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# Indigenous plant *Cannabis sativa*: a comprehensive ethnobotanical and pharmacological review

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**ABSTRACT:** *Cannabis sativa* (L.) is a plant indigenous to Central Asia and South-East Asia. It is widely used in ethnomedicines as an anti-inflammatory, antioxidant, analgesic, anticonvulsive, antidepressant, anticancer, antitumor, neuroprotective, anti-mutagenic, anti-allergic, and antibiotic. Numerous *in vitro* and *in vivo* investigations have already established these attributes of *Cannabis*. Numerous toxicological studies have demonstrated the dose-dependent toxicity of *C. sativa* against various pests. The exact identity of the phytoconstituents of *C. sativa* responsible for the observed biological effects and their mode of action at the molecular level is yet to be ascertained. This review provides a comprehensive update to the ethnomedicinal, phytochemistry, pharmacological activity, and toxicological profile of *Cannabis sativa*.

**Keywords:** *Cannabis sativa*; Phytochemistry; Ethnobotany; Pharmacology; Toxicology.

## 1. INTRODUCTION

*Cannabis sativa* L., (Cannabaceae) also known as Indian hemp, is an annual, herbaceous and dioecious plant with an erect stem reaching up to 5m. It is cultivated in India and China since ancient times [1,2]. *Cannabis sativa* is possibly among the earliest plants cultivated by man [3,4]. *Cannabis* has been extensively used by humans as a source of food, fibers, oils, textiles, biofuel, and drugs as well as for religious and recreational purposes over the centuries [5-7]. Almost all parts of the *Cannabis sativa* are utilized for a variety of use. It contains several phytoactive compounds such as cannabinoids, terpenoids, alkaloids, and flavonoids [8,9]. Cannabinoids are the most active compound, mainly stored in trichomes of female flowers [10,11]. Trans-Δ-9-tetrahydrocannabinol (D9-THC) is the most potent cannabinoid, substantially responsible for psychoactive effects [12]. Natural receptors for THC are found throughout the human body called the 'endocannabinoid system' [13].

*Cannabis* has a rich history of medicinal use dating back to ancient times. Its medicinal uses are described in ancient Ayurvedic text and the first known pharmacopeia "ShenNung Pen Ts'ao Chin" thousands of years ago [14]. *Cannabis sativa* has been indicated in the treatment of pain, nausea, depression, glaucoma, and neuralgia [15-19]. *Cannabis* is used for manufacturing fish nets in Artisanal fisheries in the Mediterranean [20] and its fibers are used for manufacturing strings, ropes, fabrics, and papers [21].

This study aims to provide a detailed account of the taxonomy, phytochemistry, ethnobotanical, pharmacological, and toxicological aspects relevant to *C. sativa*, so that it may serve as a valuable resource providing future direction for researchers.

*Cannabis sativa* (Indian hemp) (Fig. 1) is a dioecious, sometimes monoecious, annual herb of the family Cannabaceae. The stem is erect reaching up to the height of 5m which also depends on the genetic variety and the environmental conditions [22]. The palmately compound leaves with 5-7 leaflets are alternate or opposite, linear-lanceolate, tapering at both ends and with sharply serrate margins. The male inflorescence is axillary or terminal in a lax panicle and has five pale green hairy tepals (2.5-4 mm), and five anthers. The female flowers are almost sessile and occur in pairs, germinate in the axils, and terminally with one single-ovulate closely adherent perianth. The fruit is an achene, small (2-5 mm long), smooth, light brownish-grey, and a single fruit is produced per flower [23]. Leaves, bracts, and stems of the *Cannabis sativa* are richly covered by epidermal, glandular trichomes [24,25]. These glandular trichomes contain phytocannabinoids and secondary metabolites [23]. Based on fruit morphology, height, and content of psychoactive molecules, *Cannabis* is categorized into three species, *Cannabis sativa* Linnaeus*, Cannabis indica* Lamarck*, and Cannabis ruderalis* Janisch [26].

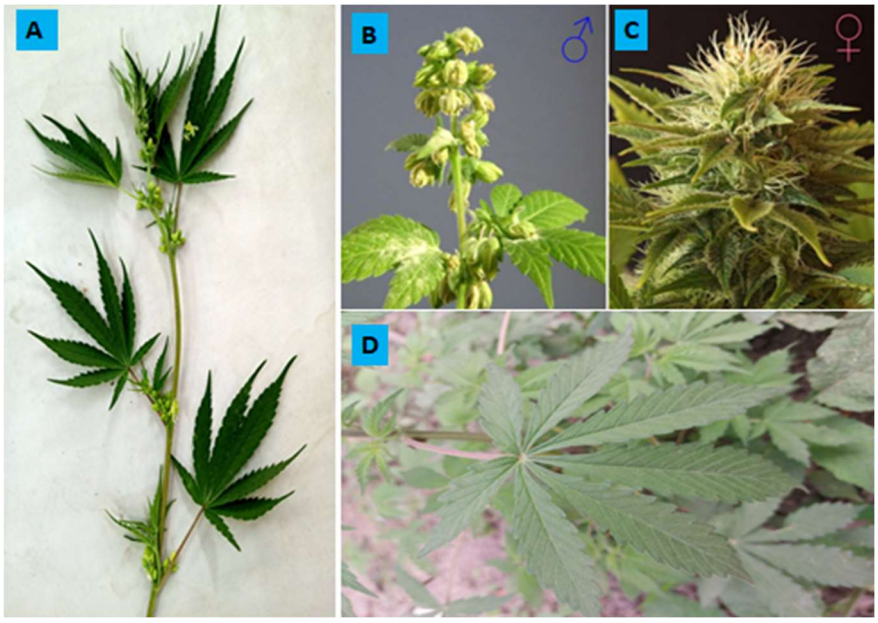


**Figure 1.***Cannabis sativa* (L.).A. Whole plant, B. Male flower, C. Female flower, D. Leaf.

## 2. ETHNOMEDICINAL USES OF *CANNABIS SATIVA*

*Cannabis* is perhaps one of the oldest cultivated species for its fiber and food, presumably being utilized for more than 10,000 years [26,27]. It is apparent from archaeological and paleontological records that Europe and Central Asia is the region of the natural origin of *Cannabis sativa* [28].

The medicinal use of *Cannabis* was believed to be from China about 5,000 years ago and credit to Emperor Chen Nung, one of the fathers of Chinese medicine [23,29-31]. *Cannabis* was prescribed for malaria, rheumatism, and fatigue in ancient China [29]. The use of *Cannabis* as medicine is extensively reported on Assyrian Clay tablets [30] and ancient Egyptian Ebers Papyrus, dated back to 3,000 years ago, which also describes the use of *Cannabis for* numerous afflictions including infection, analgesia, and vaginal contractions [3,31,32]. During the first and second centuries A.D. Romans cultivated hemp for fibers [33]. Specific mentions

of the remedial use of hemp are found in Arabic literature from the 11th century [34]. Highlighted medicinal properties of hemp include analgesic, intoxicants, narcotic, stomachic, sedative, etc. [35,36].

*Cannabis* is considered an important medicinal plant in classical Indian Ayurvedic and medicinal texts [37]. *Cannabis* has been stressed for its *Ruchya* (taste promoter), *Deepan* (digestive stimulant), *Pachana* (digestive), *Medhya* (memory booster), *Madakari* (intoxicant), *Vyavayi* (short-acting), *Grahi* (withholds secretions), and *Rasayana* (adaptogen) activities [37]. The foremost written reference to *Cannabis sativa* in India is found in the *Atharvaveda* which dates back to around 1500 BCE [38]. *Atharvaveda* considers it one of the 'five sacred plants' [13]. *Sushrut Samhita* (verses of Sushrut), maybe from the 3rd century BCE, is the direct substantiation of the medicinal use of *Cannabis*, recommending *Cannabis* for diarrhoea and phlegm [39]. Hemp is considered a holy plant in Hinduism and used as a form of 'Ganja' and 'Bhang' to worship lord Shiva, meditation, and communication with spirits [26,40]. *Cannabis sativa* was used as an organic additive in the clay plaster of the 6th century A.D. caves of Ellora, a World Heritage Site in Maharashtra, India [40]. In the Swat, North Pakistan, leaves of hemp are used in bandages for wound healing, pulverized leaves as an anodyne, sedative tonic and narcotic; juice added with milk and nuts as a cold drink ('Tandai') which generates a pleasant excitement and it is also used for Charas preparation [41].

Hemp is a rich source of various narcotics. In India, it is known as Bhang, Charas, Ganja, Marijuana, etc. Despite the number of benefits described over, the production, manufacturing, transport, purchase, and consumption of hemp is illegal and rigorously banned in India. Exceptionally, it can only be used forscientific and medical purposes under the Narcotic Drug and Psychotropic Substance Act in India [42].

## 3. CHEMOTAXONOMY OF *CANNABIS SATIVA*

*Cannabis sativa* is a chemically complex species as it contains diverse groups of phytoconstituents. An aggregate of 565 natural compounds has been identified from *Cannabis sativa* (Table 2) including 120 cannabinoids, 120 terpenoids (including 61 monoterpenes, 52 sesquiterpenoids, and 5 triterpenoids), 26 flavonoids, and 11 steroids [23, 43-46]. About 120 are identified as phytocannabinoids, because of the shared chemical structure [47]. These phytocannabinoids are lipid-soluble chemical compounds only found in *Cannabis* exhibiting the typical C21 terpenophenolic skeleton [48].

**Table 2.** Phytoconstituents and their properties.

| Chemical class | Number of constituents | Common constituents | Physiological effects | Reference |
|---|---|---|---|---|
| D9-THC | 23 | 8α-hydroxy-Δ9–tetrahydrocannabinol, β-fenchyl Δ9 -tetrahydrocannabinolate, α-fenchyl Δ9 -tetrahydrocannabinolate, epi-bornyl Δ9 -tetrahydrocannabinolate, bornyl-Δ9–tetrahydrocannabinolate | - partial agonist at both CB1 and CB2 receptors.<br>- psychoactive effects: anxiety, paranoia, perceptual alterations<br>- cognitive deficits<br>- hypolocomotion<br>- hypothermia<br>- catalepsy<br>- analgesia | [49] |
| 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 | - a few psychoactive effects on children | [50] |

| Chemical class | Number of constituents | Common constituents | Physiological effects | Reference |
|---|---|---|---|---|
| CBG (Cannabigerol) | 16 | 5-acetyl-4-hydroxy-cannabigerol, γ-eudesmyl-cannabigerolate | - do not produce psychoactive action mediated by the CB1 receptor.<br>- it is an α-2 adrenergic receptor agonist.<br>- able to inhibit the release of catecholamine with sedation, muscle relaxation, and analgesia effects.<br>- decreases acetylcholine-induced contractions in the human bladder | [51-53] |
| CBC (Cannabi-chromene) | 9 | 4-acetoxycannabichromene, 7-hydroxycannabichromane | - reduces nitric oxide, IL-10, and interferon-γ levels in peritoneal macrophages activated by LPS<br>- do not show any CB1-mediated psychoactivity. | [54,55] |
| CBD (Cannabidiol) | 7 | cannabidiolic acid (CBDA), cannabidiolmonomethyl ether(CBDM), cannabidiol-C4 (CBD-C4), cannabidivarin (CBDV) | - exerts pharmacological effects via specific molecular targets such as glycine receptors, adenosine receptors, serotonin receptors, opioid receptors, nonendocannabinoid G protein-coupled receptors, nicotinic acetylcholine receptors, proliferator-activated receptors. | [56] |
| CBND (Cannabinodiol) | 2 | Cannabinodiol(CBND-C5) and CBND-C3 (cannabinodivarin | - unknown biological properties | [23,44] |
| CBE (Cannabielsoin) | 5 | CannabielsoicacidA(CBEAC5-A), cannabielsoin (CBE), cannabielsoic acid B (CBEA-C5 B), cannabielsoic acid B-C3 (CBEA-C3 B) , and C3-cannabeilsoin (CB3-C3) | - unknown biological properties | [23] |
| CBL (Cannabicyclol) | 3 | Cannabicyclol (CBL), cannabicyclolic acid (CBLA), and cannabicyclovarin (CBLV) | - unknown biological properties | [23] |
| CBN (Cannabinol) | 11 | 8-hydroxycannabinolic acid-A and 8-hydroxycannabinol | - affinity for CB1 and CB2 receptor is low. | [47] |
| CBT (Cannabitriol) | 9 | -trans-cannabitriol, trans-BT-C5, trans-cannabitriol (-trans-CBT-C5) | nd | [23] |
| Miscellaneous | 30 | Dehydrocannabifuran (DCBF-C5), cannabifuran (CBF-C5) | nd | [23] |
| Cannabinoids 120 | | | | |
| Total Non-cannabinoids 445<br>Cannflavin C, chrysoeriol, 6-prenylapigenin, 4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene | | | | |
| Total chemicals 565 | | | | |

## 4. ANTIOXIDANT ACTIVITY

An aggregate of 545 compounds has been identified from *Cannabis sativa*. Generally, phenolic compounds (flavonoids) are responsible for antioxidant activity [46]. Drinic et al., analyzed antioxidant the activity of extracts of *C. sativa* using DPPH (2,2'-diphenyl-1-picrylhydrazyl) assay,and antioxidant activity was expressed through $EC_{50}$ values ranging from 0.1331 mg/ml to 0.4353 mg/ml and 0.2055 mg/ml to 0.7563 mg/ml for aerial parts of young and mature hemp, respectively [57]. Wang et al., and Girgih et al. reported that proteins isolated from *Cannabis* could be effectively hydrolyzed by Neutrase and these hydrolysates exhibit antioxidant activity determined by DPPH assay and $Fe^{2+}$ chelating capability [58,59]. Hydrolysates showed DPPH radical

scavenging activity ($IC_{50}$) ranging from 2.3 mg/ml to 3.5 mg/ml for different time intervals. Antioxidant assays of hemp seeds including FRAP, DPPH, and Chelating power assays suggest significant antioxidant capacity [60-62].

*C. sativa* seeds contain mainly storage proteins (albumin 25-37%, legumin 67-75%) and show antioxidant activities against human keratinocytes [63]. The antioxidant activity of hemp determined by reducing power method using solvent extracts of different polarity at different extraction times was found to range between 0.2025 to 0.866% for acetone and methanol extracts, respectively [64]. Lignanamides (cannabisin M, cannabisin N, cannabsin O, and 3,3'-dimethyl-heliotropamide) isolated from Hemp seeds show antioxidant and acetylcholinesterase inhibition activities [65].

Hemp seed extracts increase gene expression of antioxidant enzymes (SOD, glutathione peroxidase, and catalase) in a concentration-dependent manner in $H_2O_2$- challenged HepG2 cells [66]. Hemp seed oil at different concentrations improves the oxidative state of *Drosophila melanogaster* under non-stressed as well as $H_2O_2$-induced stress conditions [67]. *C. sativa* essential oils exhibit antioxidant activity with $IC_{50}$ values of 1.6 mg/ml for DPPH assay (free radical scavenging activity), 1.8 mg/ml for β-carotene/linoleic acid assay, and 0.9 mg/ml for reducing power assay [68]. Ahmed et al. reported that different organic solvent extracts of *C. sativa* leaves showed DPPH inhibition activities ranging from 34.2% to 55.57% [69].

Stem, leaves, and inflorescence of male and female hemp plants exhibit high ABTS (2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) radical cation scavenging activity, DPPH assay, TPC (Total Phenolic Content) assay and metal chelating activity [70]. *C. sativa* var. *future* inflorescence extract was used to determine the antioxidant activity *in vitro* and on an ex vivo model of human erythrocytes [71-73]. *Cannabis fibrant* extracts obtained from the inflorescence of a non-psychotropic variety of hemp (*C. sativa* var. *fibrant)* show a strong and concentration-dependent antioxidant activity [74]. Singh et al. screened the methanolic extract of hemp for antioxidant activity with DPPH assay value of 45.8% [75].

Lignanamides, cannabisins, 3,3'-demethylgrossamide, and N-*trans*-caffeoyltyramine extracted from *Cannabis* were evaluated on the mammalian arginase assay, which showed that N-*trans*-caffeoyltyramine exhibited higher antioxidant activity with $IC_{50}$ value of 20.9 µM [76].

Green synthesized silver nanoparticles of hemp leaves were used for antioxidant activity evaluation using ABTS and DPPH assays, and results ranges from 73.109% to 90.33% inhibition and 1.506% to 6.670 % inhibition for ABTS and DPPH assays, respectively [77]. Green synthesized gold nanoparticles of hemp leaves showed antioxidant activity. $IC_{50}$ values of DPPH assay for leaf crude extract and gold nanoparticles were 361 µg/ml and 196 µg/ml, respectively [78]. The DPPH radical inhibition percentage shown by green synthesized ZnO nanoparticles from hemp leaves was 88% at 1500 µg/ml [79]. Whilst these findings reveal the good antioxidant potential of *C. sativa*, further in vivo studies are warranted, particularly focusing on how these plant constituents may interfere with the antioxidant enzymes.

## 5. ANTI-CANCER ACTIVITY

Over the past years, several studies on cell cultures and animal models have demonstrated that phytocannabinoids possess potential anti-cancer properties, including the inhibition of invasion and metastasis, angiogenesis,and promote apoptosis in cancer cells [14,80-84]. Cannabinoids and their derivatives exert palliative effects in cancer patients by preventing nausea, vomiting, pain and appetite stimulation, and attenuation of wasting [85].

The discovery of the anti-cancer effect of cannabinoids can be dated back to Munson et al., who demonstrated that the administration of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), $\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC)

and cannabinol inhibited the growth of Lewis lung adenocarcinoma cells in vitro and in vivo after oral administration in mice in a dose-dependent manner [86,87]. Besides cannabinoids, terpenes and flavonoids have also been shown to exert anti-tumorigenic actions. $\Delta^9$-THC is a major psychoactive compound present in Hemp which mediates its effect by binding and activating CB1 receptors in the central nervous system [88].

THC at a concentration of 14 µM inhibited overall cell growth in the MCF-7 cell line [89]. In breast cancer cells, THC inhibited the cell cycle progression at G2/M phase by down-regulating Cdc2, and induced apoptosis via CB2 receptor [90]. McAllister et al., reported that THC at a concentration of 1.2 µM/L was able to reduce the proliferation and invasion of breast cancer cells via reducing the expression of Id-1 transcriptional factor [91]. Takeda et al., found that $\Delta^9$-THC inhibited estrodiol-induced cell proliferation by inhibiting estrogen receptor α (ER α) activation [92]. Sharma and Sharma reported that green synthesized $Cr_2O_3$ nanoparticles from *C. sativa* leaf extracts possessed potent anti-cancer activity against HepG2 cancer cell line [93]. Green synthesized Ag and ZnO nanoparticles from callus extract of *C. sativa* showed promising cytotoxic potential against HepG2 cell lines [94]. Chang et al. reported that the gold- nanoparticles synthesized using aqueous extracts of *C. sativa* leaf can be used for the therapy of acute lymphoblastic leukemia and T-cell leukemia [78]. Go et al., found that Cannabidiol (CBD), which is one of the identified cannabinoid in the *C. sativa*, has anti-cancer potential as a cytotoxic drug for Head and Neck Squamous Cell Carcinoma (HNSCC) and combinational treatment of CBD enhanced the efficacy of chemotherapeutic drugs [95]. Results obtained by treating human prostate cancer cell lines LNCaP, DU145, and PC3 with Cannabidiol (CBD) clearly indicate that CBD is a potent inhibitor of cancer cell growth and induces apoptosis in a dose-dependent manner [96]. Cannabichromene (CBC) from *C. sativa* extracts, in combination with CBD and THC, was found to induce apoptosis, cell-cycle arrest, inhibited cell migration, and affected F-actin integrity [97]. Methanolic extracts of *C. sativa* exhibit potent anti-cancer activity with an $IC_{50}$ value of 8.63 µg/ml against the colon cancer cell line, whereas, CBC and THC have $IC_{50}$ values of 6.06 and 14.33 µg/ml, respectively [98].

In contrast, THC was shown to stimulate cancer cell proliferation in breast cancer and MCF-7 cell by increasing Human Epidermal Growth Factor 2 (HER2) expression [92]. Similarly, Mckallip et al., reported that $\Delta^9$-THC exposure led to increased 4T1 mammary carcinoma growth and metastasis in mice [99].

## 6. ANTI-MICROBIAL ACTIVITY

An in vitro disk diffusion assay was carried out to evaluate the antimicrobial activity of the essential oils from three varieties of *Cannabis sativa* (Carmagnola, Fibranova and Futura) against various Gram-positive (*Clostridium bifermentas, C. butyricum, C. sporogenes, C. tyrobutyricum, Enterococcus hirae, E. faecium, Streptococcus salivarius*) and Gram-negative (*Pectobacterium carotovorum* subsp. *carotovorum, Pseudomonas corrugata, P. fluorescens, P. savastonoi* pv. *phaseolicola, P. syringae* pv. *atrofaciens, Pseudomonas viridiflava, P. campestris* pv. *pruni*) bacteria. All extracts dose-dependently inhibited these bacteria [100]. Another study showed that the aqueous and acetone extracts of the plant were active against bacteria *Pseudomonas aeruginosa*, *Vibro cholerae*, and fungi *Cryptococcus neoformans*, *Candida albicans*. The minimum inhibitory concentrations (MIC) of these extracts against the microorganisms were in the range of 5 µg/ml and 10 µg/ml [101].

Novak et al. evaluated the antibacterial activity of the essential oils of five different cultivars of *C. sativa* (SwissMix, Felina 34, Fedrina 74, Kompolti, Secuemi) against a large panel of Gram-negative and Gram-positive pathogens with only modest activity against *Acinetobacter calcoaceticus* and *Brevibacterium linens* [102]. The heat-treated retted, semi-retted, and non-retted hemp hurd powder (at 160°C for 2 h) showed efficient antibacterial activity up to 90% reduction in CFU against *E. coli* [103]. Another study showed that minimum

inhibitory concentrations (MIC) of cannabidiol (CBD) from *C. sativa* against *Salmonella newington* and *S. typhimurium* was 0.0125 µg/ml and 0.125 µg/ml, respectively [104].

The ethanolic and petroleum ether extracts of the leaves of *Cannabis sativa* exhibited antimicrobial activity against Gram-positive (*Baccilus subtilus, B. pumilus, Staphlococcus aureus, Micrococcus flavus*), Gram-negative bacteria (*Proteus vulgaris, Bordetella bronchioseptica*) and fungi (*Candida albicans, Aspergillus niger*) [105]. Satyal and Setzer screened the essential oil from Nepalese *Cannabis sativa* for antimicrobial activity with the Minimum Inhibitory Concentration (MIC) of 625 µg/mL for *Bacillus cereus*, 2500 µg/mL for *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, 625 µg/mL for *Aspergillus niger* and 1250 µg/mL for *Candida albicans* [106]. Another testing of the *Cannabis fibrant* Hexane Extract 1 (CFHE1) and *C. fibrant* Hexane Extract 2 (CFHE2) on *Staphylococcus aureus* and methicillin-resistant clinical strains led to the modest inhibitory effect with Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of 4.88 µg/ml for CFHE1, and 4.88 and 19.53 µg/ml, respectively, for CFHE2 against *Staphylococcus aureus* and MIC between 1.22 and 9.77 µg/ml and MBC between 4.88 and 78.13 µg/ml for methicillin-resistant *S. aureus* (MRSA) using vancomycin as a standard [74].

Singh et al. reported the antibacterial activity of the green synthesized Ag-nano particles from *C. sativa* against *Pseudomonas aeruginosa* and *Escherichia coli* with MBC values of 12.5 and 25 µg/mL and MIC values of 6.25 and 5 µg/mL against *P. aeruginosa* and *E. coli*, respectively [107]. Ag nanoparticles prepared from leaf extracts of *C. sativa* exhibited the highest antibacterial potential against *Escherichia coli* and *Micrococcus luteus* [108]. Additional testing of bactericidal activity of Ag-NPs and ZnO-NPs synthesized from callus extract of *C. sativa* showed that Ag-NPs exhibited the highest activity against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* with 14 mm and 12 mm zone of inhibition, respectively and ZnO-NPs showed highest activity against *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Bacillus subtilis* with an inhibition zone of 20 mm, 18 mm, and 15 mm, respectively [94]. Overall, *C. sativa* extracts have demonstrated *in vitro* activity against selected microorganisms, which should be further investigated particularly by employing *in vivo* models of infection and the molecular mechanisms underlying the antimicrobial activity of *C. sativa* extracts/constituents should also be elucidated.

## 7. PESTICIDAL ACTIVITY

There are some evidences that *Cannabis sativa* possesses pesticidal activity. The toxicity of essential oils was evaluated against larvae of *Hyalomma dromedarii and Dermanyssus gallinae* which showed $LC_{50}$ values of 73 µg/mL and 47.1 µg/mL, respectively [109]. Petroleum ether, Carbon tetrachloride, and methanol extracts of *C. sativa* have been evaluated against the *Culex quinquefasciatus* larvae. The $LC_{50}$ values of Petroleum ether, Carbon tetrachloride, and methanol extracts were 294.42 ppm, 88.51 ppm, and 160.78 ppm, respectively, after 24h of exposure [110]. Another observation showed that the $LC_{50}$ value (24h exposure) of essential oil of *C. sativa* against *Culex quinquefasciatus* was 127.3 µg/ml [111]. Rossi et al. evaluated the toxicity of *C. sativa* essential oils and observed that $LC_{50}$ values were ranging from 73.50 to 78.80 ppm for larvae and 20.13 to 67.19 ppm for pupae of *Anopheles stephensi* and *A. gambiae*, respectively [112]. Benelliet al. evaluated the toxicity of essential oils from the inflorescence of industrial hemp (*C. sativa*) cv Felina 32 and found that it was highly toxic to aphid *Myzus persicae* adult (($LD_{50}$ = 3.5 ml/L) and *Musca domestica* flies ($LD_{50}$ = 43.3 µg/adult) and moderately toxic towards *Spodoptera littoralis* larvae ($LD_{50}$ = 152.3 µg larva−1) and *C. quinquefasciatus* 3rd instar larva ($LC_{50}$ = 252.5 µL/L) [113]. Additionally, Bedini et al. evaluated the toxicity of essential oils of *C. sativa* against larvae of *Aedes albopictus*, adults of *Physa marmorata*, and nymphs of *Cleon dipterum* with $LC_{50}$ values of 301.56, 282.17 and 35.37 µL/L [114]. *C. sativa* essential oil was found

to be toxic against *Reticulitermes virginicus* with $LC_{50}$ 354µg/mL [106]. It is evident from these studies that *Cannabis sativa* can be potentially used as biopesticides. Further, detailed investigations should be carried out in the future to discover new plant-based chemical entities that could replace the harmful commercial pesticides.

## 8. ACUTE AND CHRONIC TOXICITY OF *CANNABIS* ON HUMANS

Acute *Cannabis* use negatively impacts memory and learning abilities. For instance, acute cannabis intoxication has frequently been reported to result in noticeable changes in subjective mental state with detrimental effects on neuropsychological functioning, including learning performance and resulting in decreased attention and working memory [115-118].

Pope found that extensive *Cannabis* usage was linked to lower attentional/executive system performance, as seen by lower mental flexibility, higher perseverance, and lower learning [119]. Investigations of acute effects among non-severe heavy users, higher concentrations of the psychoactive compound tetrahydrocannabinol (THC) have been linked to deficits in planning and control impulse activities, with effects lasting for up to four weeks after drug use. [120]

Compared to non-users *Cannabis* users demonstrated deficits on, visual recognition, verbal skills, delayed visual recall, and short- and long-interval prospective memory tasks [121]. In regular marijuana users, marijuana's immediate effects may have an impact on a person's cognitive-motor abilities and the brain mechanisms that control driving and coordinated movement in regular marijuana users [122]. Addiction is one of the most detrimental effects of persistent *Cannabis* use. The emotional reactions to cannabinoids are not always positive and delightful. Instead, CB1 receptor activation may also result in anxiety and panic [123]. Diagnoses of depression, along with anhedonia, agoraphobia, and suicidal ideation, were found to be significantly linked to an increased likelihood of cannabis use [124-126]. A subgroup of cannabis users may be more susceptible to developing chronic psychoses like schizophrenia due to genetic vulnerability [127].

## 9. CONCLUSION

*Cannabis* is an ethnobotanically rich and phytochemical significant therapeutic plant. Various ancient literature and multiple in vitro and in vivo studies on *Cannabis sativa* have demonstrated its remarkable medicinal potential. *C. sativa* is enriched with significant antimicrobial and antioxidant activity due to its active phytoconstituents like cannabinoids, phenolic compounds, and tannins. Investigations have revealed the toxicity of the phytoconstituents of *C. sativa*. However in-depth investigations are required to evaluate the relative toxicity and safety of the phytochemicals to better understand their clinical relevance and applications to assure adequate efficacy and safety.

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## REFERENCES

1. Russo EB, Jiang HE, Li X, Carboni A, Del Bianco F, Mandolino G, et al. Phytochemical and genetic analyses of ancient cannabis from Central Asia. J Exp Bot. 2008; 59(15): 4171-4182.
2. Crocq MA. History of cannabis and the endocannabinoid system. Dialogues Clin Neurosci. 2022; 22(3): 223-228.

3. Russo EB. History of cannabis and its preparations in saga science, and sobriquet. Chem Biodivers. 2007; 4(8): 1614-1648.
4. Zuardi AW. History of cannabis as a medicine: a review. Braz J Psychiatry. 2006; 28: 153-157.
5. Piluzza G, Delogu G, Cabras A, Marceddu S, Bullitta S. Differentiation between fiber and drug types of hemp (Cannabis sativa L.) from a collection of wild and domesticated accessions. Gen Resour Crop Evol. 2013; 60(8): 2331-2342.
6. Touw M. The religious and medicinal uses of Cannabis in China, India and Tibet. J Psychoactive Drugs. 1981; 13(1): 23-34.
7. Skoglund G, Nockert M, Holst B. Viking and early Middle Ages northern Scandinavian textiles proven to be made with hemp. Scient Rep. 2013; 3(1): 1-6.
8. Andre CM, Hausman JF, Guerriero G. Cannabis sativa: the plant of the thousand and one molecules. Front Plant Sci. 2016; 7: 19.
9. Flores-Sanchez IJ, Verpoorte R. Secondary metabolism in cannabis. Phytochemistry reviews. 2008; 7(3): 615-639.
10. Brenneisen R. Chemistry and analysis of phytocannabinoids and other Cannabis constituents. In: Marijuana and the Cannabinoids. 2007; 17-49.
11. Taura F, Sirikantaramas S, Shoyama Y, Shoyama Y, Morimoto S. Phytocannabinoids in Cannabis sativa: recent studies on biosynthetic enzymes. Chem Biodivers. 2007; 4(8): 1649-63.
12. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015; 313(24): 2456-2473.
13. Bapat SN, Cannabis: the forgotten sacred plant of India. J Ayurveda Holistic Med. 2015; 3(5): 92-96.
14. Tomko AM, Whynot EG, Ellis LD, Dupré DJ. Anti-cancer potential of cannabinoids, terpenes, and flavonoids present in cannabis. Cancers. 2020; 12(7): 1985.
15. Guindon J, Hohmann, AG. The endocannabinoid system and pain. CNS Neurol Disord-Drug Targets. 2009; 8(6): 403-421.
16. Slatkin NE. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: beyond prevention of acute emesis. J Support Oncol. 2009; 5(5 Suppl 3): 1-9.
17. Viveros MP, Marco EM. Cannabinoids, anxiety and depression. Natural products II, 2007; 227-249.
18. Järvinen T, Pate DW, Laine K. Cannabinoids in the treatment of glaucoma. Pharmacol Ther. 2002; 95(2): 203-220.
19. Liang YC, Huang CC, Hsu KS. Therapeutic potential of cannabinoids in trigeminal neuralgia. Curr Drug Targets-CNS Neurol Disord. 2004; 3(6): 507-514.
20. Savo V, La Rocca A, Caneva G, Rapallo F, Cornara, L. Plants used in artisanal fisheries on the Western Mediterranean coasts of Italy. J Ethnobiol Ethnomed. 2013; 9(1): 1-14.
21. Tang K, Struik, PC, Yin X, Thouminot C, Bjelková, et al., Comparing hemp (Cannabis sativa L.) cultivars for dual-purpose production under contrasting environments. Indust Crops Prod. 2016; 87: 33-44.
22. Farag S, Kayser O. The cannabis plant: botanical aspects. In: Handbook of cannabis and related pathologies (pp. 3-12). Academic Press. 2017.
23. Basyal P, Regmi P. Ethnobotany, Taxonomy and Phytochemistry of Cannabis sativa. Int J Med Biomed Sci. 2021; 5(2): 13-19.
24. Happyana N, Agnolet S, Muntendam R, Van Dam, et al., Analysis of cannabinoids in laser-microdissectedtrichomes of medicinal Cannabis sativa using LCMS and cryogenic NMR. Phytochemistry. 2013; 87: 51-59.
25. Huchelmann A, Boutry M, Hachez C. Plant glandular trichomes: natural cell factories of high biotechnological interest. Plant Physiol. 2017; 175(1): 6-22.

26. Schultes RE, Klein WM, Plowman T, Lockwood TE. Cannabis: an example of taxonomic neglect. Cannabis Culture. 1975; 21-38.
27. Merlin MD. Archaeological evidence for the tradition of psychoactive plant use in the old world. Econ Bot. 2003; 57(3): 295-323.
28. Long T, Wagner M, Demske D, Leipe C, Tarasov PE. Cannabis in Eurasia: origin of human use and Bronze Age trans-continental connections. Veget History Archaeobot. 2017; 26(2): 245-258.
29. Abel EL. Marihuana: the first twelve thousand years. Springer Science & Business Media. 2013.
30. Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M., et al, Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol. 2018; 227: 300-315.
31. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: ancient times to the 1980s. Epilepsy Behav. 2017; 70: 298-301.
32. Epstein HA. A natural approach to soothing atopic skin. Skinmed. 2010; 8(2): 95-97.
33. Mercuri AM, Accorsi CA, Bandini Mazzanti, M. The long history of Cannabis and its cultivation by the Romans in central Italy, shown by pollen records from Lago Albano and Lago di Nemi. Veget History Archaeobot. 2002; 11(4): 263-276.
34. Lozano I. The therapeutic use of Cannabis sativa (L.) in Arabic medicine. J Cannabis Therapeut. 2001; 1(1): 63-70.
35. Goutopoulos A, Makriyannis A. From cannabis to cannabinergics: new therapeutic opportunities. Pharmacol Ther. 2002; 95(2): 103-117.
36. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006; 66(2): 234-246.
37. Tavhare S, Acharya R. Bhanga (Cannabis sativa L.) as an activity potentiator in Ayurvedic classics and Indian alchemy (Rasashastra): A critical review. Int J Ayurvedic Med. 2016; 7(3): 136-152.
38. Russo E. Cannabis in India: ancient lore and modern medicine. In: Cannabinoids as therapeutics. Birkhäuser Basel. 2005: 1-22.
39. Kuddus M, Ginawi IA, Al-Hazimi. A. Cannabis sativa: An ancient wild edible plant of India. Emirates J Food Agricult. 2013: 736-745.
40. Singh M, Sardesai MM. Cannabis sativa (Cannabaceae) in ancient clay plaster of Ellora Caves, India. Curr Sci. 2016: 884-891.
41. Akhter N, Rashid A, Murad W, Bergmeier E. Diversity and use of ethnomedicinal plants in the region of Swat, North Pakistan. J Ethnobiol Ethnomed. 2013; 9: 25.
42. Narcotic Drugs and Psychotropic Substances Act in India, 1985. Page 11-Chapter III:8(b).
43. ElSohl M, Gu W. Constituents of Cannabis sativa. Handbook of Cannabis. 2014; 3: 1093.
44. ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. Phytocannabinoids. 2017: 1-36.
45. Jin D, Dai K, Xie Z, Chen J. Secondary metabolites profiled in cannabis inflorescences, leaves, stem barks, and roots for medicinal purposes. Scient Rep. 2020; 10(1): 1-14.
46. Al Khoury A, Sleiman R, Atoui A, Hindieh, P, Maroun RG, Bailly JD, El Khoury A. Antifungal and anti-aflatoxigenic properties of organs of Cannabis sativa L.: relation to phenolic content and antioxidant capacities. Arch Microbiol. 2021; 203(7): 4485-4492.
47. Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. Nat Prod Rep. 2016; 33(12): 1357-1392.
48. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012; 133(1): 79-97.

49. Pertwee R. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Brit J Pharmacol. 2008; 153(2): 199-215.
50. Ashton CH. Pharmacology and effects of cannabis: a brief review. Brit J Psychiatry. 2001; 178(2): 101-106.
51. Izzo A, Borrelli F, Capasso R., Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009; 30: 515-527.
52. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent α2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. Brit J Pharmacol. 2010; 159(1): 129-141.
53. Pagano E, Montanaro V, Di Girolamo A, Pistone A, Altieri V, Zjawiony JK., Capasso R. Effect of non-psychotropic plant-derived cannabinoids on bladder contractility: focus on cannabigerol. Nat Prod Commun. 2015; 10(6): 1934578X1501000653.
54. Romano B, Borrelli F, Fasolino I, Capasso R., Piscitelli F, Cascio MG, Izzo AA. The cannabinoid TRPA1 agonist cannabichromene inhibits nitric oxide production in macrophages and ameliorates murine colitis. Brit J Pharmacol. 2013; 169(1): 213-229.
55. De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P, Di Marzo V. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. J Pharmacol Exp Ther. 2008; 325(3): 1007-1015.
56. IbeasBih C, Chen T, Nunn AV, Bazelot M, Dallas M., Whalley BJ. Molecular targets of cannabidiol in neurological disorders. Neurother. 2015; 12(4): 699-730.
57. Drinić Z, Vidović S, Vladić J, Koren A, Kiprovski B, Sikora V. Effect of extraction solvent on total polyphenols content and antioxidant activity of Cannabis sativa L. Lekovitesirovine. 2018; (38): 17-21.
58. Wang XS, Tang CH, Chen L, Yang XQ. Characterization and antioxidant properties of hemp protein hydrolysates obtained with Neutrase®. Food Technol Biotechnol. 2009; 47(4) 428-434.
59. Girgih AT, Udenigwe CC, Aluko RE. In vitro antioxidant properties of hemp seed (Cannabis sativa L.) protein hydrolysate fractions. J Am Oil Chemists Soc. 2011; 88(3): 381-389.
60. Rashida A, Alia V, Khajuriaa M, Faiza S, Jamwala S, Lonea JF, Vyasa D. Antioxidant Analysis in Seeds of Four Different Accessions of Cannabis sativa L. from Jammu. Res Rev Biotechnol Biosci. 2020; 7: 1-10.
61. Girgih AT, Udenigwe CC, Aluko RE. Reverse-phase HPLC separation of hemp seed (Cannabis sativa L.) protein hydrolysate produced peptide fractions with enhanced antioxidant capacity. Plant Foods Human Nutr. 2013; 68(1): 39-46.
62. Irakli M, Tsaliki E, Kalivas A, Kleisiaris F, Sarrou E, Cook CM. Effect of genotype and growing year on the nutritional, phytochemical, and antioxidant properties of industrial hemp (Cannabis sativa L.) seeds. Antioxidants. 2019; 8(10): 491.
63. Pontonio E, Verni M, Dingeo C, Diaz-de-Cerio E, Pinto D, Rizzello CG. Impact of enzymatic and microbial bioprocessing on antioxidant properties of hemp (Cannabis sativa L.). Antioxidants. 2020; 9(12): 1258.
64. Essien EE. Effect of extraction conditions on total polyphenol contents, antioxidant and antimicrobial activities of Cannabis sativa L. Electr J Environ Agricult Food Chem. 2011; 11(04): 300-307.
65. Yan X, Tang J, dos Santos Passos C, Nurisso A, Simoes-PiresCAJiM, Fan P. Characterization of lignanamides from hemp (Cannabis sativa L.) seed and their antioxidant and acetylcholinesterase inhibitory activities. J Agricult Food Chem. 2015; 63(49): 10611-10619.
66. Hong S, Sowndhararajan K, Joo T, Lim C, Cho H, Kim S, Jhoo JW. Ethanol and supercritical fluid extracts of hemp seed (Cannabis sativa L.) increase gene expression of antioxidant enzymes in HepG2 cells. Asian Pacific J Reprod. 2015; 4(2): 147-152.

67. Vitorović J, Joković N, Radulović N, Mihajilov-Krstev T, Cvetković VJ, Jovanović N, Bernstein N. Antioxidant Activity of Hemp (Cannabis sativa L.) Seed Oil in Drosophila Melanogaster Larvae under Non-Stress and H2O2-Induced Oxidative Stress Conditions. Antioxidants. 2021; 10(6): 830.
68. Nafis A, Kasrati A, Jamali CA, Mezrioui N, Setzer W, Abbad A, Hassani L. Antioxidant activity and evidence for synergism of Cannabis sativa (L.) essential oil with antimicrobial standards. Indust Crops Prod. 2019; 137: 396-400.
69. Ahmed M, JiM, Qin P, Gu Z, Liu Y, Sikandar, A, Javeed A. Phytochemical screening, total phenolic and flavonoids contents and antioxidant activities of Citrullus colocynthis L. and Cannabis sativa L. Appl Ecol Environ Res. 2019; 17: 6961-6979.
70. Nadeem I, Khan AU, Asghar MN, Ashfaq M, Shahid S, Ahmed D. In vitro total antioxidant and radical scavenging activities of organic extracts from leaves, stem and inflorescence of Cannabis sativa L. Asian J Chem. 2012; 24(11): 5067-5072
71. Palmieri S, Fanti F, Oliva E, Viteritti E, Sergi M, Pepe A, Compagnone D. Chemical characterization and evaluation of antioxidant activity from different cultivars of Cannabis sativa L. of Abruzzo's region. Nat Prod Res. 2022: 1-5.
72. Gabotti D, Locatelli F, Cusano E, Baldoni E, Genga A, Pucci L, Mattana M. Cell suspensions of Cannabis sativa (var. futura): Effect of elicitation on metabolite content and antioxidant activity. Molecules. 2019; 24(22): 4056.
73. Palmieri S, Maggio F, Pellegrini M, Ricci A, Serio A, Paparella A, Lo Sterzo C. Effect of the Distillation Time on the Chemical Composition, Antioxidant Potential and Antimicrobial Activity of Essential Oils from Different Cannabis sativa L. Cultivars. Molecules. 2021; 26(16): 4770.
74. Muscarà C, Smeriglio A, Trombetta D, Mandalari G, La Camera E, Grassi G, Circosta C. Phytochemical characterization and biological properties of two standardized extracts from a non-psychotropic Cannabis sativa L. cannabidiol (CBD)-chemotype. Phytother Res. 2021; 35(9): 5269-5281.
75. Singh V, Gupta R., Mittal A. Phytochemical, Antimicrobial, and Antioxidant Property of Cannabis sativa. World J Pharmac Res. 217; 6(16): 454-463.
76. Bourjot M, Zedet A, Demange B, Pudlo M, Girard-Thernier C. In vitro mammalian arginase inhibitory and antioxidant effects of amide derivatives isolated from the hempseed cakes (Cannabis sativa). Planta Med. 2016; 3(03): e64-e67.
77. Csakvari AC, Moisa C, Radu DG, Olariu LM, Lupitu AI, Panda AO, Copolovici DM. Green synthesis, characterization, and antibacterial properties of silver nanoparticles obtained by using diverse varieties of Cannabis sativa leaf extracts. Molecules. 2021; 26(13): 4041.
78. Chang Y, Zheng C, Chinnathambi A, Alahmadi TA, Alharbi SA. Cytotoxicity, anti-acute leukemia, and antioxidant properties of gold nanoparticles green-synthesized using Cannabis sativa L leaf aqueous extract. Arab J Chem. 2021; 14(4): 103060.
79. Shahzadi, T, Rehman S, Riaz T, Zaib M. (2020). Eco-friendly synthesis of ZnO nanoparticles using Cannabis sativa and assessment of its activities as efficient dyes removal and antioxidant agent. Int J Environ Anal Chem. 2020: 1-19.
80. Hinz B, Ramer R. Anti-tumour actions of cannabinoids. Brit J Pharmacol. 2019; 176(10): 1384-1394.
81. Kovalchuk O, Kovalchuk I. Cannabinoids as anticancer therapeutic agents. Cell Cycle. 2020; 19(9): 961-989.
82. Velasco G, Hernández-Tiedra S, Dávila D, Lorente M. The use of cannabinoids as anticancer agents. Progress Neuro-Psychopharmacol Biol Psych. 2016; 64: 259-266.
83. Velasco G, Sánchez C, Guzmán M. Towards the use of cannabinoids as antitumour agents. Nature Rev Cancer. 2012; 12(6): 436-444.
84. Guzma M. Cannabinoids: potential anticancer agents. Nature Rev Cancer. 2003; 3(10): 745-755.
85. Hamdani SS, Bhat BA, Nissar S. Ethnobotanical study of medicinal plants of Kashmir Valley, India having anticancer properties. Int J Res Appl Sci Biotechnol. 2020; 7(4): 84-91.

86. Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA. Antineoplastic activity of cannabinoids. J Nat Cancer Inst. 1975; 55(3): 597-602.
87. Hinz B, Ramer R. Cannabinoids as anticancer drugs: current status of preclinical research. Brit J Cancer. 2022: 1-13.
88. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. Pharmacy Ther. 2017; 42(3): 180.
89. Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L, Di Marzo V. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther. 2006; 318(3): 1375-1387.
90. Caffarel MM, Sarrió D, Palacios J, Guzmán M, Sánchez C. Δ9-tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. Cancer Res. 2006; 66(13): 6615-6621.
91. McAllister SD, Christian RT, Horowitz MP, Garcia A, Desprez PY. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. Mol Cancer Ther. 2007; 6(11): 2921-2927.
92. Takeda S, Yoshida K, Nishimura H, Harada M, Okajima S, Miyoshi H, Aramaki H. Δ9-Tetrahydrocannabinol disrupts estrogen-signaling through up-regulation of estrogen receptor β (ERβ). Chem Res Toxicol. 2013; 26(7): 1073-1079.
93. Sharma UR, Sharma N. Green Synthesis, Anti-cancer and Corrosion Inhibition Activity of Cr2O3 Nanoparticles. Biointerf Res Appl Chem. 2021; 11: 8402-8412.
94. Zaka M, Hashmi SS, Siddiqui MA, Rahman L, Mushtaq S, AliH, Abbasi BH. Callus-mediated biosynthesis of Ag and ZnO nanoparticles using aqueous callus extract of Cannabis sativa: Their cytotoxic potential and clinical potential against human pathogenic bacteria and fungi. Green Processing Synthesis. 2021; 10(1): 569-584.
95. Go YY, Kim SR, Kim, DY, Chae SW, Song JJ. Cannabidiol enhances cytotoxicity of anti-cancer drugs in human head and neck squamous cell carcinoma. Scient Rep. 2020; 10(1): 1-11.
96. Sharma M., Hudson JB, Adomat H, Guns E, Cox ME. In vitro anticancer activity of plant-derived cannabidiol on prostate cancer cell lines. Pharmacol Pharmacy. 2014; 5(08): 806.
97. Anis O, Vinayaka AC, Shalev N, Namdar D, Nadarajan S, Anil SM et al. Cannabis-derived compounds cannabichromene and Δ9-tetrahydrocannabinol interact and exhibit cytotoxic activity against urothelial cell carcinoma correlated with inhibition of cell migration and cytoskeleton organization. Molecules. 2021; 26(2): 465.
98. Rožanc J, Kotnik P, Milojević M, Gradišnik L, Knez Hrnčič, M, Knez Z, Maver U. Different Cannabis sativa extraction methods result in different biological activities against a colon cancer cell line and healthy colon cells. Plants. 2021; 10(3): 566.
99. McKallip RJ, Nagarkatti M, Nagarkatti PS. Δ-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. J Immunol. 2005; 174(6): 3281-3289.
100. Nissen L, Zatta A, Stefanini I, Grandi S, Sgorbati B, Biavati B, Monti A. Characterization and antimicrobial activity of essential oils of industrial hemp varieties (Cannabis sativa L.). Fitoterapia. 2010; 81(5): 413-419.
101. Lone TA, Lone RA. Extraction of cannabinoids from Cannabis sativa L. plant and its potential antimicrobial activity. Univ J Med Dent. 2012; 1: 51-55.
102. Novak J, Zitterl-Eglseer K, Deans SG, Franz CM. Essential oils of different cultivars of Cannabis sativa L. and their antimicrobial activity. Flavour Fragrance J. 2001; 16(4): 259-262.
103. Khan BA, Wang J, Warner P, Wang H. Antibacterial properties of hemp hurd powder against E. coli. J Appl Polymer Sci. 2015: 132(10).
104. Gildea L, Ayariga JA, Ajayi OS, Xu J, Villafane R, Samuel-Foo M. Cannabis sativa CBD Extract Shows Promising Antibacterial Activity against Salmonella typhimurium and S. newington. Molecules. 2022; 27(9): 2669.
105. Wasim K, Haq I, Ashraf M. Antimicrobial studies of the leaf of cannabis sativa L. Pakistan J Pharmac Sci. 1995; 8(1): 29-38.

106. Satyal P, Setzer WN. Chemotyping and determination of antimicrobial, insecticidal, and cytotoxic properties of wild-grown Cannabis sativa from Nepal. J Med Active Plants. 2014; 3(1): 9-16.
107. Singh P, Pandit S, Garnaes J, Tunjic S, Mokkapati VRSS, Sultan A et al. Green synthesis of gold and silver nanoparticles from Cannabis sativa (industrial hemp) and their capacity for biofilm inhibition. Int J Nanomed. 2018; 13: 3571-3591.
108. Chouhan S, Guleria S. Green synthesis of AgNPs using Cannabis sativa leaf extract: Characterization, antibacterial, anti-yeast and α-amylase inhibitory activity. Mater Sci Energy Technol. 2020; 3: 536-544.
109. Tabari MA, Khodashenas A, Jafari M., Petrelli R, Cappellacci L, Nabissi M et al. Acaricidal properties of hemp (Cannabis sativa L.) essential oil against Dermanys susgallinae and Hyalomma dromedarii. Indust Crops Prod. 2020; 147: 112238.
110. Maurya P, Mohan L, Sharma P, Srivastava CN. Larval susceptibility of Aloe barbadensis and Cannabis sativa against Culex quinquefasciatus, the filariasis vector. J Environ Biol. 2008; 29(6): 941-943.
111. Pavela R. Larvicidal property of essential oils against Culexquinquefasciatus Say (Diptera: Culicidae). Indust Crops Prod. 2009; 30(2): 311-315.
112. Rossi P, Cappelli A, Marinelli O, Valzano M, Pavoni L, Bonacucina G et al. Mosquitocidal and anti-inflammatory properties of the essential oils obtained from monoecious, male, and female inflorescences of hemp (Cannabis sativa L.) and their encapsulation in nanoemulsions. Molecules. 2020; 25(15): 3451.
113. Benelli G, Pavela R, Petrelli R, Cappellacci L, Santini G, Fiorini D et al. The essential oil from industrial hemp (Cannabis sativa L.) by-products as an effective tool for insect pest management in organic crops. Indust Crops Prod. 2018; 122: 308-315.
114. Bedini S, Flamini G, Cosci F, Ascrizzi R, Benelli G, Conti B. Cannabis sativa and Humuluslupulus essential oils as novel control tools against the invasive mosquito Aedesalbopictus and fresh water snail Physellaacuta. Indust Crops Prod. 2016; 85: 318-323.
115. Kalant H. Adverse effects of cannabis on health: an update of the literature since 1996. Progress Neuro-Psychopharmacol Biol Psych. 2004; 28(5): 849-863.
116. Gonzalez R. Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance. Neuropsychol Rev. 2007; 17: 347-361.
117. Vadhan NP, Hart CL, van Gorp WG, Gunderson EW, Haney M, Foltin RW. Acute effects of smoked marijuana on decision making, as assessed by a modified gambling task, in experienced marijuana users. J Clin Exp Neuropsychol. 2007; 29(4): 357-364.
118. Lundqvist T. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. Pharmacol Biochem Behav. 2005; 81(2): 319-330.
119. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA. 1996; 275(7): 521-527.
120. Almeida PP, Novaes MAFP, Bressan RA, Lacerda ALTD. Executive functioning and cannabis use. Braz J Psychiatry. 2008; 30: 69-76.
121. McHale S, Hunt N. Executive function deficits in short-term abstinent cannabis users. Human Psychopharmacol Clin Exp. 2008; 23(5): 409-415.
122. Weinstein A, Brickner O, Lerman H, Greemland M, Bloch M, Lester H, et al. Brain imaging study of the acute effects of Δ 9-tetrahydrocannabinol (THC) on attention and motor coordination in regular users of marijuana. Psychopharmacology. 2008; 196: 119-131.
123. Moreira FA, Lutz B. The endocannabinoid system: emotion, learning and addiction. Addiction Biol. 2008; 13(2): 196-212.

124. Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. Am J Psych. 2001; 158(12): 2033-2037.
125. Tournier M, Sorbara F, Gindre C, Swendsen JD, Verdoux H. Cannabis use and anxiety in daily life: a naturalistic investigation in a non-clinical population. Psych Res. 2003; 118(1): 1-8.
126. Pedersen W. Does cannabis use lead to depression and suicidal behaviours? A population-based longitudinal study. Acta Psych Scand. 2008; 118(5): 395-403.
127. Luzi S, Morrison PD, Powell J, Di Forti M, Murray RM. What is the mechanism whereby cannabis use increases risk of psychosis? Neurotox Res. 2008; 14: 105-112.