible) at the culmination of this connection that D.E.A. would change the Timetable since all material intelligent evidence would most likely at this point have been considered by the associations in the basic rescheduling movement. In any case, on the off chance that an overall settlement requires a specific arranging course of action, D.E.A. will be giving a Final Rule (not an IFR or a Proposed Rule) regarding the rescheduling of the item.

For this situation, other N.C.E. things are incorporated (generally contained alone designed particle), the IFR would feasibly take a look after the collaboration, and the thing would be available to be advanced in all states. Having been reserved strangely by the D.E.A. during the N.D.A. cycle, no arranging has been finished by the state regulation connected with the N.C.E. thing. Due to the no planning of the things, there are opportunities for the proposal of the things by the specialists and allotted by pharmacies.

Regardless, this is not legitimate for Marijuana construed things. All states have embraced their variation of the public authority C.S.A. (Uniform Controlled Substances Act 1994), and Marijuana and its auxiliaries are remembered for Schedule I in high sums by state regulations. D.E.A. has changed the Timetable and Schedule connected with the utilization of the thing and the substance, which isn’t finished by some other power. Different specialists could require the reschedule, which the state association predominantly coordinates through an every so often deferred administrative cycle or by authorization endorsed by the state overseeing body. Various authoritative gatherings happen only for a long time every other year (National Council of State Legislatures 2018). This can delay patient permission to another weed decided thing by as much as two years in many states.

12.16 Conclusion

Cannabis or hemp, or Marijuana, is one of the most widely consumed illicit drugs worldwide and even in India. Many countries have approved cannabis for medicinal and research purposes, but India has many restrictions for its use. As per NDPS Act, if any person is found to be involved in the growth, sales, and purchase of the plant will be given imprisonment of up to 20 years or more. Even after so many restrictions, the hemp market in India is growing, and by 2025, it will reach 146.4 billion U.S. dollars. Various committees and parties are working to sanction Cannabis in India legally. In Feb 2020, Hempstreet was supported by Indian Ayurvedic medical care and Abhishek Mohan, which raised the Hemp market by 1 million U.S. dollars. As per the Controlled Substances Act, the part of the plant containing T.H.C. and cannabidiol will be considered under Schedule 1 of C.S.A. However, according to US DEA, the substance will be considered for clinical use if it is generally accessible, familiar, viable, and acknowledged. States having permission to grow the plant have adaptations as per the government and C.S.A.

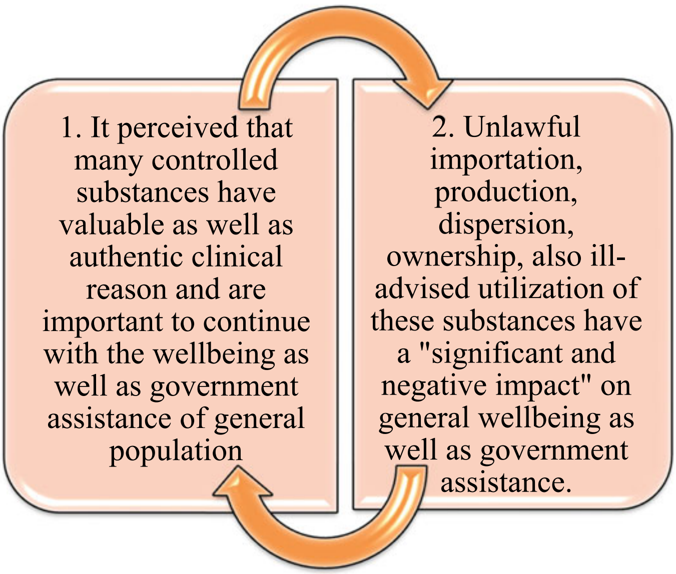

Fig. 12.1 Statements according to Controlled Substance Act

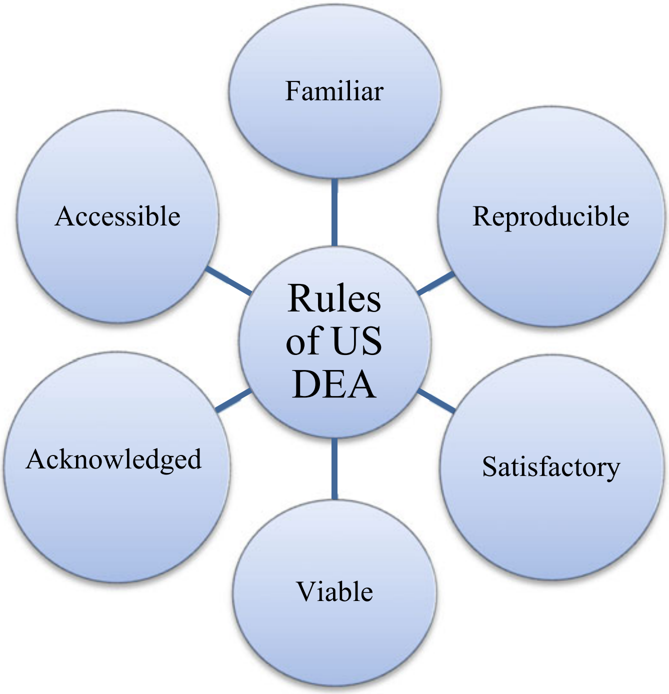

Fig. 12.2 Rules of U.S. Drug Enforcement Agency for the use of substances.

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See 21 C.F.R. § 1308.35(2011) (creating an exception for cannabis material containing T.H.C. that is not included in the definition of "marihuana"); D.E.A. Clarifies Status of Hemp in the Federal Register, U.S. D.E.A. (October 9, 2001), http://www.justice.gov/dea/pubs/pressrel/pr100901.html, Industrial Hemp Farming Act, H.R. 1831, 112th Cong. (2011)

See Fortenbery, supra note 5, at 98–101 (describing the multitude of uses for hemp)

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