Cannabis: Chemistry, extraction and therapeutic applications

Falguni Pattnaik [a,b], Sonil Nanda [b], Shobhangam Mohanty [c], Ajay K. Dalai [b,*], Vivek Kumar [a], Senthil Kumar Ponnusamy [d], Satyanarayan Naik [a]

[a] Centre for Rural Development and Technology, Indian Institute of Technology Delhi, New Delhi, India
[b] Department of Chemical and Biological Engineering, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
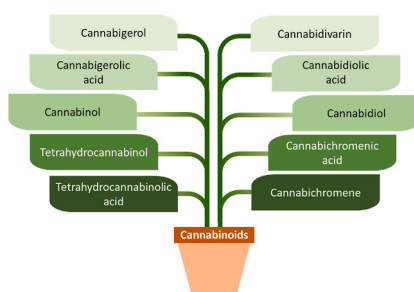[c] Department of Philosophy, Ravenshaw University, Cuttack, Odisha, India
[d] Department of Chemical Engineering, Sri Sivasubramaniya Nadar College of Engineering, Kalavakkam, Tamil Nadu, India

HIGHLIGHTS

- Cultivation and legalization of cannabis are regulated by governmental laws globally.
- Cannabinoids vary in terms of their physical chemistry and biochemistry.
- Cannabinoids have therapeutic effects against various health disorders.
- Medicinal effects are due to the interactions of cannabinoids with bio-receptors.
- Cannabinoids can be extracted from *Cannabis* plant products by eco-friendly extraction methods.

GRAPHICAL ABSTRACT

ABSTRACT

Cannabis, a genus of perennial indigenous plants is well known for its recreational and medicinal activities. *Cannabis* and its derivatives have potential therapeutic activities to treat epilepsy, anxiety, depression, tumors, cancer, Alzheimer's disease, Parkinson's disease, to name a few. This article reviews some recent literature on the bioactive constituents of *Cannabis*, commonly known as phytocannabinoids, their interactions with the different cannabinoids and non-cannabinoid receptors as well as the significances of these interactions in treating various diseases and syndromes. The biochemistry of some notable cannabinoids such as tetrahydrocannabinol, cannabidiol, cannabinol, cannabigerol, cannabichromene and their carboxylic acid derivatives is explained in the context of therapeutic activities. The medicinal features of *Cannabis*-derived terpenes are elucidated for treating several neuro and non-neuro disorders. Different extraction techniques to recover cannabinoids are systematically discussed. Besides the medicinal activities, the traditional and recreational utilities of *Cannabis* and its derivatives are presented. A brief note on the legalization of *Cannabis*-derived products is provided. This review

provides comprehensive knowledge about the medicinal properties, recreational usage, extraction techniques, legalization and some prospects of cannabinoids and terpenes extracted from *Cannabis*.

1. Introduction

Cannabis is a genus of plants in the family Cannabaceae. There are three recognized species of *Cannabis* (e.g., *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*) and more than 700 strains (Medical News Today, 2021). *Cannabis* has more than 400 bioactive components, which majorly include cannabinoids (or phytocannabinoids), polyphenols, flavonoids, terpenes, terpenoids, fatty acids, oils and waxes (Ashton, 2001; Mahlberg and Kim, 2004). The significant cannabinoids, which are researched for the assessment of therapeutic activities, are known as tetrahydrocannabinol, cannabidiol, cannabinol and their carboxylic acid derivatives. Cannabinoids and *Cannabis*-derived terpenes have promising therapeutic activities in treating certain diseases (e.g., cancer, tumors, Alzheimer's disease and Parkinson's disease) and neurological disorders (e.g., depression, anxiety, insomnia, epilepsy and seizures) (Kogan and Mechoulam, 2007).

As per the utility, *Cannabis* can be classified into drug-type *Cannabis* (containing a higher content of cannabinoids) and non-drug type or fiber-type *Cannabis* (with inadequate cannabinoid contents) (Salentijn et al., 2015). Drug-type *Cannabis* is broadly used for medicinal and recreational purposes, whereas non-drug type *Cannabis* is used for the extraction of high-quality natural fiber. Genetic markers and nucleotide polymorphisms can be used to distinguish drug-type and fiber-type *Cannabis* (Cascini et al., 2019).

In botanical aspects, *Cannabis* plants can be male, female or hermaphrodite (containing both male and female reproductive parts). Fig. 1 illustrates the aerial parts of the *Cannabis* plant including the male and female parts. The determination of gender in *Cannabis* plants is by heteromorphic chromosomes (presence of XY chromosomes in male

gametes). The identification of male and female *Cannabis* plants is difficult due to their morphological similarities. Hence, biomolecular techniques involved for gender detection screening of *Cannabis* plants at early developmental stages include sequence characterized amplified region (SCAR) markers (Techen et al., 2010), molecular cytogenetic characterization (Divashuk et al., 2014), polymerase chain reaction allele competitive extension (PACE) assays (Toth et al., 2020) and other molecular biology-based testing methods.

The leaves and female flowers of *Cannabis* plants are of significant interest because of the presence of secondary metabolites such as cannabinoids, flavonoids, terpenoids, alkaloids, lignans, anthocyanins and quinones (Gonçalves et al., 2019). The female flower is the largest reservoir of cannabinoids, usually stored in the glandular trichome spiked on the leafy surface of the flower. The male flower present in the hermaphrodite is responsible for the fertilization process by pollination, from which the female flower grows to seed. The seed, commonly known as hemp seed, is a potent plant source of omega-3 fatty acids (Watson et al., 2019). It is rare for *Cannabis* plants to form hermaphrodite flowers or bisexual inflorescence due to the flexibility of sexual phenotypes. Cross-pollination can affect the quality of secondary metabolites. To overcome such situations, male plants are removed, and the desired female plants are selected to avoid cloning for adequate secondary metabolite production.

Apart from the medicinal properties, *Cannabis* is consumed by more than 4% of the world's population, preferably aged between 15 and 64 years for recreational uses (Protti et al., 2019). The consumption of *Cannabis* for recreational purposes can be dated back to over 2500 years in many countries (Donahue, 2019). Recreational *Cannabis* practices remain illegal in most countries because of the abusive usage of some psychoactive cannabinoids (tetrahydrocannabinol), which causes psychosis and other mental disorders. However, in recent years, controlled recreational *Cannabis* is completely or partially legalized in certain countries or regions (e.g., Canada, a few states in the U.S., Georgia, Uruguay, South Africa and Australia) and decriminalized in a few other nations. However, medical *Cannabis* (or medicinal marijuana) has been legalized in many countries. Because of controversial aspects, the therapeutic applications of *Cannabis* are highly promising yet underutilized.

Due to the promising medicinal uses of cannabinoids, the legalization landscape throughout the world is rapidly evolving. There are very few review articles available on *Cannabis*, especially its chemistry, extraction methods of cannabinoids, medicinal uses, ethical concerns on usage and legalization. Moreover, narratives and reports on these aspects appear to be scattered in the literature. With a motivation to fill the gaps in the literature, the authors realize the timely necessity of developing a review article summarizing the chemistry of *Cannabis*, its socioeconomic impacts, geographical occurrence, biosynthesis and extraction of cannabinoids, therapeutic applications and legalization of *Cannabis*. This article also reviews various eco-friendly extraction techniques of cannabinoids using alcohol, butane, propane, supercritical CO_2, microwave, ultrasound and chromatography. This article also summarizes the interactions of different cannabinoids with respective receptors to demonstrate the therapeutic benefits towards acute and chronic conditions. This review article clearly provides an all-inclusive discussion on the fundamental and applied science and technology relating to *Cannabis*.

2. Geographical occurrence, ethnobotany and legalization of *Cannabis*

Cannabis is believed to be indigenous to Central and South Asia including countries such as India, Pakistan, Afghanistan, China,
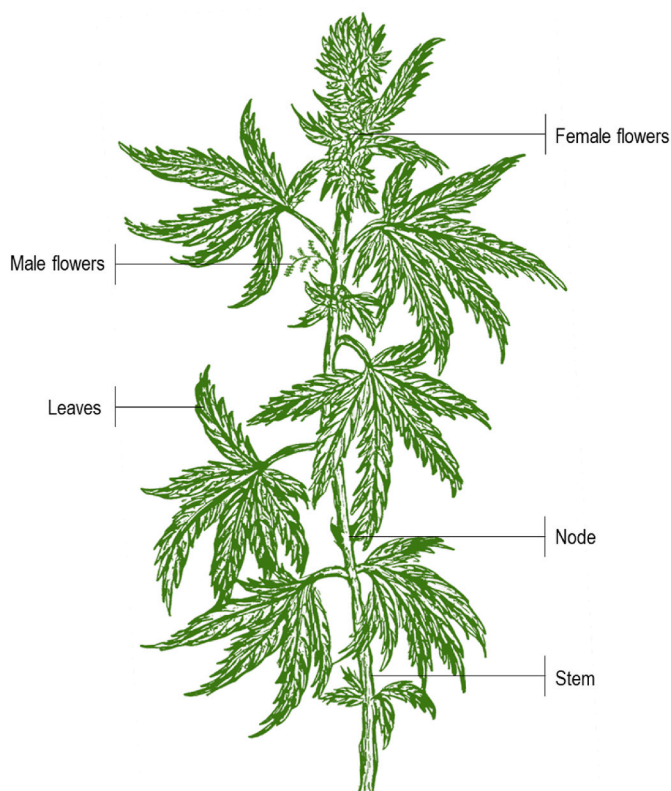

Fig. 1. Typical anatomy of a *Cannabis* plant showing male and female flowers (Note: This is a hand-drawn sketch made by Dr. Sonil Nanda).

Kazakhstan and Uzbekistan where it was considered as a native weed (Russo, 2007). *Cannabis* plants prefer a warm and humid climate, adequate sunlight exposure and nutrient-rich soil with a pH value of 5.6–6.2 for their growth. Depending on the climatic conditions, *Cannabis* plants can produce either resins or fibers. A warm and dry climate initiates a heavy production of resins, whereas mild and humid weather promotes fiber production in *Cannabis* plants (Bhatt, 2016). *C. sativa* (hemp) was considered an herbaceous perennial plant indigenous to Eastern Asia such as China, Korea and Japan. However, nowadays its cultivation is regulated worldwide for several usages like fiber, seed oil, resin and various other recreational and medicinal implementations. Some *Cannabis* plants are also adaptable to a broad spectrum of climatic conditions, which increases their potentiality for cultivation in various climatic zones worldwide (Decorte and Potter, 2015).

According to some traditional sacred scriptures in India, *Cannabis* was consumed by the ancient human civilizations as a source of inducing joy and happiness in humans (Gumbiner, 2011). In the religious texts of Hinduism in India, *Cannabis* is considered one of the five sacred plants and used in religious practices (Gumbiner, 2011). *Cannabis* was also used traditionally as a medication to cure and prevent many diseases,

conditions, syndromes and disorders (Touw, 1981; Russo, 2005; Kuddus et al., 2013). Apart from India, China and Tibet also have a rich history of using *Cannabis* in traditional medicine. For example, *Cannabis* was used as a reliever of pain during childbirth or labor and to cure insomnia (Touw, 1981). With diaspora and migration of people, the traditional culture of *Cannabis* was also widespread across the world. In the Middle East, *Cannabis* was used in the form of hemp seed oil for its aromatic fragrances (Touw, 1981; Warf, 2014). Although *Cannabis* has a rich traditional history, its legalization and decriminalization in various countries for both recreational and medicinal purposes has sharply enhanced its regulated cultivation worldwide.

Different countries have different levels and platforms of legalization of *Cannabis* cultivation and use. Partial legalization is the most widely and practically used concept in most countries. In a few countries, minor possession of recreational *Cannabis* is often refrained from being criminalized, examples of which include Belgium, Belize, Bermuda, Bolivia, Colombia, Czech Republic, Ecuador, Jamaica, Malta, Mexico, Netherlands, Paraguay, Trinidad and Tobago, and a few others (ICLY, 2020). On the contrary, a few countries in the Middle East and Asia have stringent laws to enforce substantial penalties and punishments for the

Table 1
Chemical structures and therapeutic effects of some common cannabinoids.

Cannabinoids	Chemical structure	Therapeutic effects	References
Cannabichromene (CBC)		Chronic pain, migraine and skin disorders	Oláh et al. (2016); Jiang et al. (2018)
Cannabichromenic acid (CBCA)		Anti-inflammatory, anti-microbial and analgesic agents	Oláh et al. (2016)
Cannabidiol (CBD)		Insomnia, anxiety, post-Ebola syndrome, Huntington's disease, Parkinson's disease, Alzheimer's disease, inflammatory bowel diseases and cancer	Aviello et al. (2012); Esposito et al. (2013); Reznik et al. (2016); Shannon and Opila-Lehman (2016); Maccarrone et al. (2017)
Cannabidiolic acid (CBDA)		Nausea, cancer and anti-inflammatory agent	Bolognini et al. (2013); Pellati et al. (2018)
Cannabidivarin (CBDV)		Seizures, Rett syndrome, nausea and autism spectrum disorder	Rock et al. (2013); Whalley et al. (2015); Vigli et al. (2018); Zamberletti et al. (2019)
Cannabigerol (CBG)		Inflammatory bowel disease, bladder dysfunction, Huntington's disease and tumors	Borrelli et al. (2013); Valdeolivas et al. (2015); Pagano et al. (2015); Deiana (2017)
Cannabigerolic acid (CBGA)		Metabolic disorders, cancer and cardiovascular diseases	Havelka (2019)
Cannabinol (CBN)		Anti-microbial agent	Appendino et al. (2008)
Tetrahydrocannabinol (THC)		Cancer, tumor, insomnia, loss of appetite, nausea and Alzheimer's disease	Häuser et al. (2017); Kleckner et al. (2019)
Tetrahydrocannabinolic acid (THCA)		Anti-inflammatory, Antiemetic, neuroprotective and anti-proliferative agent	Zirpel et al. (2018); Naderi et al. (2020)
Tetrahydrocannabivarin (THCV)		Loss of appetite, tumor, insomnia and neurological disorders	Deiana et al. (2012)

possession of *Cannabis* (High Times, 2021).

Canada is one of the developed countries to legalize the use of *Cannabis* for medicinal and recreational purposes. The Cannabis Act in Canada creates a stringent legal framework for controlling the cultivation of *Cannabis* plants, production of *Cannabis* products; distribution of feedstock, products and byproducts; as well as sale and possession of *Cannabis* across Canada (Government of Canada, 2020b). Moreover, Canada and most other countries have strict laws and task forces relating to *Cannabis* on several aspects to check its illegal production, use and sale, unlicensed sellers, ethical conduct of *Cannabis* industries, possession, national and international transport and drug-impaired driving, to name a few. According to a recent statistic, there are more than 329,038 licensed users of medicinal *Cannabis* in Canada (Government of Canada, 2020a). Several other countries namely Argentina, Australia, Barbados, Belgium, Belize, Brazil, Canada, Chile, Colombia, Czech Republic, Cyprus, Denmark, Ecuador, Finland, Georgia, Mexico, Netherlands, South Africa and Uruguay have legalized the use of *Cannabis* for recreational and medical purposes under controlled and regulated terms (Menon, 2020). In the U.S., the obligations imposed by the law for controlled sales, possession and consumption of *Cannabis* products for medicinal and recreational purposes vary in different states (Hammond et al., 2020). On the other hand, India has stepped forward for the controlled and regulated cultivation of medicinal and fibrous *Cannabis* plants in states like Uttarakhand and Madhya Pradesh primarily for pharmaceutical uses (Abraham, 2019; Joshi, 2020).

3. Chemistry of cannabinoids

Cannabis or marijuana is exclusively known for its bioactive constituents such as cannabinoids and terpenes. Although terpenes are present as the trace component in *Cannabis* plants, their extensive medicinal properties make them as essential as cannabinoids. Besides, *Cannabis* also contains polyphenols, flavonoids, chlorophylls, omega-3 fatty acids and other bioactive molecules. This section discusses the molecular structure and biosynthesis of various cannabinoids, their chemical or medicinal significances and interactions with the endocannabinoid system. The molecular structures and therapeutic applications of some notable cannabinoids are collectively presented in Table 1. Fig. 2 illustrates different cannabinoids derived from *Cannabis* plants.
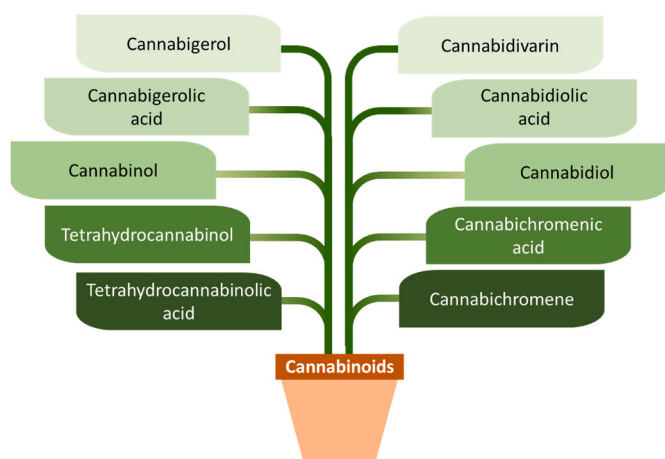
Fig. 2. Some common cannabinoids derived from *Cannabis* plants.

3.1. Cannabichromene

Cannabichromene (CBC) is a non-psychoactive cannabinoid found as a trace molecule in *Cannabis* plants. CBC is a decarboxylated form of cannabichromenic acid (CBCA) synthesized by the catalyzing effect of CBCA synthase (Thomas and ElSohly, 2016). The decarboxylation reaction of CBCA in *Cannabis* plants is facilitated by warm climatic conditions and ultraviolet rays from the sun, which removes the CO_2, thus producing CBC (Havelka, 2017). The non-psychoactive nature of CBC has attributed its weak interaction with the cannabinoid receptor type 1 (CB_1 receptor) in human beings specifically for psychoactivity (Pollastro et al., 2018). However, CBC binds with transient receptor potential cation channel subfamily V member 1 (TRPV1) and the transient receptor potential ankyrin-type1 (TRPA1) receptors with a greater affinity in humans, which makes the CBC effective for the removal of pain (Romano et al., 2013). While TRPV1 functions in the detection and regulation of body temperature (Wang and Siemens, 2015), TRPA1 is a potential target for migraine therapy (Jiang et al., 2018). Furthermore, CBC is an effective agent for skin treatments like acne owing to its anti-microbial activity (Oláh et al., 2016).

3.2. Cannabichromenic acid

Cannabichromenic acid (CBCA) is a cannabinoid synthesized from cannabigerolic acid (CBGA), including cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA) in the presence of the enzyme CBCA synthase (Morimoto et al., 1997). CBCA is eventually decarboxylated into CBC. The literature on the clinical specifications of CBCA is relatively scarce. However, CBCA is effective as an anti-inflammatory and anti-microbial cannabinoid with analgesic activities (Oláh et al., 2016).

3.3. Cannabidiol

Cannabidiol (CBD), considered the second most popular cannabinoid after THC, is non-psychoactive. CBD is structurally different from cannabidiolic acid by a carboxyl group (–COOH). Therefore, it is the decarboxylated form of CBDA formed under the influence of heat. CBD consists of an alkylresorcinol group like CBDA. The pharmacodynamics reveal that CBD has the least affinity towards the CB_1 or CB_2 receptors and it also estranges the CB_1 agonists. Hence, CBD does not create any euphoric effect like that of THC (Mechoulam et al., 2007). CBD can counteract the euphoric effects made by THC, which can reduce or balance its psychoactive effects (Morgan et al., 2010).

CBD is also effective for the treatment of several diseases like insomnia, anxiety, post-Ebola syndrome, Huntington's disease, Parkinson's disease, Alzheimer's disease, inflammatory bowel diseases and cancer (Aviello et al., 2012; Esposito et al., 2013; Reznik et al., 2016; Shannon and Opila-Lehman, 2016; Maccarrone et al., 2017). Another exciting feature of CBD is its affinity for the serotonin system (5-HT$_{1A}$ receptor), which clarifies the anti-depressant and stress removal activities (Zanelati et al., 2010).

3.4. Cannabidiolic acid

Cannabidiolic acid (CBDA) is a structural analog of cannabidiol (CBD) with a carboxylic acid (–COOH) group at the second position of the alkylresorcinol ring. Like CBD, CBDA is non-psychoactive. CBDA is converted to CBD by heating via a decarboxylation reaction. *Cannabis* plants found in the higher altitude regions and the colder climatic regions could constitute CBDA with a higher percentage. CBGA can be considered as the precursor cannabinoid of CBDA. CBGA is converted to CBDA by the catalytic effect of CBDA synthase through the cyclization of the aliphatic chain (Taura et al., 1996).

Unlike most cannabinoids, CBDA does not interact with the CB_1 or CB_2 receptors rather than acting indirectly with the endocannabinoid

system by inhibiting the cyclooxygenase-2 (COX-2) enzyme (Pellati et al., 2018). This intensifies the inflammation due to the injury and cancer. Along with other cannabinoids, CBDA increases the appetite and reduces nausea and vomiting in several animal models (Bolognini et al., 2013).

3.5. Cannabidivarin

Cannabidivarin (CBDV) is a cannabinoid structurally similar to CBDA and CBD. It consists of an alkylresorcinol ring and a lower number of carbon atoms than that of its family members such as CBDA and CBD. CBDV is considered a non-psychotropic cannabinoid as it does not cause euphoria (elevation of mood). It is mostly found in *Cannabis indica*, a species predominantly found in Asian and African countries (Iannotti et al., 2014). In the context of the medicinal uses of CBDV, the anti-convulsant activity can make it an effective drug for the treatment of seizures (Hill et al., 2012). Besides the single occurring seizures, this phytocannabinoid is effective for the treatment of recurrent seizures like epilepsy and other neuro disorders (Whalley et al., 2015). Some studies illustrate the use of CBDV in the treatment of Rett syndrome, nausea and autism spectrum disorder (ASD) in children (Rock et al., 2013; Vigli et al., 2018; Zamberletti et al., 2019).

3.6. Cannabigerol

Cannabigerol (CBG) is a non-psychoactive cannabinoid and the decarboxylated form of cannabigerolic acid (CBGA) (Aizpurua-Olaizola et al., 2016). Unlike CBGA, CBG does not undergo any catalytic conversion into other cannabinoids due to the absence of the carboxyl group (–COOH) (Taura et al., 2007). CBG is effective in the treatment of inflammatory bowel disease, bladder dysfunction, Huntington's disease, tumors and certain types of cancers in animal studies (Borrelli et al., 2013; Valdeolivas et al., 2015; Pagano et al., 2015; Deiana, 2017). Furthermore, CBG shows several instances of anti-bacterial activities and has been tested on relieving muscle contractions.

3.7. Cannabigerolic acid

Cannabigerolic acid (CBGA) is considered the precursor of various cannabinoids like THCA, CBDA and CBCA. CBGA is the carboxylic derivative of CBG. Like other cannabinoids, CBGA is also present in the glandular trichome. However, the concentration of CBGA is dependent upon the kinetics of its conversion into other cannabinoids. As shown in Fig. 3, CBGA is biosynthesized in the *Cannabis* plant through an enzymatic bioconversion process. In the first step, hexanoyl-CoA and malonyl-CoA are reacted in the presence of two enzymes like tetraketide synthase (TKS) and olivetolic acid cyclase (OAC) to form olivetolic acid (Gagne et al., 2012). Olivetolic acid is known to be the primary precursor in the formation of CBGA through prenylation reaction in the presence of aromatic prenyltransferase and geranyl pyrophosphate (GPP) (Fellermeier and Zenk, 1998).

CBGA is the precursor for the biosynthesis of THCA, CBDA and CBCA in the presence of tetrahydrocannabinolic acid (THCA) synthase, cannabidiolic acid (CBDA) synthase and cannabichromenic acid (CBCA) synthase, respectively (Fig. 4) (Taura et al., 1996; Morimoto et al., 1998; Sirikantaramas et al., 2005). CBGA has proved its effectiveness for the treatment of metabolic disorders, colon cancer and several cardiovascular diseases (Havelka, 2019).
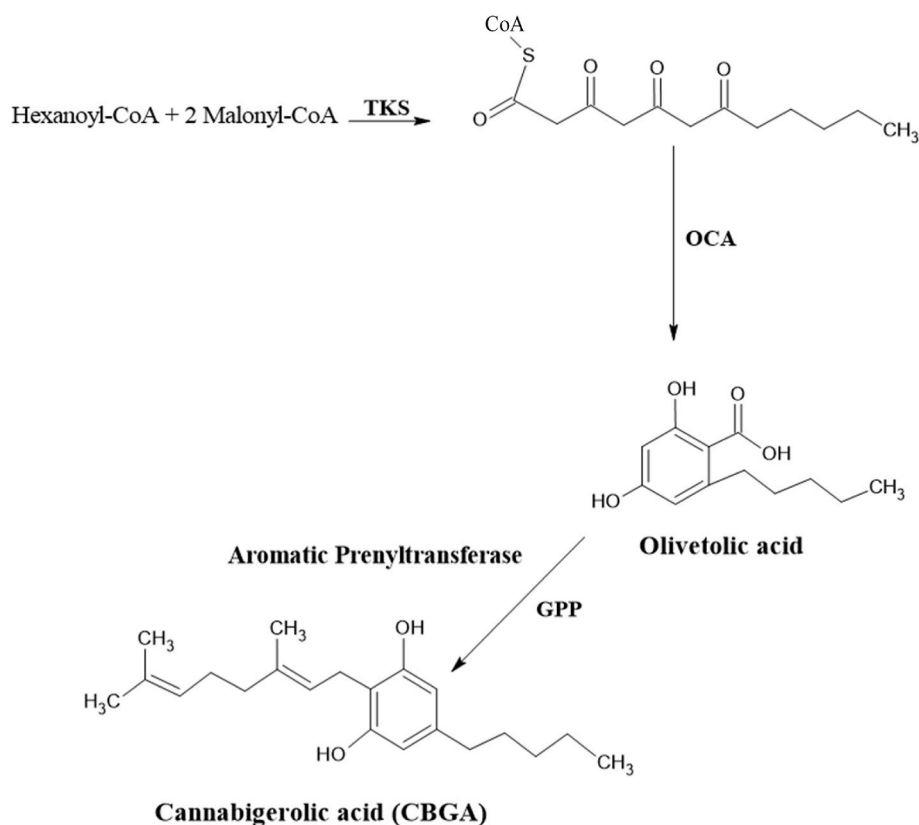

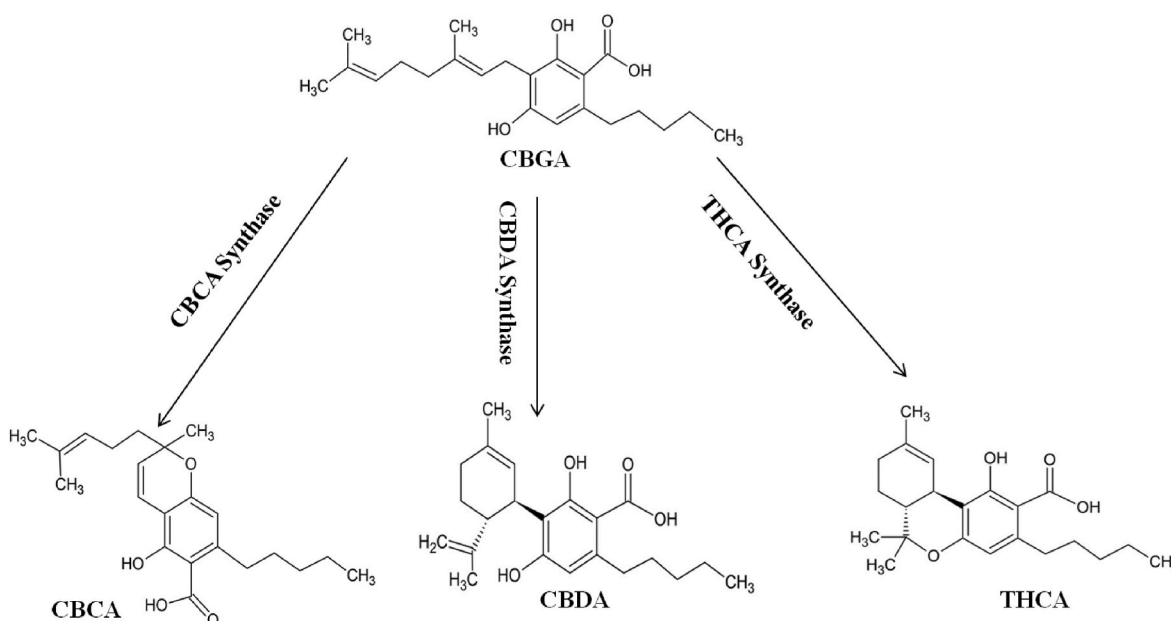**Fig. 3.** Biosynthesis of cannabigerolic acid from olivetolic acid.

Fig. 4. Enzymatic conversion of cannabigerolic acid (CBGA) into cannabichromenic acid (CBCA), cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA).

3.8. Cannabinol

Although cannabinol (CBN) is a mildly psychoactive cannabinoid, its sedative nature increases its popularity. CBN is formed in the *Cannabis* plant by the oxidative conversion of a specific part of Δ^9-tetrahydro-cannabinol (THC). CBN has anti-bacterial and anti-inflammatory effects and is also used as an efficient alternative to THC due to its intoxicating nature for increasing the appetite (Appendino et al., 2008; Galatonov et al., 2018). An antibiotic-resistant bacterium such as methicillin-resistant *Staphylococcus aureus* can be potentially countered with cannabinol with its anti-bacterial activity (Appendino et al., 2008).

3.9. Tetrahydrocannabinol

Δ^9-tetrahydrocannabinol (THC) is said to be one of the significant and potent cannabinoids having psychoactive activity. Usually, hashish (resin), marijuana and drug-type *Cannabis* contain a higher content of THC, whereas hemp (fiber-type) contains lower levels of THC (Protti et al., 2019). In the *Cannabis* plant, THC is synthesized from cannabi-gerolic acid and tetrahydrocannabinolic acid (THCA) as intermediates. Olivetolic acid reacts with geranyl pyrophosphate in the presence of a specific enzyme to produce CBGA. CBGA is subsequently converted to THCA through cyclization of the ring and further decarboxylated to form THC. The highly lipophilic nature of THC makes it rapidly soluble in the blood, which increases its potency for the treatment of cancer, tumor, insomnia, loss of appetite, nausea and Alzheimer's disease (Häuser et al., 2017; Kleckner et al., 2019). Besides these phytocannabinoids, there is an endocannabinoid system in the human body, which secretes the molecules (endocannabinoids) to activate the cannabinoid receptors namely CB_1 and CB_2 (Hippalgaonkar et al., 2011). Tetrahy-drocannabivarin (THCV) is a homolog of THC except that it has a propyl side chain instead of a pentyl side chain as in the case of THC. Hence, THCV exhibits similar effects than THC.

3.10. Tetrahydrocannabinolic acid

Tetrahydrocannabinolic acid (THCA) is a non-psychoactive and non-toxic cannabinoid (Iffland et al., 2016). THCA is the carboxylic acid derivative of THC and can be biosynthesized from CBGA in the presence

of THCA synthase (Sirikantaramas et al., 2004). In the live *Cannabis* plants, THC is present as THCA, which is converted to THC by decar-boxylation when dried or stored for a prolonged time. THCA has anti-inflammatory, anti-emetic, neuroprotective and anti-proliferative activities along with efficient curative properties for insomnia and muscle spasms (Zirpel et al., 2018; Naderi et al., 2020).
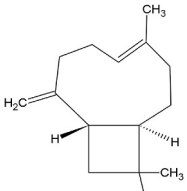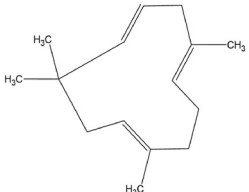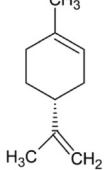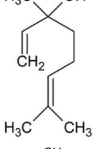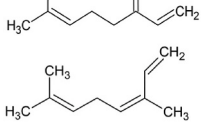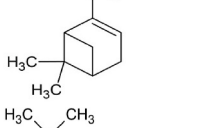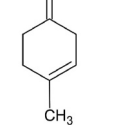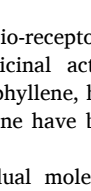
3.11. Terpenes

Several well-known terpenoids like myrcene, limonene, car-yophyllene, terpinolene, humulene, linalool, pinene and ocimene are present in certain types of *Cannabis* plants (Casano et al., 2010; Nuuti-nen, 2018; Stone, 2021). Table 2 summarizes some notable terpenes derived from *Cannabis* plants along with their therapeutic activities. Before the medicinal analysis of *Cannabis*-derived terpenes, the structure and molecular features of the terpenes should be well understood. Ter-penes are the class of organic molecules with a specific number of isoprene units collectively known as terpenoids or isoprenoids. More-over, some of the terpenes like caryophyllene and humulene are isomers to each other (de Almeida Borges et al., 2013). *Cannabis*-derived ter-penes are effective for the treatment of various diseases like cancer as well as neurological and digestive disorders through anti-oxidative, anti-inflammatory, anti-microbial, anti-convulsive and neuroprotective activities (Nuutinen, 2018). Furthermore, terpenes can be more effective for the treatment of mood and anxiety disorder by entourage or syner-gistic effects along with certain cannabinoids (Ferber et al., 2020). The major use of the essential oils is found in aromatherapy, which helps in elevating mood.

4. Therapeutic uses of *Cannabis*

The therapeutic or medicinal activities of *Cannabis* or cannabinoids can be broadly found in the treatments of various diseases, disorders, syndromes and health conditions like epilepsy, Alzheimer's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), skin dis-eases, cancer or their subsequent effects like appetite loss, chronic pain and nausea. The mechanism of the medicinal activities of a cannabinoid relies on its interactions with specific receptors in a human biological system. Fig. 5 depicts the different therapeutic effects of cannabinoids

Table 2
Summary of some promising cannabis-derived terpenes.

Terpene	*Cannabis* strain (common name)	Other sources	Chemical structures	Therapeutic activities	References
Caryophyllene	• Girl Scout Cookies (GSC) • Purple punch	• Black pepper • Clove • Cinnamon		• Anti-inflammatory • Anti-convulsive (by interaction with CB_2 receptor) • Neuroprotective activities	Mediavilla and Steinemann (1997); Gertsch et al. (2008); Stone (2021); Booth et al. (2017)
Humulene	• Gelato • GSC	• Hops		• Insomnia • Anti-depression • Anti-anxiety • Useful for digestive disorders	Novak et al. (2001); Stone (2021)
Limonene	• Strawberry banana • Wedding cake	• Lemon • Orange		• Anti-depressant • Anti-inflammatory • Anti-oxidative • Anti-viral	Mediavilla and Steinemann (1997); Lopresto et al. (2014); Stone (2021); Booth et al. (2017)
Linalool	• Kosher Kush	• Lavender		• Effective sedative • Anti-convulsive • Anti-nociceptive • Anti-oxidative • Anti-microbial	Stone (2021); Lewis et al. (2018)
Myrcene	• Ocean Grown (OG) Kush • Blue dream	• Lemongrass • Mango		• Anti-inflammatory • Anti-oxidative	Lorenzetti et al. (1991); John et al. (1999); Stone (2021); Booth et al. (2017)
Ocimene	• Clementine	• Mint • Basil		• Anti-microbial • Anti-depressant • Anti-inflammatory	Brenneisen (2007); Stone (2021); Booth et al. (2017)
Pinene	• Big smooth	• Pine • Rosemary		• Anti-inflammatory • Anti-allergic • Anti-tumor • Anti-oxidative	Günnewich et al. (2007); Jiang et al. (2011); Stone (2021); Booth et al. (2017)
Terpinolene	• XJ-13 • Jack Herer	• Cumin • Lilac		• Anti-nociceptive • Anti-oxidant • Anti-inflammatory	Mediavilla and Steinemann (1997); Beis et al. (2000); Novak et al. (2001); Stone (2021)

like THC, CBD and CBN through interactions with bio-receptors present in the human metabolic system. Various medicinal activities of *Cannabis*-derived terpenes such as myrcene, caryophyllene, humulene, pinene, linalool, limonene, terpinolene and ocimene have been illustrated in Table 2.

The endocannabinoid system secretes individual molecules like anandamide (a lipid-based neurotransmitter), which partially agonists the CB_1 receptor. This CB_1 receptor is present in the peripheral or central nervous system and modulates the pain, mood and other physiological activities (Huffman, 2005; Moore and Labroots, 2018). THC along with CBN, CBG and CBC are also effective against the CB_1 receptor creating similar effects by the endocannabinoid anandamide (Järbe et al., 2002; Morales et al., 2017). Another cannabinoid receptor, particularly the CB_2 receptor is present in the immune system regulates the immune responses by major interaction with the endocannabinoid, 2-archidonoylglycerol (Basu et al., 2011). There are several phytocannabinoids

which agonist or partial agonist the CB_2 receptor such as THC, CBN, CBG and CBC (Morales et al., 2017). The phytocannabinoids mimic the pathway of endocannabinoids in the direction of several therapeutic or medicinal activities.

The anti-convulsant activity of cannabinoids, especially CBD and THC are employed for the treatment of seizures and epilepsy (Russo, 2017). A seizure is an instantaneous or abrupt change in the human brain in an uncontrollable manner with symptoms like confusion, fear, anxiety, muscle contraction and unconsciousness. THC can decrease the effect of seizures by being an agonist to the CB_1 receptor.

Although there is no such anti-epileptic mechanism of CBD, the antiseizure effect may be due to its interaction with several non-cannabinoid receptors like 5-HT$_{1a}$, TRPV-1 (vanilloid receptor), GPR55 (orphan G-protein coupled receptor) and α3 or α1 glycine receptors attributed to the anti-inflammatory and neuroprotective effects (Devinsky et al., 2014). Recently, the U.S. Food and Drug Administration
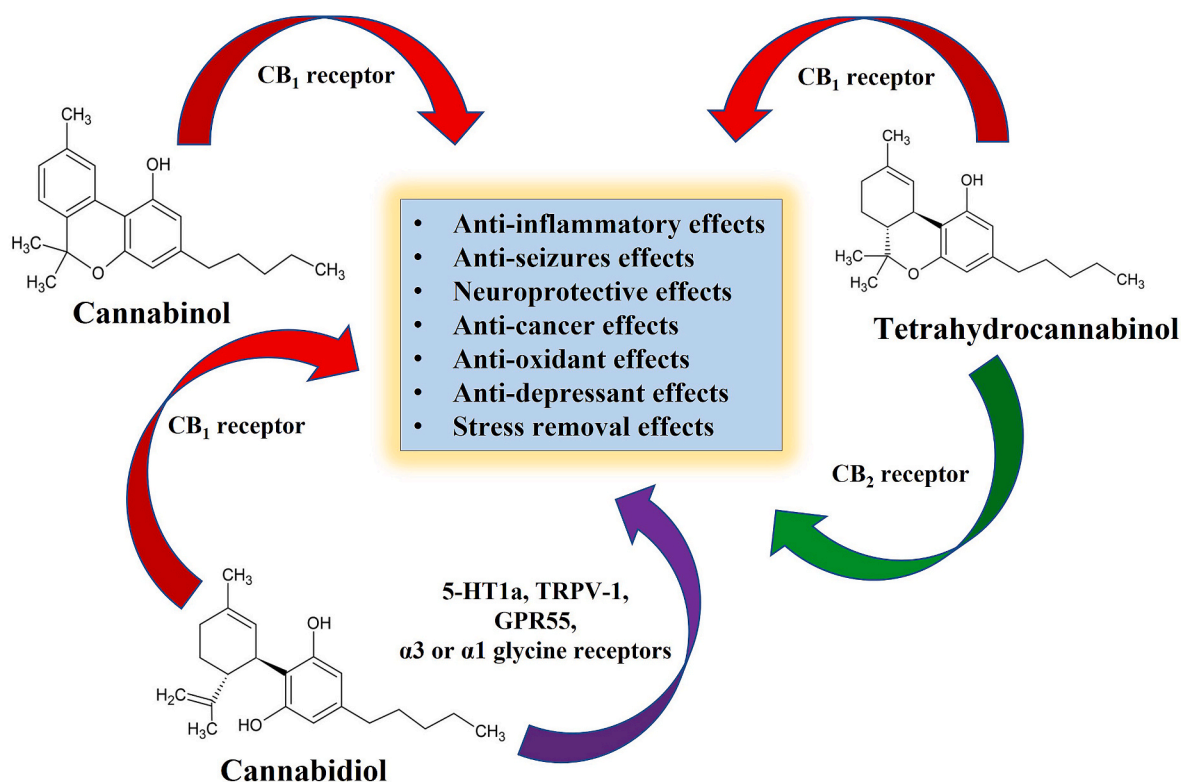
Fig. 5. Therapeutic effects of tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) through interaction with different bio-receptors in the human metabolic system.

has approved an exclusively CBD-based medicine named Epidiolex, which is used as a therapeutic drug for the treatment of severe syndromes of seizures such as Lennox-Gastaut and Dravet syndrome (U.S. Food and Drug Administration, 2018). Besides, THC can also be implemented for the treatment of seizures or epilepsy (Russo, 2019).

Alzheimer's disease is a well-known neuro disorder affecting mainly old-aged people with symptoms of memory loss. This syndrome is caused by the accumulation of β-amyloid peptide and hyperphosphorylation of tau protein, which collectively results in neuron cell death and simultaneously weakens the communication process between the neuro cells (Rajmohan and Reddy, 2017). Certain cannabinoids can hinder the subsequent activities caused by Alzheimer's disease such as oxidative stress and inflammation in the neuron cells while repairing damaged cells. To decrease the psychoactive properties and reveal anti-inflammatory activity, the CB_2 receptor agonists are effective to reduce Alzheimer's disease by modulating the accumulation of β-amyloid peptide and the hyperphosphorylation process (Aso and Ferrer, 2016).

Parkinson's disease is considered an intense neuro disorder that affects movement. In Parkinson's disease, symptoms like the stiffness of movement (bradykinesia), tremor and rigidity are the consequence of the death of nigral neurons and degradation of dopaminergic neurons (García-Arencibia et al., 2009). A study performed by Lastres-Becker et al. (2005) suggests that the neuroprotective action of cannabinoids can be effective for the treatment of Parkinson's disease. In this study, the authors have mentioned the effectiveness of THC for the reduction of dopaminergic injury with a mechanism related to both non-cannabinoid and CB_1 receptors. The medicinal implementation of CBD also proves its anti-oxidative and anti-inflammatory effect in treating Parkinson's disease. Moreover, the equivalence of CBD with THC for the treatment of Parkinson's disease can be considered as an advantage due to the non-psychoactivity of the former. Thus, CBD can be used in the treatment of Parkinson's disease for a prolonged period (Lastres-Becker et al., 2005).

PTSD syndrome is a kind of mental disorder after experiencing a petrified event that symptomizes nightmares, insomnia, excessive anxiety and staging of the traumatic incident in mind. Cannabinoids, especially THC and CBD are effective for curing stress and anxiety. These cannabinoids can reduce the anxiety level allowing sound sleep and gradually preventing the petrified memories and thoughts. THC is also effective in preventing the incidences of nightmares (Loflin et al., 2017).

Unlike THC, CBD is a non-psychoactive cannabinoid. CBD is used for treating acne, a skin disorder caused by the enhanced production of sebum and inflammation of the oil-producing sebaceous glands present under the mammalian skin. The mechanism of anti-acne activities relies on the decreasing of excessive lipid production by the sebaceous gland. Besides CBDs, several other non-psychoactive cannabinoids like CBC, CBDV and THCV are also effective for treating acne by reducing arachidonic acid influenced lipogenesis, termination of proliferation process and anti-inflammation (Oláh et al., 2016). Owing to its anti-inflammatory and analgesic properties, CBD oil can be used in the treatment of sleep disorder, stress, persistent pain and dermatological problems like epidermolysis bullosa (Chelliah et al., 2018).

Cannabinoids have also been investigated for the treatment of cancer and subsequent symptoms like nausea, loss of appetite, anxiety and pain. The activation of cannabinoid (CB) receptors and other non-cannabinoid receptors are important for anti-tumor and anti-cancer activities (Dariš et al., 2019). Therefore, along with the endocannabinoid ligands, phytocannabinoids or cannabinoids can be considered for cancer treatment because of their interaction with specific biological receptors. Cannabinoids possess anti-inflammatory and anti-oxidative activities, which are major functional properties for the inhibition of cell growth or tumor cell proliferation, thus preventing different types of tumors and cancers. These anti-tumor or anti-cancer activities are well established for animal models, which can have potential effects on human clinical trials as well (Sánchez, 2021). Cannabinoids, especially THC and CBD (or their synthetic equivalents) are implemented in preventing nausea, vomiting, loss of appetite and anxiety as the side effects of chemotherapy

Table 3
Summary of notable extraction methods for cannabinoids.

Cannabis strain (Common name)	Extraction method	Extraction conditions	Product yield	References
C. sativa L.	Ultrasound-assisted methanol extraction	• Extraction time: 15 min • Power: 130 Watt • Methanol: 80%	• Total phenolics, flavonoids and cannabinoids: 10.9 wt%	Agarwal et al. (2018)
C. sativa L.	Chloroform extraction	• Extraction time: 1.5 h • Sequential extraction for 30 min each for 3 batches with same sample	• Total cannabinoids: 152 mg/g • THC: 62 mg/g • CBN: 20 mg/g • CBD: 60 mg/g	Fairbairn and Liebmann (1973)
C. sativa L.	Ultrasonic extraction	• Solvent (methanol:chloroform) = 9:1 vol/vol • Reaction time: 10 min • Ultrasonication time: 2 min	• THCA: 229–234 mg/g	Hazekamp et al. (2004a)
Cream Caramel (CC), Medicine Woman (MW), Amnesia (A), New York Diesel (NYCD)	Ethanol-assisted supercritical CO_2 extraction	• Ethanol: 20% vol/wt • Temperature: 35 °C • Extraction time: 10 min • Flow rate: 1 mL/min • Pressure: 10 MPa	• THCA: 113 mg/g (from CC) • THCA: 119 mg/g (from MW) • THCA: 117 mg/g (from A) • THCA: 114 mg/g (from NYCD)	Aizpurua-Olaizola et al. (2014)
Hashberry (*C. sativa*:*C. indica* = 50:50)	Ethanol-assisted supercritical CO_2 extraction	• Pressure: 34 MPa • Temperature: 55 °C • Ethanol: 10 wt%	• Total cannabinoids: 18.5 wt% • THC: 26% • THCA: 50% • CBD: 1%	Rovetto and Aieta (2017)
Hemp nut	Microwave-assisted solvent extraction	• Extraction time: 30 min • Feedstock:methanol = 1:12 wt/vol	• Total cannabinoids: 6.1 μg/g • THC: 2.5 μg/g • CBD: 2.6 μg/g	Chang et al. (2017)

(Guzmán, 2003).

Besides various *Cannabis*-derived cannabinoids and terpenes, oils extracted from the hemp seed contain omega-3 fatty acids (α-linolenic acid) and omega-6 fatty acids (linoleic acid) in a ratio of 1:3 with a negligible content of psychoactive molecules (Brennan, 2020). These omega fatty acids are useful for lowering blood pressure, relieving pain and reducing the amount of bad cholesterol (low-density lipoprotein) subsequently decreasing the probability of heart stroke or any other cardiovascular disease (Brennan, 2020).

5. Extraction of bioactive compounds from *cannabis*

Extraction is the process of mass transfer from the host matrix to the medium. In an extraction process, a medium and the driving forces are two essential factors (Nanda et al., 2021). Based on the types of extraction medium and driving forces, the extraction processes are categorized into different classes or modes. Some extraction methods also operate without the extraction media (solvent-free extraction). Table 3 summarizes different extraction methods for cannabinoids.

5.1. Alcohol-based extraction

Owing to the presence of hydroxyl groups, cannabinoids can be considered relatively polar molecules. Therefore, polar solvents such as methanol, ethanol, acetonitrile, dimethylsulfoxide and iso-propanol are used as the extraction medium for certain cannabinoids (Namdar et al., 2018). Ethanol-based extraction of cannabinoids is a widely acceptable extraction process worldwide both for medicinal and recreational *Cannabis*. The molecular structure of ethanol is the primary factor for dissolving a wide variety of constituents. Ethanol is a solvent with a hydroxyl group and a hydrocarbon chain, which makes it a universal solvent. Usually, the alcohol extraction process can be performed with or without the implication of heat. The hot extraction process, implemented using a Soxhlet apparatus, operates with the heating of the solvent followed by the condensation of volatile vapors. Soxhlet extraction is the most efficient solvent extraction process due to the less time consumption, higher mass transfer, enhanced solubility and higher yields (Nanda et al., 2013).

The solvent extraction process can also be challenging in the extraction of chlorophylls and waxes, which need various other processes for the purification of cannabinoids (Flockhart et al., 2010). Furthermore, with the high heating, some carboxylic group-containing molecules (e.g., THCA, CBDA, CBCA and CBGA) are decarboxylated, which may hamper the compounds of interest. Hence, seeing the polarity and efficacy of ethanol, cold extraction can be implemented efficiently to reduce the mass transfer of unwanted content and the occurrence of undesired reactions (June-Wells, 2020).

Apart from ethanol, various other solvents can be used in the extraction of cannabinoids such as dichloromethane, chloroform, toluene and trimethyl pentene (Fairbairn and Liebmann, 1973; Schmidt and Coco, 2003). One of the pioneering studies by Fairbairn and Liebmann (1973) demonstrated the extraction of cannabinoids from *C. sativa* L. using chloroform as the extraction solvent. The total yield of cannabinoids from the chloroform extraction of *C. sativa* L. in 1.5 h was 152 mg/g, which constituted THC (62 mg/g), CBD (60 mg/g) and CBN (20 mg/g). However, for the extraction of food-grade and medicinal bioactive compounds, the solvent used for the extraction process should be completely non-hazardous.

5.2. Supercritical CO_2 extraction

Supercritical fluid extraction is one of the modern methods of bioactive compound extraction with several advantages over conventional solvent extraction (Reddy et al., 2014). Although the solvent extraction process holds a larger yield of extractives, supercritical fluid extraction is a highly selective and convenient fractionation of the product (Viganó et al., 2016; Pattnaik et al., 2021a). Supercritical CO_2 extraction is tremendously favorable due to the enormous availability of CO_2, operations at ambient temperatures and solvent (CO_2) recyclability (Liu et al., 2014). Supercritical CO_2 refers to the state of CO_2 above its critical point temperature and critical pressure of 31.1 °C and 7.4 MPa. Fig. 6 illustrates the phase diagram of CO_2 where it possesses higher diffusivity and lower density stimulating higher mass transfer efficacy.

Depending upon the temperature and pressure, the solubility of the constituents in supercritical CO_2 can be tailored. The selectivity of different cannabinoids in supercritical CO_2 is due to the differences in polarity and molecular weight. Therefore, the temperature and pressure of the process can be tailored depending upon the extraction of specific cannabinoids. Moreover, supercritical CO_2 extraction of cannabinoids produces a lower content of chlorophyll unlike other solvent extraction processes, which decreases the cost of downstream processes (Hemp Gazette, 2021). Furthermore, liquid CO_2 or subcritical CO_2 at a lower pressure (<10 MPa) can be used for the extraction of various aromatic compounds like caryophyllene, humulene, limonene, farnesene and
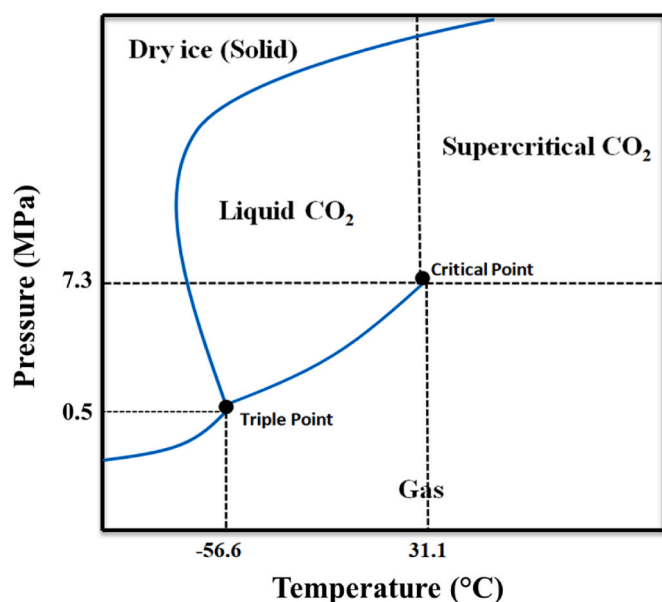
Fig. 6. Phase diagram of CO_2.

eucalyptol (Naz et al., 2017; Pattnaik et al., 2021b).

From the molecular structure of the cannabinoids, the presence of the hydroxyl group creates a polar moiety in the cannabinoid molecules. Therefore, the inclusion of a polar solvent like ethanol can assist the supercritical CO_2 extraction process by enhancing the yields of cannabinoids with a reduced extraction time. Ethanol-assisted supercritical CO_2 extraction of cannabinoids performed by Rovetto and Aieta (2017) determined that the use of co-solvent in the extraction of cannabinoids can increase the yield, enhance the extraction efficiency and lessen the use of CO_2. In their work, the authors performed ethanol-assisted supercritical CO_2 extraction of a hybrid strain of *Cannabis* (*C. sativa* and *C. sativa* = 50:50) at the CO_2 pressure of 34 MPa and a temperature of 55 °C with 10 wt% ethanol (Rovetto and Aieta, 2017). The yield of total cannabinoids was found to be 18.5 wt% of which THC, THCA and CBD constituted 26%, 50% and 1%, respectively. In another study, Aizpurua-Olaizola et al. (2014) performed ethanol-assisted supercritical CO_2 extraction of various strains of *Cannabis* such as Cream Caramel, Medicine Woman, Amnesia and New York Diesel using CO_2 pressure of 10 MPa with the flow rate of 1 mL/min at a temperature of 35 °C for the extraction time of 10 min in the presence of 20% ethanol. From this extraction process, THCA yields were estimated to be 113, 119, 117 and 114 mg/g from Cream Caramel, Medicine Woman, Amnesia and New York Diesel strains, respectively. By investigating the extraction parameters of these two studies, it can be concluded that by increasing the amount of ethanol, the CO_2 pressure can be decreased significantly. Therefore, supercritical fluid extraction or ethanol-assisted supercritical fluid extraction of cannabinoids can be considered as one of the competent and eco-friendly methods of extraction over conventional product separation processes.

5.3. Butane or propane-based extraction

Butane and propane usually exist as gases at room temperature, but they can be compressed to a liquid state to facilitate the extraction due to their relatively moderate non-polar nature. The mild nature of the solvent can efficiently extract the cannabinoids and the terpenoids due to the moderate polarity of the molecules. The cannabinoids extracted using butane and propane as compressed solvents are called butane hash oil (BHO) and propane hash oil (PHO), respectively (Meehan-Attrash and Strongin, 2020). In this extraction process, the gases are purged into the extraction vessel and pressurized to convert them into liquid form.

The system is then heated to a specific temperature to expedite the extraction of cannabinoids from the *Cannabis* samples.

In butane or propane-based extraction, the gases are compressed into the extractor and condensed by an ice-cold water jacket. After the extraction, the gases are expelled from the extraction vessel, recovered and reused. This extraction process is similar to that of liquid CO_2 extraction. There are several advantages of butane or propane extraction over supercritical CO_2 extraction. Unlike supercritical CO_2 extraction, butane or propane extraction yields more significant contents of flavoring agents like terpenoids, which enhance the flavor of *Cannabis* extract (Moreno et al., 2020).

Butane or propane-based extraction methods have some disadvantages such as flammability of gases and the presence of toxic traces of gases in the extracts (Al-Zouabi et al., 2018). However, propane is less toxic than butane (Sugie et al., 2004). Therefore, it is considered a safe solvent for food and flavor industries to extract flavors, essential oils and other value-added compounds from the spices.

5.4. Microwave-assisted solvent extraction

Microwave-assisted pretreatment, digestion, heating and other methods involve electromagnetic irradiation of frequency between 300 MHz and 300 GHz (Sarker et al., 2021). The difference between conventional solvent extraction and microwave-assisted extraction is the implementation of the driving force (microwave) in the extraction process. The conventional solvent extraction process is carried out with convection heating, whereas in microwave-assisted extraction, the solvent extraction is assisted by microwave heating. There are several advantages of microwave-assisted solvent extraction over conventional extraction such as uniform heating, lower extraction time, high performance, more economical usage of solvent and a greener approach (Chang et al., 2017). The microwave extraction process is operated by the two-fold mechanism of heating, which is the ionic conduction and rotational energy of the molecules.

Chang et al. (2017) implemented the microwave-assisted process to extract cannabinoids from hemp nuts. They also compared the cannabinoids yield from microwave-assisted extraction with other extraction methods involving solvents, supercritical fluids and ultrasound. The microwave-assisted extraction revealed the highest yield of cannabinoids constituting a higher amount of CBD and THC. In this study, the researchers performed microwave-assisted solvent extraction using methanol as the extraction solvent where the feedstock-to-methanol ratio was 1:12 (w/v). With a reaction time of 30 min, the total cannabinoid yield was found to be 6.1 μg/g constituting majorly THC (2.5 μg/g) and CBD (2.6 μg/g) (Chang et al., 2017).

Drinić et al. (2020) also found microwave-assisted extraction as an innovative and faster extraction process in comparison with other methods. In their study, the optimization of the extraction process was done by the Box-Behnken design. The extraction process was performed using various experimental parameters such as ethanol concentration, extraction time and feedstock-to-solvent ratio. The highest cannabinoid yield was reported to be 38.1 mg/mL constituting CBD (0.25 mg/mL), THC (0.03 mg/mL) and various phenolic compounds at an ethanol concentration of 30% (v/v), feedstock-to-solvent ratio of 5 g/mL for an extraction time of 20 min. In another extraction condition (ethanol concentration of 70%, extraction time of 20 min and feedstock-to-solvent ratio of 5 g/mL), the highest yields of CBD and THC were reported to be 1.84 and 0.06 mg/mL, respectively with the total yield of cannabinoids as 27.6 mg/mL. It can be concluded that in the microwave-assisted ethanol extraction of *Cannabis*, the yield of cannabinoids, especially CBD and THC is dependent on the ethanol concentration irrespective of the extraction time and feedstock-to-solvent ratio.

5.5. Ultrasound-assisted solvent extraction

Ultrasound is the driving force for the recovery of bioactive

components including cannabinoids in assisted solvent extraction processes (Nanda et al., 2014; De Vita et al., 2020). This process has similar advantages similar to that of microwave-assisted extraction such as lower power consumption, less solvent consumption, higher productivity and eco-friendliness (Chang et al., 2017). In this process of extraction, ultrasound disrupts the waxy cuticles around the glandular trichomes, which contain a significant amount of cannabinoids, thus dissolving the extracted molecules (Brighenti et al., 2017). Apart from the cannabinoids, ultrasound-assisted solvent extraction efficiently recovers polyphenols, terpenoids and flavonoids (Agarwal et al., 2018).

In a study by Agarwal et al. (2018), 80% (v/v) methanol was used as a solvent to extract cannabinoids from *C. sativa* L. using ultrasonication with the power of 130 W for a reaction time of 15 min. Nearly 10.9 wt% of extractives were recovered which contained phenolic compounds, flavonoids and cannabinoids. In another study, Hazekamp et al. (2004a), performed ultrasonic-assisted solvent extraction of cannabinoids from *C. sativa* L. using a solvent system consisting of methanol and chloroform at a volumetric ratio of 9:1 for a reaction time of 10 min. The ultrasonication time was reported to be 2 min in the total reaction time. Approximately 229–234 mg/g of THCA, one of the major cannabinoids, was obtained with the potential to be further decarboxylated to obtain THC.

5.6. Solvent-free extraction

Different alcohols, supercritical CO_2, butane, propane and other solvents are used to extract cannabinoids. However, certain solvent-free extraction processes are also available to extract cannabinoids. Cannabinoids are majorly amassed in the glandular trichome present on the leafy part of the *Cannabis* plant where they are protected from the outer atmosphere by the waxy layer (Mahlberg and Kim, 2004). Hence, it is comparatively easier to extract the cannabinoids from glandular trichomes by applying mechanical forces by pressing and heating without taking any organic solvents. In such solvent-free extraction processes, the glandular trichomes are separated from the leafy part of the pant by mechanical sieving or centrifugation of plant biomass in ice-cold water. The separated glandular trichomes are called kief. This separated kief is placed between two hot metal plates with moderate temperatures and limited pressure to melt the waxy material and produce a sticky *Cannabis* concentrate enriched with cannabinoids and terpenoids (known as rosin) (Cold Creek Extracts, 2021). As a replacement for kief, high-quality *Cannabis* flowers and buds are also used to carry out solvent-free extraction.

5.7. Chromatography-based extraction

Several separation methods are implemented for the isolation of cannabinoids among which include chromatographic methods such as centrifugal partition, mixed-mode column chromatography and high-pressure liquid chromatography. Other chromatographic methods such as overpressured layer chromatography and mixed-mode column chromatography can be implemented for the separation and isolation of the cannabinoids (Oroszlan et al., 1987; Hung et al., 2015). Furthermore, molecular distillation can be explored to isolate cannabinoids based on their molecular weight and boiling point.

In centrifugal partition chromatography, cannabinoids are separated based on their partition coefficient. The stationary phase is immobilized in the column by centrifugation while the mobile phase is purged into the column at an elevated pressure to reach a high flow rate. By using a chromatographic technique, Hazekamp et al. (2004b) established two different methods to separate the acidic and neutral cannabinoids. Acidic cannabinoids such as THCA, CBGA and CBDA were separated from *Cannabis* extract using a two-phase system constituted by hexane, methanol and water with a volumetric ratio of 5:3:2. Hexane was the stationary phase immobilized with centrifugation at 500 rpm. Methanol/water (3:2 vol/vol) was the mobile phase at a flow rate of 4

mL/min. The methanol-to-water ratio was increased to 4.5:0.5 to fractionate the acidic cannabinoids. Similarly, for the neutral cannabinoids such as THC, CBN, CBD and CBG, another two-phase system was implemented with the combination of hexane, acetone and acetonitrile at a ratio of 5:2:3 (Hazekamp et al., 2004b).

Different preparative or semi-preparative high-pressure liquid chromatography columns are also used to separate valuable cannabinoids from *Cannabis*. Martinenghi et al. (2020) isolated CBDA and CBD from *Cannabis* extract using a semi-preparative reverse phase C18 column using step-gradient solvent flow. The mixture of methanol and water was taken as the mobile phase. After the separation process, the fractions were further purified using column chromatography with a solvent system of petroleum ether-ethyl acetate whose ratio was varied from 8:2 to 5:5. The purified fractions were characterized by mass spectrometry and applied for the anti-microbial activity against methicillin-resistant *S. aureus* (Martinenghi et al., 2020).

6. Conclusions

The traditional history of *Cannabis* can create new insights into the recovery of natural products for potential implementation for treating various chronic and acute diseases, syndromes, conditions and disorders. Therapeutic applications of the different cannabinoids can be demonstrated through their synergistic interactions with different biological receptors in human beings. The medicinal activities of various cannabinoids in animal models can be further explored to ascertain their benefits to humans. Several extraction processes involving solvents such as alcohols, supercritical fluids, butane, propane as well as driving forces viz. microwave, ultrasound and heating can be used to extract cannabinoids and other bioactive compounds from *Cannabis* extracts. This review paper gives collective information about the geographical, physicochemical, medicinal and socio-economic features of *Cannabis* and different bioactive compounds, especially cannabinoids and terpenoids.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors would also like to state that the discussion on the recreational and medicinal properties of *Cannabis* provided in this article is solely based on the published literature and online sources available in the public domain. The views, opinions, commentaries and perspectives provided in this article do not, in any way, endorse any particular geographical location, group, organization, cultivation, production, sales, possession, consumption, usage, commercialization as well as concerning laws and legislation relating to *Cannabis* and its derived products in any country.

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