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Bioactive Terpenoids in Cannabis: A Critical Review

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Terpenoids, also referred as terpenes have been used extensively in drug related industry due to pharmaceutical properties. These have driven the emergence of studies on terpenoid from plant. *Cannabis sativa* plant is one of the common natural sources of terpenoids and cannabinoids. The cannabis produces and accumulates terpenoids in grandular trichomes. The grandular trichomes are abundant on the surface of female inflorescence. About 140 terpenoids are known in cannabis and some of them have medicinal potential in treatment of pain, inflammatory, cognition, epilepsy and immune functioning. The biological effect of terpenoid from cannabis is mainly attributed to limonene, myrcene, pinene, linalool, ß-caryophyllene, caryophyllene oxide, nerolidol and phytol. The different composition of terpenoids are responsible in exhibit the unique organoleptic properties and influence the medicinal qualities of difference cannabis strains and varieties. This article aims to review the cannabis plant for terpenoid, terpenoid biosynthesis and its pharmacological activities. The terpenoids from cannabis could be valuable natural resources for drug development.

Keywords: ***Cannabis sativa*, terpenoids, cannabinoids, inflammatory, organoleptic**

INTRODUCTION

Cannabis, with the scientific name of *Cannabis sativa* L., is also known as marijuana. It produces a resin that contains many terpenes and cannabinoids metabolites (Booth & Bohlmann, 2019). They come from the family Cannabaceae or Cannabidaceae, which is a family of dicotyledonous plants that contains only two genera Humulus and Cannabis. *Humulus lupulus* is a perennial climbing herb widely cultivated for its inflorescences, used to flavour beer. *C. sativa* (hemp) is cultivated in temperate and tropical regions for its fiber, and for the drug, which is also known for various names such as ganja, charas, bang, and pot (Hodgson, 2012). The plant has been used for its drug effects in India for almost 3500 years. Cannabis varieties that are low in psychoactive cannabinoids are used for the production of fibre and oilseed (Booth & Bohlmann, 2019). Cannabis is indigenous and originating from Central Asia and upper southern Asia (Clarke & and Merlin, 2013). Even though cannabis has been illegal in many countries, it has slowly evolved and being legalised in many countries. On the 1st November 2018, unlicensed cannabis based products were moved from Schedule 1 to Schedule 2 in the UK, enabling them to be prescribed for the first time. Canada too legalized marijuana in 2018. Nowadays, certain state in United States, cannabis is widely available and advertises in non-medical setting such as coffee shops and tobacco stores (Levinsohn and Hill, 2020).

The genus Cannabis comprises one species, *Cannabis sativa* L. (Figure 1), with highly polymorphic subspecies *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. These subspecies differ in their phenotypic characteristics and chemical profile (Small, 2017). The inflorescence is the main product of cannabis. Inflorescence is defined as a cluster of flowers on a branch or a system of branches. In horticultural practice, Cannabis is propagated by rooted cuttings, with two bracts and a solitary flower primordium developing in the axil of each stipulate leaf.According to Hazekamp et al. (2016), cannabis interbreeding has contributed to the enormous phenotypic and chemical diversity of cannabis cultivars that are in use today.

Cannabis contains hundreds of specialized metabolites with potential bioactivity, including cannabinoids, terpenes, and flavonoids, which are produced and accumulated in the glandular trichomes that are highly abundant mainly on female inflorescences (Raman et al. 2017). The upper inflorescences have significantly higher amounts of cannabinoids and terpenoids than those lower down on the stem (Namdar et al. 2018). The most valuable cannabis product today is the terpene and cannabinoid-rich resin. The resin is produced and accumulates in glandular trichomes that densely cover the surfaces of female (pistillate) inflorescences and, to a lesser degree, the foliage of male and female plants (Booth et al. 2019). Each part of the plant is harvested differently, depending on the purpose of use. It is a highly valued agricultural crop for many reasons. The durable fibres of the woody trunk that are known as hemp, have been used to produce rope and twine, as well as fine or rough cloth.

Figure 1: *Cannabis sativa* L.

The cannabis plant is also a good source of pulp in producing up to five times as much cellulose per acre per year as trees. Cannabis seeds are used as food by man, poultry, and other birds, as well as furnishing hemp seed oil for paint and soap (Hodgson, 2012). Different cannabis types and products derived from them are called strains. The strains may be distinguished by morphological features or the differences in the chemical composition of the resin. But due to mass production of illegal cannabis, the strains are defined poorly (Booth & Bohlmann, 2019).

Phytochemical properties of *C. sativa*

Phytochemical compounds are naturally found in plants which provide benefit to protect the plant from disease and damage. Phytochemicals are classified as primary or secondary constituents, depending on their role and pathway in plant metabolisms. Primary constituents include common sugar, amino acid, protein, purines, pyrimidines of nucleic acids, and chlorophyll. Secondary constituents are alkaloid, terpenes, flavonoids, ligand, plant steroids, curcumin, saponin, phenolics, flavonoids and glucosides (Saxena et al. 2013) (Table S1).

In cannabis, the main phytochemical compounds are phytocannabinoid, terpenoid, alkaloid and flavonoid. According Russo and Marcu (2017), tetrahydrocannabinol from cannabinoids are the most prominently studied compared to other bioactive compounds? Cannabinoids are terpenophenolic compounds (Rodziewicz et al. 2019). Cannabinoids originate from the condensation of olivetolic acid, in the polyetide pathway; and geranyl pyrophosphate from the methylerythritol pathway to form cannabigerolic acid. Catalysation by three oxidative cyclases will form cannabidiolic acid, tetrahydrocannabinolic acid and cannabichromic acid. Cannabidiolic acid and tetrahydrocannabinolic acid are decarboxylated to form cannabidiol and delta-9-tetrahydrocannibinol (Elkins et al. 2019). The studies on cannabinoid are diversified until the clinical trial of pure cannabinoid and synthetic analogue (Fischedick et al. 2010; Levinsohn and Hill, 2020). To date, the researchers are swift the focuses to the terpenoid. It might be due to terpenoids have potential as instigator for phytocannabinoid (Namdar et al. 2019).

OVERVIEW OF TERPENOID

Terpenoid are also known as isoprenoids or terpenes and are made up of isoprene molecules (Cicek et al.2011, Cox- Georgian et al. 2019). Each isoprene molecule contains five carbon atoms with double bonds. The simplest terpenes are monoterpenes that contain two isoprene molecules. Sesquiterpenes have three isoprene molecules and diterpenes have four isoprene molecules. Terpenoids are lipophilic, interacts with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, second messenger systems and enzymes (Russo, 2011). Terpenoids are responsible for the plant's aroma; in addition, they possess specific medical effects and may act synergistically with cannabinoids (Aizpurua-Olaizola et al. 2016).

β-myrcene, limonene, trans-ocimene and α-terpinolene are the most abundant monoterpenes in Cannabis inflorescences, while β-caryophyllene and α-humulene are the most represented sesquiterpenes (Ternelli et al, 2020). Namdar et al (2018) exhibited that the amount of terpenoid and cannabinoids in the uppermost of the inflorescence of the plant were higher compared as when moving towards the lower part of the stem. The term 'phytochemical polymorphism' was coined to describe adaptation of the plant, whereby larger production such as limonene and pinene in flowers that are repellent to insects (Nerio et al., 2010), while lower leaves expresses higher concentrations of bitter sesquiterpenoids that act as anti-feedants for grazing animals. Russo (2011) suggests that even a small amount of terpenes significantly affects the activity of cannabinoids.

BIOSYNTHESIS OF TERPENOID

In cannabis, terpenoid biosynthesis (Figure 2) involves two pathways to produce the general 5-carbon isoprenoid diphosphate precursors of all terpenes; i) plastidial methylerythritol phosphate (MEP) pathway, ii) cytosolic mevalonate (MEV) pathway. These pathways control the different substrate pools for terpene synthases. There are seven steps in plastidial methylerythritol phosphate pathway. During this pathway, pyruvate and glyceraldehyde-3- phosphate are converted to isopentenyl diphosphate and dimethylallyl diphosphate. Enzymes might be important for flux regulation through this pathway include the first two and final two steps: 1-deoxy-D-xylulose 5- phosphate synthase, 1-deoxy-D-xylulose 5- phosphate reductase, 4-hydroxy-3-methylbut-2-enyl diphosphate synthase and 4-hydroxy-3-methylbut-2-enyl diphosphate reductase.

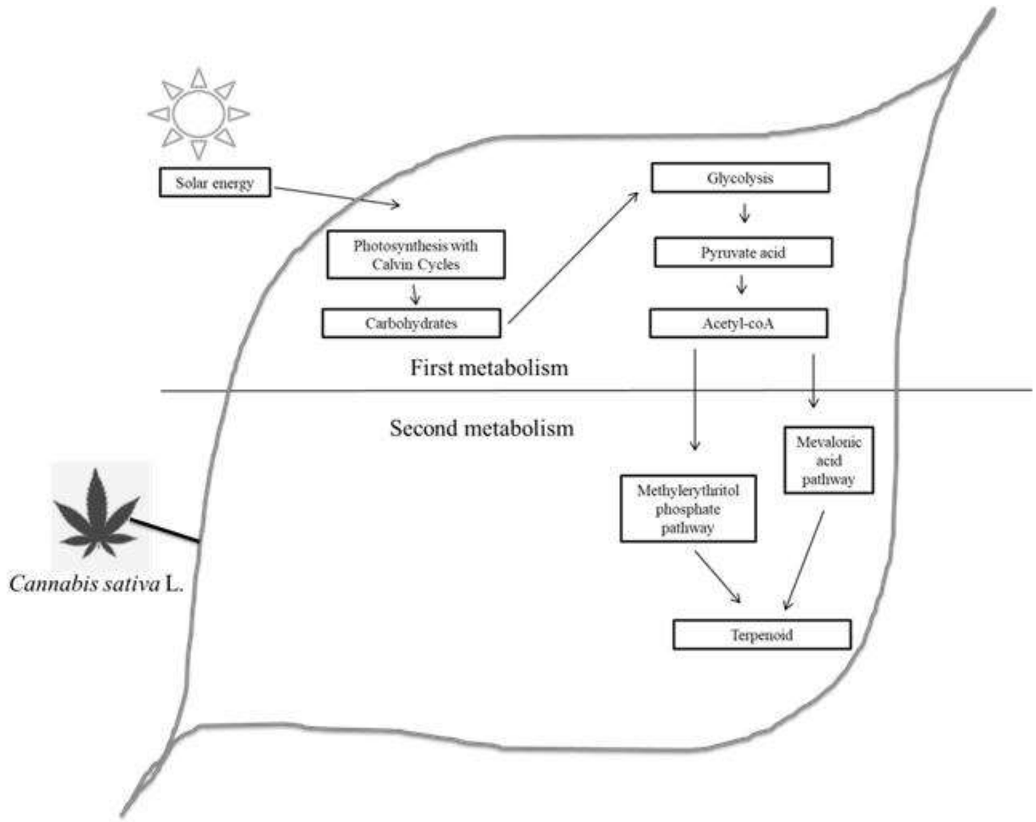

Figure 2: Plant primary and secondary metabolic pathway in plant to produce terpenoid

The three units of acetyl-CoA are converted into isopentenyl diphosphate, which is then isomerized to dimethylallyl diphosphate by isopentenyl diphosphate isomerase. A rate limiting step in this six step pathways is 3-hydroxy-3-methylglutaryl-CoA reductase.

The mevalonate are produces isopentenyl diphosphate and dimethylallyl diphosphate are condensed into longer chain isoprenoid diphosphate by prenyltransferases. The geranyl diphosphate synthase and farnesyl diphosphate are involved and condensed one unit of isopentenyl diphosphate and one or two units of dimethylallyl diphosphate to form 10- and 15-carbon linear trans isoprenoid diphosphate units of the MEP pathway. The farnesyl diphosphate is the 15-carbon precursor of sesquiterpenes and is commonly produced from 5-carbon isoprenoid diphosphate unit of cytosolic mevalonate pathway (Booth et al. 2017).

Zager et al. (2019) studied on gene network of terpenoid accumulation in cannabis by isolating the glandular trichomes from nine commercial cannabis strains. They used the flower buds to quantify terpenoid and cannabinoid. Integrative analyses revealed a coexpression network of genes involved in the biosynthesis of terpenoid from imported precursor. The study also identified and functionally evaluated the biosynthesis of the major monoterpenes and sesquiterpenes in terpene synthase gene. The gene that encode the enzymes with the activities not previously describe in cannabis namely CsTPS18VF and CsTPS19BL (nerolidol/linalool synthases), CsTPS16CC (germacrene B synthase), and CsTPS20CT (hedycaryol synthase) were explained in this study.

EXTRACTION OF TERPENOIDS

Terpenoids are secondary metabolites of plants and are extremely volatile. In general, three main terpene groups have been identified in *C. sativa* oil, which are monoterpenes, sesquiterpenes and terpene alcohols (Russo, 2011). Usually extraction method for terpenenoid involve breaking the plant cells to release their chemical constituents; extracting the sample using a suitable solvent or through distillation or the trapping of compounds; separating the desired terpene from other undesired contents of the extracts that confound analysis and quantification; and use an appropriate method of analysis such as thin layer chromatography, gas chromatography, or liquid chromatography. Non-volatile terpenoid can be extracted using a very nonpolar organic solvent such as hexane. Terpenoid with more carbon will elute more slowly than lower molecular weight compounds, but cyclized terpenoid can elute faster than the corresponding non-cyclized terpenoid with the same carbon number because of their more compact size. (Jiang et al. 2016).

While conducting a comparative study of terpenoid and cannabinoid potencies of flower and supercritical fluid CO_2 (SC‑CO_2) extract from six cannabis chemovars, Sexton et al. (2017) employed a validated high-performance liquid chromatography (HPLC)/diode array detector methodology for quantification of seven cannabinoids and developed an internal gas chromatography (GC)-mass spectrometry (MS) method for quantification of 42 terpenes. This study showed that the relative potencies of terpenoids and cannabinoids in flower versus concentrate were significantly different, whereby cannabinoid potency increased for Δ9-tetrahydrocannabinol, and cannabidiol in concentrates compared to flower. The same study also found that monoterpenes were lost in the extraction process whilst a ketone, monoterpene alcohols and sesquiterpenes increased by a few factors.

The relatively volatile monoterpenes degradation to almost non-traceable levels, losing most of the total extracted amount. These drying methods also altered the amounts of sesquiterpenes perceived, reducing the gained amount to almost half. The lowest damage to terpenoid and cannabinoid compositions was detected when samples were dried under a very gentle stream of nitrogen. Both monoterpenes and sesquiterpenes remained almost intact. A study by Namdar et al. (2018) showed that the effects of gas flow and rotary evaporation on the amount of cannabinoids detected were essentially negligible. But, evaporation by speed-vac vacuum reduced the amounts of Δ^9-tetrahydrocannabinol and cannabigerol to two-thirds. Calibrating the composition and amounts of active compounds produced by the plant is important to increase the effectiveness of patient treatment with cannabis. Standardization of the growing processes will lead to reproducible quality and quantity of active phytochemicals and as a result, to the ability to prescribe medical cannabis to patients as a regulated medicine.

For good agricultural practice, such as environmentally friendly, lower energy consumption, and for optimal production of active compounds in flowers, careful control of the light source intensity and location can be useful. Changing the light source position and settings, and further pruning the lowermost inflorescences, may have more impact on the accumulated amounts of the desired compounds in the remaining cannabis flowers (Namdar et al. 2018). The same study by Namdar et al. (2018) also showed that standardizing the method used for cannabis extraction is highly important for this plant's medicalization. It also demonstrated that polar solvents are best for the extraction of cannabinoids, whereas the most adequate method for a more comprehensive extract of all active compounds is a mixture of polar and non-polar solvents, such as n-hexane and ethanol, both permitted for use by the Food and Drug Administration (FDA).

BENEFITS OF TERPENOID IN CANNABIS

Medical cannabis refers to the use of cannabis as medical therapy to treat disease or alleviate symptoms. There are several promising applications based on the combined use of cannabinoids and terpenes, such as new acne therapies utilizing cannabinoids with the monoterpenes limonene, linalool, and pinene or new antiseptic agents with cannabigerol and pinene. (Russo, 2011)

Myrcene

Myrcene is a monoterpene compound in *Cannabis sativa* plant. A study by Jansen et al. (2019) showed that Myrcene, together with Nerolidol caused the activation of Transient Receptor Potential ion channel, TRPV1. TRPV1 is a nociceptor channel, and are targets for pungent plant compounds and, and are also target for cannabinoids (Iannoti et al. 2014). This study showed potential analgesia effect for formulations of medication containing myrcene.

However, a study by Harris et al. in 2019 refutes this claim, whereby a study with rats receiving various doses of extract without terpenes, isolated terpenes, Δ^9-tetrahydrocannabinol, or the full extract, showed that only rats receiving Δ^9-tetrahydrocannabinol alone produced analgesia effect.

β - Caryophyllene

β - Caryophyllene is a sesquiterpenoid, and was first to be approved as a dietary cannabinoid. It also contributes to the spiciness of black pepper; and one of the major constituent of rosemary, cloves and copaiba. Besides Δ^9-tetrahydrocannabinol, cannabidiol and cannabinol, it also binds to endocannabinoid receptors, and is known as an atypical cannabinoid. Since it targets the CB2 receptor, it is a therapeutic target for treatment of inflammation, pain, atherosclerosis, and osteoporosis (Gertsch, 2008). It has shown many benefits such as for osteoarthritis (Rufino et al.2015), anxiety and depression (Bahi et al.2014)

α- and β-pinene

α- and β-pinene are 2 isomers, representatives of the monoterpenes group, and are found in many plants' essential oils. These two phytochemicals exhibit diverse biological activities, leading them to various applications and uses, such as fungicidal agents, flavours, fragrances, and antiviral and antimicrobial agents (Silva et al. 2012). It is commonly found in coniferous plants like pine. It is also a strong bronchodilator.

POTENTIAL PHARMACOLOGICAL USES OF TERPENOID FROM CANNABIS

Terpenoids are considered as pharmacology versatile due to their lipophilic nature. The lipophilic nature might be one of important properties in enhancing the interaction between cell membranes, neuronal with muscle ion channel, neurotransmitter receptors, G-protein coupled receptor, second messengers' system and enzymes. These properties will permit the passive migration across biological membranes and entrance into the blood stream. The migration will be an influencing factor for activities in brain, heart, and other vital organs (Nahtigal et al. 2016).

ENTOURAGE EFFECT

Entourage effect is the synergistic effect between cannabinoids and terpenes (Ternelli et al., 2020). Looking into the relevance of terpenoids into the activity of cannabis, terpenoid compounds have the potential to exhibit synergistic activity with cannabinoids. For example, high dose of cannabidiol (CBD) has shown to induce sebocyte apoptosis. Russo (2011) have suggested that the terpenoid limonene which can inhibit *Propionibacterium* acnes, a pathogen in acne and can be used with CBD to inhibit formation of acne. Another example by Russo (2011) is the use of CBG together with pinene, whereby pinene enhances the permeability of the drug and works together to combat Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection.

A study by Finlay et al. (2020) designed to determine whether terpenes in the cannabis plant have detectable receptor-mediated activity, or modify the activity of Δ9-tetrahydrocannabinol, cannabidiol, or the endocannabinoid 2-arachidonylglycerol at the cannabinoid receptors. The study concluded that the five terpenes studied did not contribute to the putative entourage effect directly through cannabinoid receptors. But this study is only to rule out that direct cannabinoid receptor as being the mechanism by which an entourage effect is mediated, and focus on other mechanisms on how this effect works. Other non-cannabinoid targets for terpenes have also been proposed, including the suggestion that limonene may exhibit anxiolytic-like activity *via* a GABAergic mechanism. (Lima et al.2013; Almeida et al. 2012). But these data do not definitely reflect direct GABA receptor effects.

But since terpenoids are volatile, it is possible that its effects may be of sensory too, such as patients who showed improvements in Hamilton Depression Scores when they were exposed to citrus fragrance after being diagnosed with depression. (Finlay et al. 2020) But some study has an opinion that an entourage-related mechanism of action may not be necessary, and that terpenes may merely have their own biological activity, and interact functionally with the activity of Δ^9-tetrahydrocannabinol (Murataeva et al. 2016)

ANTIOXIDANT ACTIVITY

In cannabis plant, the main functions of terpenoids are associated with plant protection against predator and for attracting pollinating insect (Gallily et al., 2018). The terpenoids are also contributing as anti-oxidative agent which beneficial to the plant itself. There are three modes of antioxidant mode of actions: (i) quenching of single oxygen, (ii) hydrogen transfer and (iii) electron transfer. The terpenoids from cannabis play an important role as antioxidant in defending the body against free radical attack. The free radicals are generated during energy metabolisms, environmental deterioration, inadequate nutrition and exposure to irritation or stress. In human, free radicals are associated with the neurodegeneration, cardiovascular deterioration, diabetis and cardiovascular disease. The antioxidants are acting by delaying or inhibiting the oxidation from lipid and facilitating the repairing of damage cells (Nahtigal et al. 2016).A study by Nafis et al. (2019) was conducted to determine the antioxidant activity of *C. sativa* from Morocco. The Moroccan *C. sativa* consist of terpenoids compound such as (E)-caryophyllene (35.0%), α-humulene (12.8%) and caryophyllene oxide (10.6%). All the compounds were quantified and analysed using gas chromatography/mass spectrometry (GS/MS). The results for antioxidant test showed that the *C. sativa* exhibit moderate potency with the result of IC50 =1.6 ± 0.1mg/mL for 2,2- di- phenyl-1-picrylhydrazyl (DPPH) assay, IC50=1.8 ± 0.2 mg/mL for β-carotene/linoleic acid assay, and IC50=0.9 ± 0.1mg/mL for ferric reducing power assay. Therefore, *C. sativa* are considered as a potential sources of natural antioxidant.

ANTI-INFLAMMATORY ACTIVITY

Inflammation is a normal response to infection which can caused pain, redness, swelling and loss of function. A number of in vitro, in vivo and clinical studies suggest that cannabis has the antiinflammatory properties. Gallily et al. (2018) studied on anti-inflammatory properties of terpenoids from cannabis. The three types of samples were prepared from three monoecious non psychoactive chemotypes of hemps which harvested in August to September 2016. The samples were collected from pre Alpine region of Slovenia (Upper Savinja Valley). The essential oil from female flower (upper third of the plant) were prepared by steam distillation and terpenoids were analysed first using gas chromatography/mass spectrometry (GS/MS). The results suggested that the terpenoids in *C. sativa* have potential to diminute acute inflammation symptoms.

ANTIMICROBIAL ACTIVITY

Nafis et al. (2019) showed that *C. sativa* which characterized dominance of sesquiterpenes compounds namely (E)-caryophyllene, α-humulene and caryophyllene oxide considered as potential natural antimicrobial agent. The results showed that the minimum inhibitory concentration values of *C. sativa* in the range from 1.2 to 37.8 mg/mL. The antimicrobial properties of *C. sativa* were studied against six pathogenic bacteria such as *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa* (DSM50090), clinically isolated *Klebsiella pneumoniae*, *Bacillus subtilis* (ATCC9524), *Micrococcus luteus* (ATCC 10240), and *Staphylococcus aureus* (CCMM B3), and four pathogenic clinically isolated *Candida* strains provided by the Moroccan coordinated collection of microorganisms: *Candida albicans* CCMM-L4 and *Candida glabrata* CCMM-L7 (from vaginal sampling), *Candida krusei* CCMM-L10 (from human blood) and *Candida parapsilosis* CCMM-L18 (human skin). The study also evaluated the synergistic effect of *C. sativa* with conventional antibiotic such as fluconazole and ciprofloxacin. The results showed that combination between *C. sativa* with the antibiotic considered as a promising strategy to overcome the intense use of antibiotics against some infection diseases. Synergistic interactions of *C. sativa* in combination with antibiotics are one of the novel ways to overcome the drug resistance.

THERAPY FOR EPILEPSY

Epilepsy is a chronic hyper excitability disease which is complex with a variety of distinct syndromes. It is neurological disorder which recognized as one of the common nervous system disorder. There are a lot of alternative treatments for epilepsy. One of potential treatment is using cannabis. The cannabis consists of psychoactive compound that aid in reducing the epileptic seizures. This treatment is believed to be safe for epilepsy treatment in children. The treatments for children are more challenged and required more effective therapy in order to prevent short or long term side effects (Babayeva et al., 2014). A study and survey was conducted by Suraev et al. (2018) to investigate the use of the cannabis extract in treating childhood epilepsy. The average total dosage of terpenoids in cannabis extract was 128.8 ± 222.8 (range 0 – 1,087) µg/kg/day. The highest dosed terpenoids were β-caryophyllene (54.9%), β-myrcene (23.5%), and α-pinene (7.8%).

CONCLUSION

Cannabis has many phytochemical compounds that are worthy to be explored, especially the terpenoids. As they produce large volume of terpenes, they are a good candidate for exploring this family of compounds. In view of the potential and many proven benefits of terpenes, it is important to diversify the study on potential medical. Investigation of the biochemical targets of the cannabis terpenoids, along with their mechanisms of action, in the human body system can be useful to produce more compounds of medicinal value. Crop improvement via genetic transformation is possible for future study. More research also should be carried out on genes that encode enzymes for the biosynthesis of terpenes, and factor that control the expression such as the regulation of cell-type specific gene expression in the development of glandular trichomes, plant architecture, and onset of female flowering. A larger number of cannabis types need to be properly genotyped and phenotypically characterized, in order to identify all the strains, so that reproducible results and varieties can be achieved to be used in studies or the industry. Countries that have legalized cannabis can head the challenge to study further on this plant, and discover more from this extraordinary plant.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed in write-up of manuscript. All authors read and approved the final version.

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