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An Overview of the Phytochemistry of Cannabis sativa L.

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ABSTRACT

Cannabis sativa L. is an important herbaceous species originating from Central Asia, which has been used in folk medicine and as a source of textile fiber since the dawn of times. This fast-growing plant has recently seen a resurgence of interest because of its multi-purpose applications; it is indeed a treasure trove of phytochemicals and a rich source of both cellulosic and woody fibers. Equally highly interested in this plant are the pharmaceutical and construction sectors, since its metabolites show potent bioactivities on human health and its outer and inner stem tissues can be used to make bioplastics and concrete-like material, respectively. Phytocannabinoids are terpenophenolic secondary metabolites predominantly produced in *Cannabis sativa* L. The principal active constituent is Δ^9-tetrahydrocannabinol (THC), which binds to endocannabinoid. Cannabinoids represent the most studied group of compounds, mainly due to their wide range of pharmaceutical effects in humans, including psychotropic activities. The therapeutic and commercial interests of some terpenes and phenolic compounds, and in particular stilbenoids and lignans, are also highlighted in view of the most recent literature data. In this review, the rich spectrum of hemp phytochemicals possess by Cannabis is discussed with a view to highlighting them and their importance.

Keywords: *Cannabis*, Lignin, Cannabinoids, Terpenes, Lignans, Phytochemical profile.

INTRODUCTION

The concept of *Cannabis* as a monotypic genus containing just a single highly polymorphic species is widely accepted, although there has been a long-standing debate among taxonomists regarding classification of the existing varieties. Other previously described species, including *C. indica* Lam. and *C. ruderalis* Janisch., are now recognised as varieties of *C. sativa* L. based on morphological, anatomical, phytochemical and genetic studies [1] [2]. *Cannabis sativa* L. (Cannabaceae) is one of the first plants cultivated by man and one of the oldest plant sources of fibre, food and remedies. *C. sativa* L. is an annual, herbaceous, taprooted and predominantly dioecious plant. Its height (0.2–6 m) and degree of branching depend on both genetic and environmental factors. Staminate (male) plants are usually taller but less robust than pistillate (female) plants. The leaves are petiolate, palmately compound, with an odd number [3] [4] of coarsely serrate, lanceolate leaflets. The male inflorescence is a lax panicle or compound cyme composed of many individual, yellowish green, pedicellate flowers containing five pendulous anthers. The pistillate flowers are green, sometimes purple to red, sessile, grouped in apical leaf axils or terminals of branches.

It has a long history of medical use in the Middle East and Asia, dating back to the sixth century BC. During a period of colonial expansion in the early nineteenth century, cannabis found a way to Western Europe as a medicine to alleviate a variety of conditions, such as pain, spasms, dysentery, depression, sleep disturbance and loss of appetite. In the beginning of the twentieth century, due to the availability of substitute drugs, absence of quality control and the risk of abuse and intoxication, cannabis medication fell into disuse. Phytochemical analysis of cannabis in the 1940s and 1960s led to the discovery of a unique group of terpenophenolic secondary metabolites, known as cannabinoids, of which

trans–Δ^9-tetrahydrocannabinol (THC) was shown to be the primary active constituent which is responsible for the plant's psychoactive effect [5]. Many natural products besides cannabinoids have been isolated from cannabis, including terpenes, flavonoids, steroids and nitrogenous compounds. Up to date, 750 constituents have been identified from cannabis, out of which over 100 are classified as cannabinoids [6].

Cannabis (Cannabis sativa, or hemp) and its constituents-in particular the cannabinoids, have been the focus of extensive chemical and biological research for almost half a century since the discovery of the chemical structure of its major active constituent, Δ^9-tetrahydrocannabinol (Δ^9-THC). The plant's behavioral and psychotropic effects are attributed to its content of this class of compounds, the cannabinoids, primarily Δ^9-THC, which is produced mainly in the leaves and flower buds of the plant. Besides Δ^9-THC, there are also non-psychoactive cannabinoids with several medicinal functions, such as cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG), along with other non-cannabinoid constituents belonging to diverse classes of natural products. Today, more than 560 constituents have been identified in cannabis [7]. The recent discoveries of the medicinal properties of cannabis and the cannabinoids in addition to their potential applications in the treatment of a number of serious illnesses, such as glaucoma, depression, neuralgia, multiple sclerosis, Alzheimer's, and alleviation of symptoms of HIV/AIDS and cancer, have given momentum to the quest for further understanding the phytochemistry of this plant. This review presents an overview of phytochemical constituents of cannabis and its chemical constituents. Particular emphasis is placed on the newly-identified/isolated compounds. In addition, techniques for isolation of cannabis constituents and analytical methods used for qualitative and quantitative analysis of cannabis and its products are also reviewed.

Phytochemical profile

The term cannabinoids is used for a number of chemicals found in the extracts of *Cannabis sativa*. *Cannabis sativa* produces unique secondary metabolites consisting of alkyl resorcinol and monoterpene groups. The plant Cannabis sativa contains more than 60 terpenophenolic compounds, named phytocannabinoids. The best studied phytocannabinoid is Δ^9-tetrahydrocannabinol (TCH) which binds specific G-protein-coupled receptors named cannabinoid (CB1 and CB2) receptors, it is the main active component which has been shown to induce acute transient psychotic reactions in previously well individuals when administered as an isolated compound [8].

Δ^9- tetrahydrocannabinolic acid (THCA), a product of the cannabinoid class, is the primary psychoactive agent. This compound is produced as an acid in the glandular trichomes of inflorescence bracts and undergoes decarboxylation with age or heating to Δ^9-tetrahydrocannabinol (THC) [9] [10]. Still there are other components in this chemical mixture, such as cannabidiol (CBD) and cannabigerol, which may also play a role in modulating the effects of TCH [11]. A number of cannabis components that do not activate the receptors are often called cannabinoids.

Phytocannabinoids

Phytocannabinoids represent a group of C21 or C22 (for the carboxylated forms) terpenophenolic compounds predominantly produced in *Cannabis.* More than 90 different cannabinoids have been reported in the literature, although some of these are break down products [12]; [13]; [14]; [15] and they are generally classified into 10 subclasses (Brenneisen,2007). Cannabis may contain over 60 classical cannabinoid (tricyclic dibenzopyran) compounds and some, such as cannabidiol, may modulate the response to THC. Cannabinoids (cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabicyclol (CBL), cannabielsoin (CBE), cannabinol (CBN), cannabinodiol (CBND), cannabitriol

(CBT)) nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, sugars, hydrocarbons, simple alcohols, simple aldehydes, simple ketones, simple acids, fatty acids, simple esters, lactones, steroids, terpenes, non-cannabinoid phenols, flavonoids, vitamins, pigments and elements are the chemical classes compounds of *Cannabis sativa* which has been identified [16] [17].

Δ^9-tetrahydrocannabinol (TCH)

The cannabis plant (*Cannabis sativa*) contains many compounds, but Δ^9-tetrahydrocannabinol (THC) is the main psychoactive ingredient. THC breaks down to produce cannabinol and was identified along with cannabidiol (the main non-psychoactive component) [18] [19]. However, THC was not isolated, synthesized, and stereochemically defined until the 1960s [20]. THC is concentrated in the flowering head of the female plant and selective growing in the past 5– 10 years has substantially increased THC content from 1-3% THC in the "flowerpower" era to 6–13% and above.

Terpenes

Terpenes form the largest group of phytochemicals, with more than 100 molecules identified in *Cannabis* [21] [22]. Terpenes are responsible for the odor and flavor of the different *Cannabis* strains. They have therefore likely contributed to the selection of *Cannabis* narcotic strains under human domestication [23]. Terpenes are classified in diverse families according to the number of repeating units of 5-carbon building blocks (isoprene units), such as monoterpenes with 10 carbons, sesquiterpenes with 15carbons, and triterpenes derived froma 30-carbon skeleton. Terpene yield and distribution in the plant vary according to numerous parameters, such as processes for obtaining essential oil, environmental conditions, or maturity of the plant [24] [25]. Mono-and sesquiterpenes have been detected in flowers, roots, and leaves of *Cannabis*, with the secretory glandular hairs as main production site. Monoterpenes dominate generally the volatile terpene profile and include mainly D-limonene, β-myrcene, α- and β-pinene, terpinolene and linalool. Sesquiterpenes, and β-caryophyllene and α- humulene in particular, occur also to a large extent in *Cannabis* extracts.

Terpenes, along with cannabinoids, have successfully been used as chemotaxonomic markers in *Cannabis,* as they are both considered as the main physiologically active secondary metabolites [26]. When grown in standardized conditions, a significant and positive correlation was found between the level of terpenes and cannabinoids [2]. This may be explained by the fact that mono- and sesquiterpenes are synthesized in the same glandular trichomes in which the cannabinoids are produced [5]. This association was, however, not confirmed on a larger panel of samples coming from different origins [12].

Cannabidiol (CBD)

Cannabidiol was isolated in 1940 [18] and its absolute configuration established by synthesis of (-)-CBD as (-)-trans-(1R, 6R) [19]. The optical rotation of cannabidivarin was reported as [α] D-139.5-(chloroform) [20]. All of the known CBD-type cannabinoids have trans-(1R, 6R) absolute configuration and presumably also negative optical rotation.

Phenolic Compounds

Phenolic compounds, also known as phenylpropanoids, constitute one of the most widely distributed group of secondary metabolites in the plant kingdom. They present more than 10,000 different structures, including phenolic acids, such benzoic and hydroxycinnamic acids, flavonoids such as flavonols and flavones, stilbenes and lignans [6]. In *Cannabis*, about 20 flavonoids have been identified, mainly belonging to the flavones and flavonol sub classes [17]. These include the *O*-glycoside versions of the aglycones apigenin, luteolin, kaempferol and quercetin, as well as cannflavin A and cannflavin B, which are methylated isoprenoid flavones that are unique to *Cannabis* [20].

Phenolic amides and ligninamides have also been described in *Cannabis* fruits and roots [8]; [9]. The lignanamides belong to the lignan class of compounds

and include cannabisin-like compounds (of the types A-,B-,C-,D-,E-,F-,and G) and grossamide [23]. Similar compounds such as cannabisin D, have been described in *Cannabis* leaves, where it was strongly induced upon the UV-C treatment [21]. Interesting amounts of lignans were recently found in the hydrophilic extract of hempseeds. The hempseed lignin profile was shown to be dominated by syringaresinol and medioresinol, followed by secoisolariciresinol, lariciresinol, and pinoresinol [25]. Hempseeds contain, however, about 20-times less total lignans than flax seeds, a well-known source of lignans.

Interestingly, the lignin content of hulled hemp seeds represents only 1% of the content in whole seed [3]. Nineteen stilbenes have been isolated in *Cannabis* with characteristic structural back bones such as spirans, phenanthrenes and bibenzyls [17]. They include molecules such as cannabistilbene I, IIa and IIb, as well as dihydroresveratrol. Interestingly, bibenzyl stilbenes, including the putative 3-*O* methylbatatasin, were strongly induced in *Cannabis* leaves by UV radiations [20].

Noncannabinoid

Noncannabinoid, the geranylated flavone cannflavin A (Figure 4), is 30 times more potent than aspirin as an inhibitor of prostaglandin E2 [27] [28]. Six new non-cannabinoid constituents were isolated from a high potency *Cannabis sativa* L. variety, namely 5-acetoxy-6- geranyl-3-n-pentyl-1,4-benzoquinone, 4,5-dihydroxy-2,3,6- trimethoxy-9,10-dihydrophenanthrene, 4,7-dimethoxy-1,2,5-trihydroxyphenanthrene, cannflavin C and b-sitosteryl-3-O-b-D-glucopyranoside-20- O-palmitate, 4-hydroxy-2,3,6,7- tetramethoxy-9,10-dihydrophenanthrene. In addition, five known compounds, a-cannabispiranol, chrysoeriol, 6- prenylapigenin, cannflavin A and b-acetyl cannabispiranol were identified. Non-cannabinoid constituents isolated from cannabis include flavonoids, spiroindans, dihydrostilbenes, dihydrophenanthrenes, sterols and alkaloids, among others [8] [9].

CONCLUSION

Cannabis sativa is a unique versatile plant, which can provide high biomass quantities in a short time. To date, more than 540 phytochemicals have been described in *Cannabis* and their pharmacological properties appear to go much beyond psychotic effects, with the capacity to address needs like the relief of chemotherapy-derived nausea and anorexia, and symptomatic mitigation of multiple sclerosis. *Cannabis* medicinal use and much research still need to be undertaken to provide patients with a medicine that is safe, efficacious and of the appropriate quality.

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