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Ethnobotany, Taxonomy and Phytochemistry of Cannabis sativa.

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Abstract:

Introduction: Cannabis is an annual dioecious plant, which shares its origins with the inception of the first agricultural human societies in Asia. Over the course of time different parts of the plant have been utilized for therapeutic and recreational purposes. Linnaeus was the first person to describe Cannabis as *Cannabis sativa* (*C.sativa*). Numerous bioactive phytochemicals are extracted from *C. sativa* that signal for medicinal development.

Methods: The review aims to provide a different perspective of the ethnobotanical, taxonomy and chemical aspects from the ancient times of *C. sativa*. The study was conducted with the review of scientific papers from Pubmed, Scopus, Wiley Online Library, Springer, Elseveir, Science Direct, Taylor Francis and online textbooks of *C. sativa.*

Results: *C. sativa* has its origin from Asia. It has traditional spiritual, household and therapeutic uses. Cannabis is a monotypic genera with three different varieties: C sativa var. sativa, C sativa var. indica, C sativa var. ruderalis. A total of 565 chemicals (120 cannabinoids and 445 non cannabinoids) have been recorded in Cannabis.

Conclusions: Cannabis is an ethnobotanical rich and phytochemical significant therapeutic plant. Because of lack of scientific research, the taxonomic aspects are still hidden. This study recommends exploratory study on ethnobotanical, taxonomical and phytochemicals of Nepalese Cannabis.

Keywords: *Cannabis; Tetrahydrocannabinol; Ethnobotany; Taxonomy; Cannabinoids.*

1. Introduction

One of the earliest domesticated plant Cannabis, had long been considered as one of the most significant crops.(1) Cannabis is well known for its versatility including major uses as fibers, food, oil, medicine, recreation and religious purposes since Millennium.(2) Its cultivation and use are supposed to be 5000 to 6000 years old. Its cultivation for textile and fiber originated from Egypt and Western Asia. Later it was introduced subsequently to Europe and other parts of the world. (3) The use of Cannabis as medicine can be seen in almost all the old religions.

Cannabis is found in a variety of habitats and altitudes ranging from sea level to the alpine foothills of the Himalayas from which it possibly originated. Most of the great plant explorers of 19th and 20th century have all placed the geographic origin of cosmopolitanism in Central Asia and are believed to expand to East and South Asia and Westward to Europe by human activity.(4,5)

Linnaeus was the first person to describe Cannabis as Cannabis sativa (*C.sativa*) .(6) The taxonomy of Cannabis has been a matter of interest for its taxoniocal aspects since the 19th century.

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Cannabis is considered a taxonomically controversial plant.(5,7,8) Some consider the genus Cannabis as monotypic i.e *C. sativa*,(6) and some as polytypic.(7,9)

It contains a number of chemically active compounds such as Cannabinoids, terpenoids, flavonoids and alkaloids.(10) Among these compounds, the most active compounds are Cannabinoids, which are a class of terpenophenolic compounds which are mainly accumulated in the trichome cavity.(11) Cannabinoids are identified and are categorized into 11 subclasses. These different classes of chemicals are of great importance from pharmacological scenarios. The study aims to perform a review on ethnobotany taxonomy, and phytochemistry with respect to *C.sativa*.

2. Methods

This study was reviewed with the phrase Cannabis and Uses, Cannabis and Taxonomy, Cannabis and Phytochemistry, Cannabis and Human Civilization. The phrases were searched on Google Scholar. The searched published research articles were reviewed for the perspective of *C. sativa*. We reviewed 36 papers available from Pubmed, Scopus, Wiley Online Library, Springer, Taylor and Frankis, and available online textbooks related to Cannabis.

3. Results

Ethnobotany:

Cannabis sativa L. is considered as one of the oldest cultivated species for its fibres and food. Many early civilizations have raised forward some strong evidence regarding the historic use of *Cannabis*.(12) Its first use was as fibres originated from Egypt and Western Asia at around 2300 BC and later at 700 BC, they started using it to cure eye diseases, pain management, antipyretic, anti-inflammatory and analgesic.(13) The first medicinal use of *Cannabis* was believed to be from China about 5000 years ago. The first written record of *Cannabis* use was made in Pharmacopoeia of Sheng Nung, one of the fathers of Chinese medicine.(14) The use of *Cannabis* to western world appears to be much later, during the early nineteenth century.(4)

This boon plant is of great importance as per religious belief too. Hinduism uses this plant as a form of Ganja and Bhang to worship Lord shiva, meditation and communication with the spirits.(9) Likewise, it was supposed that Bhang was only the source of nourishment for Siddartha Gautam Buddha during his six years of asceticism, which clarifies its huge significance for Buddhism.(15)

In particular, with the conquest of India, the voluptuous uses of *C. sativa* were better known across the European continent. Garcia da Orta and Cristobal Acosta, two Portuguese doctors, wrote about the effects of *C. sativa*, which included euphoria, sedation, stimulation of appetite, hallucinations, and aphrodisiac effects.(16) During the British colonialism of the East India Company, *C. sativa* was marketed in Asia through a variety of formulations such as Bhang, Ganja or Charas. Ganja and Charas are preparations of flower and resin with high psychoactive contents. (17) On the contrary, Bhang has a low psychotropic effect comparable to that of some Western alcoholic drinks. Despite the benefits described above, it was strongly prohibited in the twentieth century due to its remarkable psychoactive effects and was removed from the British Pharmacopoeia in 1932 and included as a banned substance for therapeutic use, in the Act of the Parliament of the United Kingdom, Misuse of Drugs Regulation Act in 1971.(18) In 1937 production, possession or transfer of *C. sativa* was forbidden in the USA due to federal law "The Marihuana Tax Act".(19) Despite these restrictions, the use of *C. sativa* as a local and traditional medicine by shamans and healers, an intense pharmacological research on its chemical components, and several socio-cultural debates on it continued. Today many indigenous communities in the world use *C. sativa* derivatives for several diseases. In the Miandam area of Swat, North Pakistan, leaves of *C. sativa* are used for wound healing; powdered leaves as anodyne, sedative, tonic and narcotic. (20) Some livestock farmers in Uganda

and Kenya use *C. sativa* as an ethnoveterinary remedy.(21) Lastly, even in some isolated ethnic groups of the Caucasus, the traditional use of *Cannabis* as a traditional remedy is preserved.(22) Different ethnic communities of Nepal uses its bark fibres used for rough clothes (Bhangaurâ), sacks, bags, Resinous exudates of the stem, and young leaves and inflorescence yields intoxicating drug 'Gânâ" (Attar), which is applied on body to treat pneumonia and fever, Seeds are roasted and pickled. Oil extracted from seeds used to treat gout.(23)

Taxonomy

Cannabis L. is a dioecious or sometimes monoecious annual herb placed in the family cannabaceae (Figure 1.1). Normally it may attain up to a height of up to 3m. Leaves are alternate or opposite and are palmately compound with up to 11 leaflets with serrate margin. Male inflorescence is always axillary or terminal in a lax panicle while female inflorescence axillary and in rosette. The male flower consists of five pale green hairy sepals about 2.5-4 mm long and five pendulous stamens with slender filaments. The female flowers are almost sessile and occur in pairs. The fruit is an achene, contains a single seed with a hard shell tightly covered by the thin wall of the ovary , and it is ellipsoid, slightly compressed, smooth, about 2-5 mm long, generally brownish and mottled.(8) (Figure 1.2) *Cannabis* is rich in trichomes, epidermal glandular protuberances covering the leaves, bracts and stems of the plant.(11) Trichomes are basically divided into two general classes: non-glandular and glandular. (24) Glandular trichomes are further divided into capitate-stalked, capitate sessile and bulbous trichomes, which are mainly found in bracts, floral leaves, stem and leaves. (Figure 2) Among all these forms of trichomes, the capitate stalked and capitate sessile trichomes are densely found on bracts and floral leaves while bulbous trichomes are densely found on the stem.(25) These glandular trichomes enclose secondary metabolites as phytocannabinoids, responsible for the defense and interaction with herbivores and pests. (26)

The genus *Cannabis* is sharply delimited up to generic level but the species delimitation is still a long controversy since the time of Linnaeus. Wind pollination, no internal barrier to successful hybridization and selection by humans are the main cause of the awaiting clear cut species delimitation of *Cannabis*.(6) Since the time of Linnaeus the dispute of considering *Cannabis* as monotypic or polytypic genera is still the same. Linnaeus was the first person to describe *Cannabis* as *Cannabis sativa*. Later Lamark described another species *Cannabis indica* differing from the former species on the basis of leaf character.(9) Schultes *et. al.* categorized *Cannabis* into three species: *C sativa, C indica, C ruderalis* on the basis of fruit morphology. (9) On the basis of chemotaxonomic study of Hillig and Mahlberg concluded the polytypic genera with the same three species by Schultes *et al*. (7,9) On the basis of natural taxonomy study by Small and Cronquist strongly concluded it as monotypic genera which is well accepted.(6) Likewise, Gilmore *et al* strongly concluded the species as monotypic on the basis of molecular level work.(27)

So, until the strong and well accepted molecular and phylogenetic findings will come till then considering monotypic genera as *Cannabis sativa* and categorizing other earlier considered species as infra species are well acknowledged.

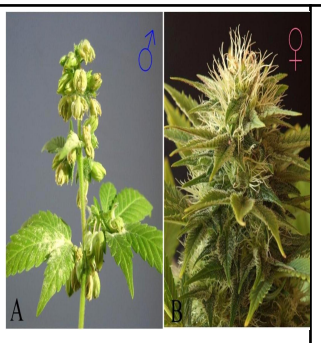

Figure 1.1. Male (A) and Female (B) Plant.

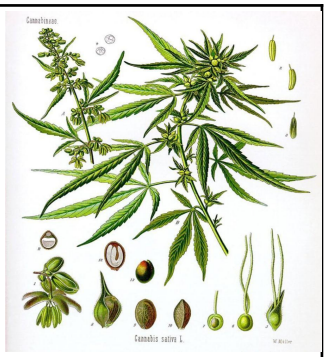

Figure 1.2. Morphology of *C. sativa.*

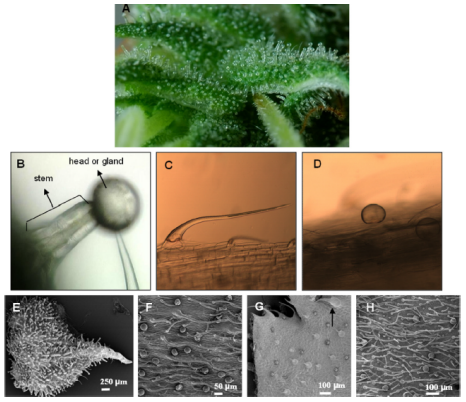

Figure 2. Trichomes of *Cannabis sativa* L.
A. trichomes of the flower, B. Capitate- stalked trichomes C. Capitate- sessile trichomes, D. bulbous trichomes, E. trichomes on the bract, F. trichomes on the stem, G. trichomes on the adaxial surface of a floral leaf; a big capitate- sessile trichome is indicated with an arrow, H. trichomes on the abaxial surface of a leaf; small capitate-sessile and bulbous trichomes.

Table 1: List of Phytochemicals in *C. sativa* by Chemical class.

Chemical class	**Number of constituents**	**Common constituents**
D9-THC	23	8α-hydroxy-Δ9–tetrahydrocannabinol, β-fenchyl Δ9 -tetrahydrocannabinolate, α-fenchyl Δ9 -tetrahydrocannabinolate, epi-bornyl Δ9 -tetrahydrocannabinolate, bornyl-Δ9–tetrahydrocannabinolate
D8-THC	5	Δ8-trans-tetrahydrocannabinol (Δ8-THC), Δ8-trans-tetrahydrocannabinolic acid-A (Δ8 - THCA), 10α-hydroxy-Δ8-tetra-hydrocannabinol, 10βhydroxy-Δ8-tetrahydrocannabinol, 10aα-hydroxy-10-oxo-Δ8 –tetrahydrocannabinol.
CBG	16	5-acetyl-4-hydroxy-cannabigerol, γ-eudesmyl-cannabigerolate.
CBC	9	4-acetoxycannabichromene, 7-hydroxycannabichromane
CBD	7	cannabidiolic acid (CBDA), cannabidiol monomethyl ether(CBDM), cannabidiol-C4 (CBD-C4), cannabidivarin (CBDV)
CBND	2	Cannabinodiol(CBND-C5) and CBND-C3 (cannabinodivarin)
CBE	5	Cannabielsoic acidA(CBEAC5-A), cannabielsoin (CBE), cannabielsoic acid B (CBEA-C5 B), cannabielsoic acid B-C3 (CBEA-C3 B) , and C3-cannabeilsoin (CB3-C3)
CBL	3	Cannabicyclol (CBL), cannabicyclolic acid (CBLA), and cannabicyclovarin (CBLV)
CBN	11	8-hydroxycannabinolic acid-A and 8-hydroxycannabinol
CBT	9	-trans-cannabitriol, trans-BT-C5, trans-cannabitriol (-trans-CBT-C5)
Miscellaneous	30	Dehydrocannabifuran (DCBF-C5), cannabifuran (CBF-C5)
Total Cannabinoids	120	
Total Non-cannabinoids	445	Cannflavin C, chrysoeriol, 6-prenylapigenin, 4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene
Total chemicals	565	

Secondary metabolites of *C. sativa*:

1. Phytocannabinoids : These are the lipid soluble chemical compounds only found in *Cannabis* exhibiting the typical c_{21} terpenophenolic skeleton.(31) Phytocannabinoids often known as cannabinoids are chemicals of interest since thousands of years as some of these compounds are psychoactive and boon for the pharmacological aspect. Altogether till this date the number of cannabinoids identified are 120. These are mainly synthesized in the numerous hairs (Trichome) presented more or less throughout the plant. (32) Female plants are much richer in trichomes than male.(8) Capitate stalked trichomes store maximum cannabinoids of all the trichomes types. Its capitate (head) parts consist of disk cells which are presumed to be the site of cannabinoid production.(33)

All the phytocannabinoids can be categorized into 11 general types: D-9THC, D-8THC, CBG, CBC, CBD, CBND, CBE, CBL, CBN, CBT and miscellaneous types.(34) These phytocannabinoids can also be categorized into neutral and acidic (carboxylated) cannabinoids. (35) The precursors of *Cannabis* are synthesized from two pathways: the polyketide and the deoxyxylulose pathway. From the polyketide pathways, olivetolic acid is derived and from the DOXP/MEP pathway, geranyl diphosphate (GPP) is derived. Both are condensed by the prenylase geranyl diphosphate to form CBGA, which ultimately forms CBDA, D-9THC and CBCA.(28) Among all the types mentioned above all are equally important from a pharmacological point of view and the THC types are psychoactive in nature. The number of constituents in 11 types of cannabinoids are given below in table number.

2. Flavonoids: These are significantly important in the biochemistry, physiology and ecology of plants, which plays an important role in both human and animal nutrition and health.(36) In *Cannabis* more than 20 flavonoids are reported. (37) Common flavonoids in *Cannabis* are cannflavin A, cannflavin B. *Cannabis* flavonoids have been isolated and detected from flower, leaves, twigs and pollen. (38)

3. Terpenes: These are another major plant metabolic group. In *Cannabis*, 120 terpens have been identified: 61 monoterpens, 52 sesquiterpens, 2 triterpens, 1 diterpene and 4 terpenoid derivatives.(28) The terpens are responsible for the flavor to *Cannabis*. Limonene, myrcene and pinene are the most common and highly volatile terpenes found in *Cannabis*. (8) These compounds have strong insect and herbivores repellent properties.(26) It has been suggested that terpene composition of the essential oil could be useful for the chemotaxonomic analysis of *Cannabis*.(7) Terpenes have been detected and isolated from the essential oil from flowers, roots and leaves.(29)

4. Alkaloids: These are basic, nitrogenous compounds derived from amino acids. In *Cannabis*, 10 alkaloids have been isolated from root, leaves, stem, pollen and seeds. (29)

5. Lignaamides and phenolic amids: *Cannabis* fruits have yielded 11 compounds identified as phenolic amides and lignanamides. N-trans-coumaroyl tyramine, N-trans-feruloyl tyramide and N-trans-caffeoyl tyramine are phenolic amides, while Cannabisin-A,B,C,D,E,F,G and grossamide are lignanamide.(29)

5. Conclusions

Cannabis is ethnobotanical rich and phytochemical significant therapeutic plants. Because of the lack of advanced molecular taxonomic research, the taxonomic aspects of *C. sativa* are still hidden. 567 phytochemicals reported highlights its value for drug development. This study recommends exploratory study on ethnobotanical, taxonomical and phytochemicals.

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