

# Medical *Cannabis sativa* (Marijuana or drug type): Psychoactive molecule, $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC)

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**Abstract:** This review paper highlights about Medical *Cannabis sativa* (Marijuana or drug type) containing psychoactive molecule,  $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC) as a part of educational awareness programme in India. *Cannabis sativa* and *Cannabis indica* were originally a **native** of **India** growing as a wild notorious noxious weed in the Indian Himalayan region. Marijuana (Charas, Ganja and Bhang in India) is a mind-altering (psychoactive) drug, produced by the *Cannabis sativa* plant. Marijuana (Charas, Ganja or Bhang drink in India) is an illicit drug containing very high levels (25-35%) of narcotic psychoactive molecule,  $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC) is banned and prohibited in India. Import, export, local sales and cultivation of *Cannabis* are illegal and prohibited in India. Phytocannabinoids ( $\Delta^9$ -Tetrahydrocannabinol- $\Delta^9$ -THC, and Cannabidiol- CBD) have attained a global attention recently due to the therapeutic potentials in Parkinson's disease, Schizophrenia, cancers, pain, anxiety, depression other neurological disorders as well as the Food and Drug Administration (FDA) approval of Epidiolex for Dravet syndrome and Lennox-Gauss Syndrome.  $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC) is known as the substance that makes a person feel a "high," while Cannabidiol (CBD) often promotes a feeling of relaxation. However, the adverse effects of Marijuana (medicinal cannabis) comes from studies of recreational users of marijuana led to the impaired short-term memory; impaired motor coordination; altered judgment; and paranoia or psychosis at high doses. The quality control of Cannabis products, contamination and adulteration of *Cannabis* products in Cannabis industry is another major issue. Therefore, a detailed study with clinical trials is warranted and this knowledge should be shared and explained to the customers.

**Key Words:** Bhang, *Cannabis sativa*, Charas, Ganja, Illicit drug, Narcotic drug, Psychoactive molecule, Schizophrenia,

## I. Introduction

*Cannabis sativa* is an economically and medicinally important plant species with a wide ranges of applications from producing fibre for clothing; seed for animal and human nutrition, and psychoactive compounds for medicinal, religious, and recreational use (1-34). Cannabis is the most commonly found noxious weed, cultivated, trafficked, and abused notorious illicit drug worldwide (1-30). For nearly a century, Cannabis has been stigmatized and criminalized across the globe, but in recent years, there has been a growing interest in Cannabis due to the therapeutic potential of phytocannabinoids (96). According to the survey report of World Health Organization (WHO), marijuana consumption has an annual prevalence rate of approximately 147 million individuals or nearly 2.5% of the global population (1-30). *Cannabis sativa* and *Cannabis indica* were originally a native of **India** growing as a wild notorious noxious weed in the Indian Himalayan region (1-33). Cannabis is also known as the **Pot gold** of Indian Himalayan Region. Cannabis has been used for thousands of years for recreational, medicinal, or religious purposes (1-35, 98-128). Many 19th-century practitioners described medicinal properties to Cannabis after the drug found its way to Europe during a period of colonial expansion into Africa and Asia (1-40). For example, William B. O'Shaughnessy, an Irish physician working at the Medical College and Hospital in Calcutta, West Bengal, India first introduced Cannabis (Indian hemp) to Western medicine as a treatment for tetanus and other convulsive diseases (1-33, 98-128).

Cannabis has gained a lot of popularity in the last few decades for not only being an **illicit drug** but for its medicinal values from ancient times and a potential source for modern drugs to treat several targets for human wellness (1-40, 98-128). The pharmacologic and therapeutic properties of preparations of *Cannabis sativa* and  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) its most psychoactive compound, have been extensively reviewed (1-40, 98-128). There is still a huge prejudice in society in relation to medical Cannabis due to its recreational use. In India, *Cannabis sativa* is also commonly known as Indian hemp, marijuana, Bhang, Ganja, and Charas, which are banned in India as an **illicit drug** (1-30). Sales and cultivation of Cannabis are **illegal** in India. However, this scenario is changing, and the social resistance is decreasing for the medicinal use of Cannabis (1-40, 98-

128). The plant derivatives were identified as **psychoactive** compound,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC or THC) and Cannabidiol (CBD), as well as, the endocannabinoid system, Cannabinoid receptors type 1 and type 2 (CB1 and CB2, respectively) (1-53). Phytocannabinoids have attained a global attention recently due to the therapeutic potentials in Parkinson's disease, Schizophrenia, cancers, pain, anxiety, depression other neurological disorders as well as the Food and Drug Administration (FDA) approval of Epidiolex for Dravet syndrome and Lennox-Gauss Syndrome (1-86). As interest in Cannabis expands throughout the globe, many issues have arisen concerning the lack of cultivation standards, overall quality control of Cannabis products, contamination and adulteration of Cannabis products (89-97).

## II. Cannabis has a long history in India

Cannabis has a long history in India, recorded in legends and religion (1-35). According to *Ayurveda* in India, the medicinal value of the Cannabis plants was well documented as Vijaya and often known as Desi Vijaya (1-33). The meaning of Vijaya is nothing but a **Victory**. This was the first Indian written evidence to support the medicinal value of Cannabis plants which was well documented in *Ayurveda* in India (1-33). The earliest written reference to Cannabis in India may occur in the *Atharvaveda*, dating to about 2500 BCE (1-33). Initial uses of Cannabis date back to almost 5000 years in **India** which was well documented in *Ayurveda* (1-33). The history of Cannabis use is rooted in the Asian subcontinent particularly in India, Bhutan, Nepal, China, Pakistan, Afghanistan, and other countries like Morocco, Persians Iran (1-33). It is found in various habitats ranging from sea level to the temperate and alpine foothills of the **Indian Himalaya Region** from where it was probably spread over the last 10,000 years (1-34). Therefore, medicinal uses of *Cannabis* might have started from **Indian Himalayan civilization** and moved to another civilization through consecutive millennia (1-33). Many of the historians believed that Indian Himalayan Region was the centre of origin of Cannabis sativa and Cannabis indica (1-40, 98-128).

### Cannabis sativa: Wind Pollinated and Dioecious

Further *Cannabis sativa* L. is a wind-pollinated, dioecious herb (i.e., the male and female reproductive structures are on separate plants), although monoecious plants can occur in some populations (1-40). Additionally, the species *Cannabis sativa* L. and *Cannabis indica* are a potential source of fibre, food, oil, and protein (1-40). However, Cannabis research work remains years behind than other crops because of the long legacy of prohibition and stigmatization (1-40). Most of the Cannabis varieties in the market today are hybrids (**700** hybrid strains) with both *Cannabis sativa* and *Cannabis indica* genetics (1-40). The  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol), the psychoactive molecule is largely concentrated around the flowering parts of the female plant (41-53). The leaves and male plants have less  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol), while the stalks and seeds contain almost none (41-53).

The Cannabis plant (*Cannabis sativa* L.) is broadly distributed and grows in temperate and tropical areas like India, China, Pakistan, Iran, Morocco, Afghanistan, Bhutan, and Nepal (1-40). Together with tobacco, alcohol and caffeine, Cannabis, Marijuana (Charas, Ganja and Bhang in India) is one of the most widely consumed drugs throughout the world, and has been used as a drug and a source of fibre since historical times (1-45). Herbal Cannabis consists of the dried flowering tops and leaves. Cannabis resin is a compressed solid made from the resinous parts of the plant, and female flowers (1-50). The leaves of Cannabis sativa are reasonably characteristic. Further, Cannabis and Cannabis resin can both be positively identified by low-power microscopy, where the appearance of glandular trichomes and cystolithic hairs is diagnostic (1-50). Cannabis oil (hash oil) is often produced locally from cannabis or cannabis resin by means of solvent extraction (1-60). Intensive indoor cultivation has become widespread in Europe and elsewhere. This is based on improved seed varieties and procedures such as artificial heating and lighting, hydroponic cultivation in nutrient solutions and propagation of cuttings of female plants (1-50). It leads to a high production of flowering material (sometimes known as 'skunk') (1-45). As with other naturally occurring drugs of misuse (e.g. heroin and cocaine), total synthesis is not currently an economic proposition (1-50). No precursors to THC are listed in the United Nations 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1-50). Cannabis was included as a controlled drug in the United Nations' Single Convention on Narcotic Drugs, held in 1961, and its use is illegal in most countries (88).

### Psychoactive molecule, $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC)

THC stands for  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC). It is a Cannabinoid molecule in marijuana and hemp too (1-53, 98-128). The credit of the discovery of **Cannabidiol** (CBD) in 1963 and  **$\Delta^9$ -tetrahydrocannabinol (THC)** in 1964 isolated from *Cannabis sativa* attributed to Dr. Raphael Mechoulam and his team (1-53). Professor **Raphael Mechoulam**, the Godfather of Cannabis Science was active in Cannabinoids Research work at the Hebrew University of Jerusalem, Israel died at the age of 92 on 9th March 2023 (1-53). Cannabis (hash) Red oil is a solvent extract of Cannabis and Red oil is a dark viscous liquid (1-60). Cannabis is almost always smoked, often mixed with tobacco (1-50). Almost all consumption of herbal cannabis and resin is of illicit material (1-53). Some therapeutic benefit as an analgesic has been claimed for cannabis, and **Dronabinol** is a licensed medicine in some countries for the treatment of nausea in cancer chemotherapy (1-53). Cannabis products and  $\Delta^9$ -THC ( $\Delta^9$ -

tetrahydrocannabinol) are under international control. Imported herbal Cannabis occurs as compressed blocks of dried brown vegetable matter comprising the flowering tops, leaves, stalks and seeds of *Cannabis sativa* (1-50). Cannabis resin is usually produced in 250-g blocks, many of which carry a brand mark impression (1-25). Cannabis and cannabis resin are listed in Schedules I and IV of the United Nations 1961 Single Convention on Narcotic Drugs, In Article 1 (1-50). Along with a number of its isomers and stereochemical variants,  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) is listed in Schedule I of the United Nations 1971 Convention on Psychotropic Substances (1-50, 98-128).

The major active principle in all cannabis products is  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) (Molecular formula:  $C_{21}H_{30}O_2$ ; Molecular weight: 314.4 g/mol) also known by its International Non-Proprietary Name (INN) as Dronabinol (1-50). The unsaturated bond in the cyclohexene ring is located between C-9 and C-10 in the more common dibenzopyran ring numbering system (1-53). There are four stereoisomers of THC, but only the (-)-trans isomer occurs naturally (CAS-1972-08-03) (1-50). The fully systematic name for this THC isomer is (-)- (6*aR*,10*aR*)-6,6,9-trimethyl-3-pentyl- 6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol (20-53). Two related substances,  $\Delta^9$ - tetrahydrocannabinol-2-Oic acid and  $\Delta^9$ -tetrahydrocannabinol-4-oic acid (THCA), are also present in cannabis, sometimes in large amounts (1-50). During smoking, THCA is partly converted to THC. The active isomer  $\Delta^8$ -THC, in which the unsaturated bond in the cyclohexene ring is located between C-8 and C-9, is found in much smaller amounts (1-50). The  $\Delta^9$ -tetrahydrocannabinol, the major psychoactive principle of cannabis, showed the partial ring numbering system in the more common dibenzofuran system (1-50). Other closely related substances that occur in Cannabis include Cannabidiol (CBD) and, in aged samples, Cannabinol (CBN), both of which have quite different pharmacological effects to THC (1-53). Other compounds include the Cannabivarin and Cannabichromenes which are collectively known as Cannabinoids (1-60). Unlike many psychoactive substances, Cannabinoids are not nitrogenous bases (1-53).

$\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) is recognized as the main psychoactive ingredient of Cannabis (1-54).  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) is the narcotic substance that causes people who use marijuana (Charas, Ganja or Bhang in India) to feel high (1-55, 98-128).  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) is just one of the 580 different substances and 100 different Cannabinoid molecules that have been detected in marijuana (Medical Cannabis sativa) (1-55, 98-128). Marijuana is made up of many components called phytoannabinoids, but  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) is the most recognized (1-55). Another important Cannabinoid molecule that has received major interest is Cannabidiol (CBD) (1-60). THC is known as the substance that makes a person feel a "high," while CBD often promotes a feeling of relaxation (1-50, 98-128). Two of these components,  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) and Cannabidiol (CBD), have effects that are commonly known to people who used marijuana and the chronic effects associated with cannabis use disorder are well-known (1-60). It has been found that people with long term use of marijuana often experience impaired cognitive functioning, memory loss, trouble concentrating, decreased problem-solving skills, low ability to control emotions, and difficulty making decisions (1-65). This is mainly due to the fact that Medical Cannabis sativa (marijuana or drug type) contains very high level (25-37% of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) content (1-60).

The pharmacology of cannabis is complicated by the presence of a wide range of cannabinoids. At small doses, Cannabis produces euphoria, relief of anxiety, sedation and drowsiness (1-60). In some respects, the effects are similar to those caused by alcohol (1-65). Anandamide has been identified as the endogenous ligand for the Cannabinoid receptor and has pharmacological properties similar to those of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) (20-60). When cannabis is smoked, THC can be detected in plasma within seconds of inhalation; it has a half-life of 2 hours (20-65). Following the smoking of the equivalent of 10–15 mg over a period of 5–7 minutes, peak plasma levels of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) are around 100  $\mu\text{g/L}$  (20-57). It is highly lipophilic and widely distributed in the body (1-60). Two active metabolites are formed: 11-hydroxy-  $\Delta^9$ -THC and 8 $\beta$ -hydroxy-  $\Delta^9$ -THC (50-57). The first is further metabolised to  $\Delta^9$ -THC -11-oic acid. Two inactive substances are also formed 8 $\alpha$ -hydroxy-  $\Delta^9$ -THC and 8 $\alpha$ ,11-dihydroxy-  $\Delta^9$ -THC, and many other minor metabolites, most of which appear in the urine and faeces as glucuronide conjugates (1-65). Some metabolites can be detected in the urine for up to 2 weeks following smoking or ingestion (45-55). There is little evidence for damage to organ systems among moderate users, but consumption with tobacco carries all of the risks of that substance (40-65). Most interest in the adverse properties of cannabis has centred on its association with schizophrenia, although it is still unclear if there is a causative relation between mental health and cannabis. Fatalities directly attributable to cannabis are rare (20-65).

### III. The definition of Marijuana (Medical Cannabis or drug type)

The concentration of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol), the primary psychoactive component of Cannabis (*sativa*, *indica*, and *ruderalis*) more than 0.3% is defined as the Medical Cannabis sativa (Marijuana or drug type) (1-87). In general, the level of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) in Cannabis is higher than 0.3% is considered as the Marijuana or drug type (1-55). On the other hand the level of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) below 0.3% is designated as Hemp (Industrial Cannabis or fiber or food type) (1-35). Most of the Marijuana hybrids have very higher level (25-35%) of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol). Another interesting fact is that marijuana that is available today is more powerful than the marijuana of the 1960s, containing

higher levels (25-35%) of the active ingredient  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol), which is the psychoactive component in weed (54-86, 98-128).

Whiting et al., (2015) (88) Medical Cannabis refers to the use of Cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms (88). Cannabinoids can be administered orally, sublingually, or topically; they can be smoked, inhaled, mixed with food, or made into tea (88). They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of Cannabidiol, or manufactured synthetically (88). Prescribed Cannabinoids include dronabinol capsules, Nabilone capsules, and the oromucosal spray Nabiximols (88). Some countries have legalized medicinal-grade Cannabis for chronically ill patients (88). Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis (88). In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis; other countries have similar laws (88).

### Medical Cannabis sativa (Marijuana or drug type)

Marijuana (Charas, Ganja and Bhang in India) is a mind-altering (psychoactive) drug produced by the *Cannabis sativa* plant (1-86, 98-128). The use and acceptance of medicinal Cannabis (Marijuana) continues to evolve as shown by the growing number of countries now permitting use for specific medical indications (1-86). Marijuana (Medicinal Cannabis) is a therapy that has gained much of world wide attention in recent years (1-67, 98-128). Marijuana has over 580 constituents.  $\Delta$ 9-tetrahydrocannabinol ( $\Delta$ 9-THC) is believed to be the main ingredient that produces the psychoactive effect (1-80). The narcotic principle Cannabinoids,  $\Delta$ 9-tetrahydrocannabinol (THC) and Cannabidiol-CBD in the Cannabis sativa develops only when it matures, reaching its maximum at about the time of flowering and then gradually declining and beginning to disappear when the leaves and flowers turn yellow (1-80). Marijuana (Ganja, and Charas in India) is derived from the flowering tops of female plants and twigs, which are covered with resinous exudation (1-45). Marijuana (Charas or Ganja in India) is the resinous exudation secreted by the leaves, young twigs, bark of stem and even the young fruit of the female Cannabis plant (1-40, 98-128). Marijuana (Charas or Ganja in India) is the resinous matter collected from the leaves and flowering tops and constitutes the active principle of the plant (1-45). Marijuana (Charas or Ganja in India) is a greenish mass with a peculiar characteristic odour (1-40). Marijuana (Charas or Ganja) are the mostly smoked, while Bhang in India is always taken by mouth either in the form of a beverage or a confection (1-35, 98-128).

The **female inflorescence** is the main product of Medical *Cannabis sativa* (Marijuana or drug type) (1-45). *Cannabis sativa* has developed full of glandular type of **trichomes** (1-55). Many cannabinoids, terpenes, and phenolic compounds are produced within glandular trichomes in *Cannabis sativa* inflorescences (1-40). Marijuana is a Schedule I Narcotic substance under the Controlled Substances Act, meaning that it has a high potential for abuse, and a lack of accepted safety for use under medical supervision (40-86). Although some states within the United States have allowed the use of marijuana for medicinal purpose, it is the U.S. Food and Drug Administration that has the federal authority to approve drugs for medicinal use in the USA (29-86). The import and export of Charas (Marijuana or drug type) into India was entirely prohibited by the Government of India nearly two decades ago. The consumption of Cannabis resin (Charas) is prohibited everywhere in India (1-38).

A number of preparations of Marijuana (Ganja and Bhang in India) for oral consumption are also used in various parts of the India (1-34, 98-128). Marijuana (Medicinal Cannabis) produces large quantities of Cannabinoids and other diverse secondary metabolites in the glandular trichomes predominantly found on the female reproductive organs (1-34). At least 113 Cannabinoids and over 120 terpenes have been identified from the resin produced by the trichomes (1-34). However, the two predominant target Cannabinoids from medicinal cannabis remain: D9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) (34). When the acid forms of these secondary metabolites are decarboxylated to their neutral forms  $\Delta$ 9-tetrahydrocannabinol (THC) and Cannabidiol (CBD), respectively, they can interact with the mammalian endocannabinoid system for the treatment of non-communicable illnesses including sleep disorders, multiple sclerosis, appetite stimulation, and epilepsy (1-34).

Marijuana is grown in the United States, Canada, Mexico, South America, Caribbean, and Asia (20-75). It can be cultivated in both outdoor and indoor settings (25-86). Common street names include: Aunt Mary, BC Bud, Blunts, Boom, Chronic, Dope, Gangster, Ganja, Grass, Hash, Herb, Hydro, Indo, Joint, Kif, Mary Jane, Mota, Pot, Reefer, Sinsemilla, Skunk, Smoke, Weed, and Yerba (25-86). Marijuana is a dry, shredded green/brown mix of flowers, stems, seeds, and leaves from the Cannabis sativa plant (25-85, 98-128). The mixture typically is green, brown, or gray in color and may resemble tobacco (50-86). Marijuana is usually smoked as a cigarette (called a joint) or in a pipe or bong (20-80). It is also smoked in blunts, which are cigars that have been emptied of tobacco and refilled with marijuana, sometimes in combination with another drug (20-85). Marijuana is also mixed with foods or brewed as a tea (25-60, 98-128).

In the United States and Canada, Cannabis-derived products are consumed for both medical and recreational purposes in a variety of ways (1-86). These include smoking or inhaling from cigarettes (joints), pipes (bowls), water pipes (bongs, hookahs), and blunts (cigars filled with Cannabis); eating or drinking food products and beverages; or vaporizing the product (29-86). These

different modes are used to consume different cannabis products, including cannabis “buds” (dried cannabis flowers); Cannabis resin (Charas, Ganja, hashish, bubble hash); and Cannabis oil (butane honey oil, shatter, wax, crumble) (50-86). The oil, which may contain up to 75 percent of  $\Delta^9$ -tetrahydrocannabinol (THC) versus 5 to 20 percent in the herb or resin is extracted from Cannabis plant material using organic solvents, such as ethanol, hexane, and butane (45-86, 98-128). This can be either smoked or vaporized by pressing the extracted oil against the heated surface of an oil rig pipe (dabbing) (50-86). Cannabinoids can also be absorbed through the skin and mucosal tissues, so topical creams, patches, vaginal sprays, and rectal suppositories are sometimes employed and used as a form of administering  $\Delta^9$ -tetrahydrocannabinol (THC) (55-86, 98-128). A broad selection of Cannabis-derived products are also available in the form of food and snack items, beverages, clothing, and health and beauty aid products (35-86).

When marijuana is smoked, the active ingredient  $\Delta^9$ -tetrahydrocannabinol (THC) passes from the lungs and into the bloodstream, which carries the chemical to the organs throughout the body, including the brain (1-68, 98-128). In the brain,  $\Delta^9$ -tetrahydrocannabinol (THC) connects to specific sites called Cannabinoid receptors CB1 and CB2 on nerve cells and influences the activity of those cells. Many of these receptors are found in the parts of the brain that influence: Pleasure, memory, thought, concentration, sensory and time perception, and coordinated movement (1-86). The short-term effects of marijuana include: Problems with memory and learning, distorted perception, difficulty in thinking and problem-solving, and loss of coordination (20-86, 98-128). The effect of marijuana on perception and coordination are responsible for serious impairments in learning, associative processes, and psychomotor behaviour (driving abilities) (25-86). Long term, regular use can lead to physical dependence and withdrawal following discontinuation, as well as psychological addiction or dependence (45-86, 98-128).

Clinical studies showed that the physiological, psychological, and behavioural effects of marijuana vary among individuals and presented a list of common responses to Cannabinoids, as described in the scientific literature: dizziness, nausea, tachycardia, facial flushing, dry mouth, and tremor initially merriment, and happiness (45-86, 98-128). Further high doses leads to disinhibition, relaxation, increased sociability, and talkativeness, enhanced sensory perception (50-86), giving rise to increased appreciation of music, art, and touch, Heightened imagination leading to a subjective sense of increased creativity, Time distortions, Illusions, delusions, and hallucinations are rare except at high doses, Impaired judgment, reduced coordination, and ataxia, which can impede driving ability or lead to an increase in risk-taking behaviour, emotional lability, incongruity of affect, dysphoria, disorganized thinking, inability to converse logically, agitation, paranoia, confusion, restlessness, anxiety, drowsiness, and panic attacks may occur, especially in inexperienced users or in those who have taken a large dose, increased appetite and short-term memory impairment are common (40-86, 98-128).

Short-term physical effects from marijuana use may include: Sedation, bloodshot eyes, increased heart rate, coughing from lung irritation, increased appetite, and increased blood pressure (although prolonged use may cause a decrease in blood pressure) (45-86, 98-128). Marijuana smokers experience serious health problems such as bronchitis, emphysema, and bronchial asthma (46-86). Extended use may cause suppression of the immune system (50-86, 98-128).

Withdrawal from chronic use of high doses of marijuana causes physical signs including headache, shakiness, sweating, and stomach pains and nausea (45-86). Marijuana withdrawal symptoms also include behavioural signs such as: Restlessness, irritability, sleep difficulties, and decreased appetite (50-86, 98-128). No deaths from overdose of marijuana have been reported (46-86). Hashish and hashish oil are drugs made from the Cannabis plant that are like marijuana (50-86). Hashish (hash) consists of the THC-rich resinous material of the cannabis plant, which is collected, dried, and then compressed into a variety of forms, such as balls, cakes, or cookie like sheets (45-86). Pieces are then broken off, placed in pipes or mixed with tobacco and placed in pipes or cigarettes, and smoked (45-86). The main sources of hashish are the Middle East, North Africa, Pakistan, and Afghanistan (40-86). Hashish oil (hash oil, liquid hash, cannabis oil) is produced by extracting the Cannabinoids from the plant material with a solvent (35-86). The color and odour of the extract will vary, depending on the solvent used. A drop or two of this liquid on a cigarette is equal to a single marijuana joint (30-86). Like marijuana, hashish and hashish oil are both Schedule I Narcotic drugs (35-86, 98-128).

#### IV. Screening Test for the detection of THC

Biochemical assessment of marijuana involved measurement of the THC metabolite THC-COOH in urine (54). THC-COOH has a relatively long half-life (28–60 hr, depending on sampling time frame) and typical urine screening tests remain positive for 30 hours after a single use and for as long as 30 days after abstinence in a heavy regular marijuana user (50-86). The use of high sensitivity quantitative analysis for total THC-COOH provides a much more complete picture of adolescent marijuana use compared to the usual immunoassay screening method (54-86). This is probably due to relatively infrequent use of marijuana in adolescents, such that urine THC-COOH levels fall below the urine screen cut off in many individuals (54-86). This study also reported that while 92% of participants who reported marijuana use in the past 3 days were biochemically confirmed as exposed, only 54% of those who reported use in past 3 months were biochemically positive (54-86). Thus, a combination of biochemical screening and self-report may be necessary to fully characterize marijuana use patterns (54-86). Therefore, quantitative screening

for THC and nicotine exposure will provide greater insight into patterns and doses of co-substance use, and may enhance the understanding of dose-related aspects of addiction and pathophysiology of adverse health effects associated with dual use (54-85, 98-128). A caveat is that high sensitivity chromatographic screening is expected to cost 4–5 times more than commonly used immunoassay methods (54-86).

The Du-Quenois test is considered to be specific for Cannabinols. The **Duquenois reagent** used in the Rapid Modified **Duquenois–Levine test** (also known as the simple **Rapid Duquenois Test**), is an established screening test for the presence of Cannabis (54-85). It is based on the reaction of Cannabis extracts with *p*-dimethylbenzaldehyde. This produces a violet blue coloration that is extractable into chloroform (54-86). The mass spectrum of  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) shows major ions at  $m/z = 299, 231, 314, 43, 41, 295, 55$  and 271 (54-86). Using gas chromatography, the limit of detection of  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) in blood is 0.3  $\mu\text{g/L}$  (54-86).

### ***Cannabis sativa* (Marijuana): Harmful Adverse Effects**

Acute and chronic side effects related to Cannabis (Marijuana) are gastrointestinal disorders, fatigue, hypotension, nausea, paranoia, psychiatric symptoms, dizziness, impaired neurocognitive, psychomotor performances, attention and memory deficits, increase of psychiatric disorders, risk for addiction, airway trauma and lung diseases (54-86, 98-128). Regarding the synthetic Cannabinoids, acute adverse events are tachycardia, acute myocardial infarction, acute kidney injury, seizure, sedation, confusion and impaired motor skills, while the prolonged use is associated with withdrawal symptoms, including restlessness, anxiety and mood swings (54-86, 98-128). Considering the several adverse effects, the treatment with Cannabis (Marijuana) is contraindicated in patients with psychiatric, cardiovascular, renal or liver diseases (54--86, 98-128). In addition, Cannabinoids cross the placenta even at lower doses and are carried to breast milk, thus they are not recommended for pregnant and lactating women, as they can cause newborn weight-loss and neurobehavioral disorders (54-86).

During acute Cannabis (Marijuana) intoxication, the user's sociability and sensitivity to certain stimuli (e.g., colors, music) may be enhanced, the perception of time is altered, and the appetite for sweet and fatty foods is heightened (45-86, 98-128). Some users report feeling relaxed or experiencing a pleasurable "rush" or "buzz" after smoking Cannabis (Marijuana) (40-86, 98-128). These subjective effects are often associated with decreased short-term memory, dry mouth, and impaired perception and motor skills (45-86, 98-128). When very high blood levels of  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) are attained, the person may experience panic attacks, paranoid thoughts, and hallucinations (45-86). Furthermore, as legalized medical and recreational Cannabis (Marijuana) availability increase worldwide, the impairment of **driving abilities** during acute intoxication has become a public safety issue (45-86, 98-128).

In addition to  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) dosage, two main factors influence the intensity and duration of acute intoxication: individual differences in the rate of absorption and metabolism of  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol), and the loss of sensitivity to its pharmacological actions (45-86, 98-128). Prolonged CB1 receptor occupation as a consequence of the sustained use of Cannabis can trigger a process of desensitization, rendering subjects tolerant to the central and peripheral effects of  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) and other Cannabinoid agonists (1-86). Animals exposed repeatedly to  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) display decreased CB1 receptor levels as well as impaired coupling between CB1 and its transducing G-proteins (1-86). Similarly, in humans, imaging studies have shown that chronic Cannabis (Marijuana) use leads to a down-regulation of CB1 receptors in the cortical regions of the brain and that this effect can be reversed by abstinence (35-86, 98-128).

The impairments in brain connectivity is associated with exposure to marijuana (Charas, Ganja and Bhang in India) in adolescence are consistent with preclinical findings indicating that the Cannabinoid system plays a prominent role in synapse formation during brain development (54-86, 98-128). Regular marijuana (Charas, Ganja and Bhang in India) use is associated with an increased risk of anxiety and depression, but causality has not been established (54-86, 98-128). Marijuana (Medical Cannabis or drug type) is also linked with psychoses (including those associated with schizophrenia), especially among people with a pre-existing genetic vulnerability, and exacerbates the course of illness in patients with schizophrenia (54-86, 98-128).

Marijuana (Medical *Cannabis sativa*) can be addictive, so it is important to be aware of the effects and risks of  $\Delta$ 9-tetrahydrocannabinol ( $\Delta$ 9-THC) (54-86, 98-128). Its potential medicinal uses, and the risks of substances that contain  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) (54-86).  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) is available in a variety of forms (45-86). The method of administration often depends on why  $\Delta$ 9-THC ( $\Delta$ 9-tetrahydrocannabinol) is being used and what it is intended to treat (54-86). Cannabis is usually smoked, often mixed with tobacco or in a smoking device (bong) (47-86, 98-128). Because THC has a low water solubility, ingestion of Cannabis leads to poor absorption (54-86). The average 'reefer' cigarette contains around 200 mg of herbal Cannabis or cannabis resin (54-86). In many countries, herbal Cannabis and Cannabis resin are formally known as marijuana and hashish (or just 'hash') respectively (54-86). Cannabis (Marijuana) cigarettes may be termed reefers, joints or spliffs (56-86). Street terms for cannabis/cannabis resin include bhang, Charas, pot, dope, ganja, hemp, weed, blow, grass and many others (54-86, 98-128).

Some of the ways it can be consumed include by: **Inhalation:** This is the fastest method of administration and produces effects within minutes. Recent reports suggested that vaping  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) oil may pose serious and potentially fatal safety risks (54-86). The National Institutes of Health (NIH), Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC), USA recommend avoiding all vaping an e-cigarette produces, particularly those that use  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) oil (54-86). **Oral ingestion:**  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) can be taken by mouth in the form of capsules, edibles, tinctures, or oils. This method of delivery produces slower, longer-lasting effects (54-86). **Topical application:**  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) can also be included in lotions, balms, salves, oils, and bath salts that are then applied to the skin (50-86). The effects of this method are usually localized, which means that they are unlikely to have psychoactive effects (54-86). However, such products may be helpful in reducing pain and inflammation. **Sublingual administration:**  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) can also be consumed as lozenges, sprays, or dissolvable strips that are placed under the tongue and dissolved (50-86). Someone with a Marijuana (Medical *Cannabis sativa*) addiction may realize that their drug use is affecting them physically, mentally, and emotionally (54-86, 98-128).

According to the Substance Abuse and Mental Health Services Administration (SAMHSA), marijuana (Charas, Ganja and Bhang in India) use can have negative impacts on brain and body function (54-86). Studies have found that some of these consequences include. Impaired memory, Impaired motor skills (increased risk of injury), Paranoia, Higher risk of psychosis, Cognitive impairment (lower IQ), Dropping out of school, Inability to fulfill work commitments, Financial instability, Dysfunctional parent-child relationships, Having friends who use marijuana, Poor self-esteem, Thrill-seeking or impulsive behaviour, Mental health issues, Loss of IQ points (these cannot be recovered even if someone stops using marijuana), Relationship issues, Reduced school success, Slower reaction time while driving or playing sports, Depression and anxiety, Premature birth, and stillbirth (54-86, 98-128).

Most health care experts agreed that dependence on a Marijuana (Medical *Cannabis sativa*) substance is accompanied by a build-up of tolerance to that substance, requiring increasingly larger amounts to get the same effects, and leading to withdrawal symptoms, when someone stops using the substance (54-86). Most Marijuana (Medical *Cannabis sativa* or drug type) smokers experienced neither tolerance nor withdrawal (50-86). Most early research into marijuana addiction revealed that marijuana use rarely produced tolerance and withdrawal (54-86, 98-128). But the marijuana that is available today is more powerful than the marijuana of the 1960s, containing higher levels (25-35%) of the active ingredient  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol), which is the psychoactive component in weed (54-86, 98-128).

In addition, it has been found that marijuana (Charas, Ganja, Bhang in India) dependence may affect the ability to respond to the neurotransmitter dopamine, which allows to feel pleasure (50-86). In one study, those who had marijuana dependence had fewer positive emotions, higher stress levels, and increased irritability has been observed (54-86, 98-128). Today's research showed that tolerance does develop to  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) and that withdrawal symptoms do occur in some people (50-86). Studies of those who chronically use and then quit marijuana (Charas, Ganja and Bhang in India) showed that they experience these withdrawal symptoms such as Anxiety and insomnia, Loss of appetite, Excessive salivation, Decreased pulse, Irritability, Increased mood swings, Increase in aggressive behaviour, and higher potency factor (54-86, 98-128). The number of people seeking treatment for marijuana (Charas, Ganja and Bhang in India) abuse has increased significantly (54-86). According to studies, the number of children and teenagers in treatment for marijuana dependence and abuse has increased by 142% since 1992 (54-86). As with most substances of abuse, people who abuse marijuana usually decide to seek help when their use of the drug becomes painful due to increasing negative consequences (50-86). Many who seek treatment for marijuana do so due to pressure from family, friends, schools, employers, or the criminal justice system (54-86). In addition, marijuana dependence has been linked with a lack of motivation (50-86). Someone who is addicted may lack the drive to engage in activities, pursue goals, or keep up with responsibilities, including school and work (54-86). People develop Cannabis dependence for different reasons, so it is important to address any underlying issues. For instance, those who use marijuana (Charas, Ganja and Bhang in India) to cope with anxiety, depression, or sleep disorders can find more appropriate treatment types including lifestyle changes, therapy, and medication to help relieve their symptoms (54-86, 98-128).

$\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol), the primary psychoactive component of Cannabis (*sativa*, *indica*, and *ruderalis*), has been reported to affect fear memory, expression, consolidation, and extinction (87, 98-128). In addition, Cannabidiol (CBD), another component of the plant, has also been reported to impact fear memory (87). Marijuana (Medical cannabis or drug type) is widely used to self-medicate for a variety of medical conditions, including disorders rooted in fear learning such as post-traumatic stress disorder (PTSD) (87). Behaviourally, in many respects Cannabidiol (CBD) has been shown to produce effects which are opposite those of  $\Delta 9$ -THC ( $\Delta 9$ -tetrahydrocannabinol) (87).

The adverse effects of Marijuana (medicinal cannabis) comes from studies of recreational users of marijuana (35-86, 98-128). Short-term use of Cannabis (Marijuana) has led to impaired short-term memory; impaired motor coordination; altered judgment; and paranoia or psychosis at high doses (45-86). Long term or heavy use of Cannabis (Marijuana) especially in

individuals who begin using as adolescents, has led to addiction; altered brain development; cognitive impairment; poor educational outcomes (e.g., dropping out of school); and diminished life satisfaction (45-86). Long-term or heavy use of Cannabis (Marijuana) is also associated with chronic bronchitis and an increased risk of chronic psychosis-related health disorders, including schizophrenia and variants of depression, in persons with a predisposition to such disorders (50-86). Vascular conditions, including myocardial infarction, stroke, and transient ischemic attack, have also been associated with cannabis use (47-86). The use of Cannabis (Marijuana) for management of symptoms in neurodegenerative diseases, such as Parkinson's, Alzheimer's, and MS, has provided data related to impaired cognition in these individuals (50-86, 98-128).

Other negative adverse effects reported with acute Cannabis (Marijuana) use include hyperemesis syndrome, impaired coordination and performance, anxiety, suicidal ideations or tendencies, and psychotic symptoms, whereas chronic effects may include mood disturbances, exacerbation of psychotic disorders, cannabis use disorders, withdrawal syndrome, and neurocognitive impairments, as well as cardiovascular and respiratory conditions (50-86). Long-term studies evaluating adverse effects of chronic medicinal Cannabis (Marijuana) use are needed to conclusively evaluate the risks when used for an extended period of time (45-86, 98-128).

In one of the study reported by Whiting, et al., (2015) (88), there was moderate-quality evidence to support the use of Cannabinoids for the treatment of chronic pain and spasticity (88). There was low-quality evidence suggesting that Cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term adverse events (AEs) (88). The Common adverse events (AEs) included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination (88). There was an increased risk of short-term AEs with Cannabinoids, including serious adverse events (AEs) (88).

#### V. Phytocannabinoid based Drugs

The U.S. Food and Drug Administration (FDA) has licensed three drugs based on Cannabinoids (1-86). Dronabinol, the generic name for synthetic  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol), is marketed under the trade name of Marinol<sup>®</sup> and is clinically indicated to counteract the nausea and vomiting associated with chemotherapy and to stimulate appetite in AIDS patients affected by wasting syndrome (1-86). Marinol is a synthetic version of  $\Delta^9$ -tetrahydrocannabinol (THC) in a capsule (also referred to as dronabinol) (50-86). This medication is prescribed for the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer and to stimulate appetite in acquired immune deficiency syndrome (AIDS) patients (29-86). Marinol is a Schedule III drug under the Controlled Substances Act (50-86). A synthetic analog of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol), Nabilone (Cesamet<sup>®</sup>), is prescribed for similar indications (1-86). Both Dronabinol and Nabilone are given orally and have a slow onset of action (25-86). In July 2016 the FDA approved Syndros<sup>®</sup>, a liquid formulation of Dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies (20-86). The agent is also indicated for treating anorexia associated with weight loss in patients with AIDS (1-86).

Two additional Cannabinoid-based medications have been examined by the FDA. Nabiximols (Sativex<sup>®</sup>) is an ethanol cannabis extract composed of  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) and Cannabidiol (CBD) in a one-to-one ratio (45-86). Nabiximols is administered as an oromucosal spray and is indicated in the symptomatic relief of multiple sclerosis and as an adjunctive analgesic treatment in cancer patients (1-86). As of September 2016, Nabiximols has been launched in 15 countries, including Canada, Germany, Italy, Spain, the United Kingdom, and has been approved in a further 12, but not in the United States (45-86). In response to the urgent need expressed by parents of children with intractable epilepsy, in 2013 the FDA allowed investigational new drug studies of Epidiolex<sup>®</sup>, a concentrated CBD oil (>98 percent CBD), also developed by GW Pharmaceuticals, as an anti-seizure medication for Dravet and Lennox-Gastaut syndromes (1-86). Syndros is an oral Dronabinol (THC) solution that is used for the treatment of anorexia associated with weight loss in patients who have failed to respond adequately to conventional antiemetic treatments (50-86). Syndros is a Schedule II drug under the Controlled Substances Act (50-86). Epidiolex is an oral solution of cannabidiol (CBD) that has no more than 0.1% THC, used to treat two epilepsy conditions, Dravet syndrome and Lennox-Gastaut syndrome (39-86). Epidiolex is a Schedule V drug under the Controlled Substances Act (40-86). Tinctures of Cannabis (ethanolic extracts) were once common, but were removed from pharmacopoeias many years ago (30-86). Herbal Cannabis (known as 'Cannabis flos'), with a nominal THC content of 18 %, is available as a prescription medicine in The Netherlands (25-86). It is indicated for multiple sclerosis, certain types of pain and other neurological conditions (50-86). An extract of Cannabis (Sativex) has been licensed in Canada (1-86).



## Contamination and Adulteration of Cannabis Products

Today there is an emerging interest in Cannabis, concerns have arisen about the possible contaminations of hemp with pesticides, heavy metals, microbial pathogens, and carcinogenic compounds during the cultivation, manufacturing, and packaging processes (89-97). This is of particular concern for those turning to Cannabis for medicinal purposes, especially those with compromised immune systems (89-97). It has been reported that Cannabis derived products are often contaminated by microbes, heavy metals, pesticides, carcinogens, and debris, which must be addressed to ensure the safety of consumers (89-97). The large economic potential and illicit aspect of Cannabis has given rise to numerous potentially hazardous natural contaminants or artificial adulterants being reported in crude cannabis and cannabis preparations (89-97). Most frequent natural contaminants consist of degradation products, microbial contamination (e.g., fungi, bacteria), and heavy metals (89-97). These contaminants are usually introduced during cultivation and storage (89-97). Growth enhancers and pest control chemicals are the most common risks to both the producer and the consumer (89-97). Cannabis can also be contaminated for marketing purposes. This usually entails adding substances (e.g., tiny glass beads, lead) to increase the weight of the cannabis product or adding psychotropic substances (e.g., tobacco, calamus) and cholinergic compounds to either enhance the efficacy of low-quality cannabis or to alleviate its side effects (89-97). Additionally, some extraction and inhalation methods used for certain dosing formulations (tinctures, butane hash oil, “dabs”) can result in substantial pesticide and solvent contamination (89-97). These contaminants are imminent threats that directly impact public health and wellness, particularly to the immunocompromised and pediatric patients who take Cannabis products as a treatment for numerous human disorders including cancer patients and those suffering from epileptic seizures (89-97).

## VI. Conclusion

This review paper is a part of Educational Awareness Programme highlighting about Medical *Cannabis sativa* (Marijuana or drug type). Medical *Cannabis sativa* is also known as Charas, Ganja and Bhang in India. *Cannabis sativa* is one of the oldest medicinal plant of Indian origin. Further, there is a major difference between Medical *Cannabis sativa* (High THC levels of about 25-35%) and Industrial Cannabis sativa, Hemp (Low THC levels of 0.2-0.3%). Cannabis has gained a lot of popularity in the last few decades for not only being **an illicit drug** but for its medicinal values from ancient times and a potential source for modern drugs to treat several targets for human wellness. Marijuana (Medical *Cannabis sativa*) can be addictive, so it is important to be aware of the effects and risks of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) (54-86). Its potential medicinal uses, and the risks of substances that contain  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) (54-86).  $\Delta^9$ -THC ( $\Delta^9$ -tetrahydrocannabinol) is available in a variety of forms.

Many psychoactive synthetic Cannabinoid analogues of naturally occurring Cannabinoids are available on the consumer market and are sold under misleading names, like “spice” or “incense. Studies have reported serious health effects associated with the use of synthetic Cannabinoids. However, addition of synthetic Cannabinoids to Cannabis products could expose consumers to the risk of adverse effects, overdoses, and death.  $\Delta^9$ -THC and CBD are the most studied Cannabinoids since they have been reviewed and approved as drugs for specific indications by regulatory agencies. Overall, research based on well-established principles of botanical and natural products chemistry and robust quality control can help in understanding the safety and potential uses of Cannabis for various medical purposes.

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