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Cannabinoids: Their origin, biosynthesis, quality control and impact on human health

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Abstract
The cannabis or hemp plant has been known thousands years ago in almost all parts of the world, and involves three main strains; *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis enters East Africa by the Arabian merchants. It was certainly used in Ethiopia by the 13th century where it likely entered via trade routes across the Red Sea. In Ethiopia cannabis is cultivated in Alemaya, Shebendia, Shashemene and Debre Berehan areas. The cannabis plant consists of hundreds of chemical constituents called cannabinoids, which can be extracted out by different methods of extraction which are further isolated using chromatographic methods of separation. Δ9-Tetrahydrocanabinol, cannabidiol and cannabinol are the most prevalent natural cannabinoids. Δ9-Tetrahydrocanabinol being psychoactive determines the potency of cannabis plant. The cannabinoid content of cannabis plant depends of cannabis strain, growth stage at the time of collection, season of collection, environmental conditions where cannabis is grown. The plant was used for several purposes in different parts of the world in the past for decoration, food source, medicine, and fiber. Currently cannabinoids provides various therapeutic benefits for the treatment of several clinical conditions like chemotherapy induced nausea/vomiting, muscle spasticity, Alzheimer's disease, eating disorders, and glaucoma. However the clinical evidence for the use of cannabinoids for long term management of glaucoma is not strong enough.

Keywords: Cannabis, Cannabinoids, Tetrahydrocannabinol, Cannabidiol, Cannabinol

Introduction
Objectives
General objective
To provide a literature view of the origin, biosynthesis, quality control and impact of cannabinoids on human health.

Specific objectives
- To review current evidence on the history, taxonomy and distribution of cannabis
- To provide brief overview of chemistry and extraction of cannabinoids
- To explore current evidence on the identification and quantification of cannabinoids
- To review current evidence traditional and modern pharmacological uses of cannabis and cannabinoids

Methodology
Brief review of literatures that are related to origin, biosynthesis, quality control and impact on human health of cannabis and cannabinoids were conducted using electronic databases like PubMed, Medline and Google scholar. After reading the abstracts of each article those which are closely related to my work are referenced.

Introduction
Cannabis plant has been used for several hundreds of years both recreationally and medicinally and was known to Chinese medicine for pain-relief and hallucination properties [1].
The term "cannabinoids" is used for the typical C_{21} groups of compounds present in *Cannabis sativa L.* (family moracea) and includes their analogues and transformation products. Cannabinoids are constituent elements of cannabis plant. The amount of cannabinoid varies not only due to the difference in strains of cannabis but also growth factors, genetics of plant, geographic and climatic factors with in the same strain. In a typical plant, the concentration of cannabinoids increases in the order: large leaves, small leaves, flowers, bracts, with stems containing very little. The THC content of high-quality cannabis might be in the range 0.5–1% for large leaves, 1–3% for small leaves, 3–7% for flowering tops, 5–10% for bracts, 14–25% for resin, and up to 60% in cannabis oil [2].

Δ9-tetrahydrocannabinol (Δ9-THC) is the most active constituent of this plant is elucidated between 1940s and 1960s [1].

1.1 Historical background

The cannabis or hemp plant which grows in almost all parts of the world has been known since antiquity mainly the tall plant used for the manufacture of textiles and rope with minimal use for its medicinal value in those fiber producing areas [3, 4]. It is believed that knowledge of these discovered in the Himalayan region of central Asia and extended gradually from there to India, Asia Minor, North Africa, and across the desert to sub-Saharan Africa and the rest of the African continent [22]. Crushed cannabis seeds were utilized as source of food in Asia during the famine period and continue to be used as baby food in sub-Saharan Africa [11]. In China preparations from the flowers and resin of *C. sativa* have been used for the treatment of menstrual disorders, gout, rheumatism, malaria, constipation, and absent-mindedness since ~2700 BC [13].

In India, the plant was used both medically and non-medically. The weaker preparations 'bhang' which was taken by mouth, and the slightly stronger preparation 'ganja' was smoked during the festival of Durga Puja, family celebrations to induce a relaxed and sociable mood and a good appetite, but the most potent preparation, 'charas' (known elsewhere as hashish) was not used for these purposes rather its use were regarded as 'bad characters' or outcasts. Cannabis is known to have sedative, relaxant, anxiolytic and anticonvulsant actions which made it useful in the treatment of alcohol and opiate withdrawal, Analgesia, appetite stimulation, antipyretic and antibacterial effects, and relief of diarrhea.

During the Napoleonic invasion of Egypt in 1798 two French scholars, De Sacy and Rouyer, described the plant, and the practice and effects of hashish smoking, and they collected samples of the material to take back to France for further study. The famous French psychiatrist Moreau de Tours described in detail the mental effects of high doses of hashish, and proposed the use of hashish to produce a model psychosis [4].

In the United Kingdom of O'Shaughnessy observed the use of cannabis in Indian traditional medicine, for the treatment of spastic and convulsive disorders such as hydrophobia (rabies), tetanus, cholera and delirium tremens. He sent supplies of the material to a pharmaceutical firm in London for analysis and clinical trials. The extracts of cannabis were adopted into the British Pharmacopoeia and later into the American Pharmacopeia, and were widely used in the English-speaking world as sedative, hypnotic and anticonvulsant agents in the late 19th and early 20th centuries. Yet, by the time that cannabis was dropped from the British Pharmacopoeia in 1932 and the American Pharmacopeia in 1941 due variability in its composition, and too short and unpredictable shelf life. Therefore, cannabis would have to be substantially improved as a drug if it were to regain clinical interest [4] but in the United States in late 19th to early 20th century Cannabis extract and medications were marketed by pharmaceutical companies over-the counter [5]. Cannabis entered Eastern Africa via Egypt and Ethiopia, most likely carried by Arab merchants. It was certainly used in Ethiopia by the 13th century where it likely entered via trade routes across the Red Sea [31].

2. Taxonomy and Distribution of cannabis

Cannabis cultivars are considered as part of one genus, Cannabis, family Cannabaceae, order Urticales. Two accepted genera of Cannabaceae are Cannabis and Humulus (hops). There is, however, an ongoing debate concerning the taxonomic differentiation within the Cannabis genus [26]

The current systematic classification of Cannabis is

Division : Angiosperms
Class : Dicotyledon
Subclass : Archichlamydeae
Order : Urticales
Family : Cannabinaceae
Genus : Cannabis
Species: sativa L. [8].

The three principal Cannabis species are *Cannabis sativa, Cannabis indica, and Cannabis ruderalis*. Sativa and indica being the most common species of cannabis are rich in THC typically used in the production of marijuana for both medicinal and recreational purposes. Ruderalis, is lesser-known, and have much lower levels of THC [20]. *Cannabis Sativa* is considered to be the most commonly grown of the cannabis strains. It generally reaches quite a large size up to 19 feet tall, have firm stems [20], delicate leaves and smooth seeds that have no marbling or flecked patterns, takes relatively long time to flower, and any changes in light won't have quite as strong an effect on a sativa as it will on other cannabis species [11].

An Indica plant, characterized by its short, stocky structure, and generally reaches a maximum height of only about 10 feet [20, 11]. Have rounder and less delicate leaves than their sativa counterparts. The seeds are also smooth but generally have a marble-like pattern. Indicas flower rather quickly, and are very responsive to light changes [11].

Ruderalis plants tend to be the smallest of the cannabis group in height and girth [19]. They only reach a maximum height of about two feet tall, but their branches and leaves are extremely dense, making this a particularly bushy plant [11]. It functions more like wild cannabis, whereas indica, sativa, and their hybrids are usually produced under very controlled environments [20].

The highest levels of cannabis production in the world take place on the African continent. Ten thousand five hundred metric tons or roughly 25 percent of global production of cannabis herb is estimated to have taken place in Africa in 2005. It takes place in all sub-regions, with major seizures being made in North Africa (Morocco and Egypt), West Africa (Nigeria and Ghana), East Africa (Tanzania and Kenya), and Southern Africa (South Africa, Swaziland, Lesotho, Malawi, and Zambia) [29].

2.1 Cannabis in Ethiopia

In most urban centers of Ethiopia, cannabis is more commonly known as hashish, but this actually refers to marijuana. In some rural or traditional communities, it is also referred to as by the Amharic/Geez name, etse-faris. Marijuana is made from the dried leaves, twigs and flower parts of the cannabis plant; it is consumed by inhalation as smoke. Similar to the classification in most other countries with functional regulatory systems in place, marijuana/hashish/cannabis is also considered illegal in Ethiopia.

The cannabis plant in Ethiopia is reported to grow in many places across a wide range of geography. More notably, it is cultivated in Alemaya, Shebendia, Shashemene and Debre Berehan areas. Among all the places, of special interest is the cultivation of cannabis in the Shashemene area which was offered by Emperor Haile Selassie in 1966 to Rasteferians of

Jamaican origin. Since then, this area has been recognized for its ties to Rastafarianism and for the production and quality of its cannabis. However, in most of these places cannabis is usually cultivated in inaccessible locations where enforcement of laws is difficult to achieve. Such places include those which had never traditionally cultivated the plant. There is also evidence that some cannabis is smuggled into Ethiopia from West Africa by traffickers [33].

3. Chemistry and Biosynthesis of Cannabinoids

3.1 Chemistry

Cannabis plant and its products consist of an enormous variety of chemicals [12]. It is very complex in its chemistry due to the vast number of its constituents and their possible interaction with one another. As shown in the figure below (Figure 1) isolates from the plant consists of both cannabinoid ad non-cannabinoid components. These compounds represent almost all of the chemical classes including mono-and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids, among others. The best-known and the most specific class of Cannabis constituents is the C21 terpeno-phenolic cannabinoids [14, 26].

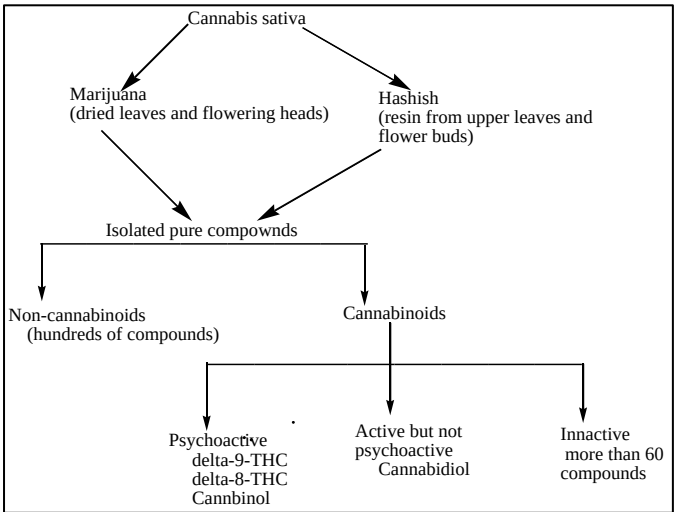


Fig 1: Relationships between crude cannabis products and pure cannabinoids [4].

Phytocannabinoids are only known to occur naturally in significant quantity in the cannabis plant, and are concentrated in a viscous resin that is produced in glandular structures known as trichomes. More than 104 different cannabinoids have been identified in cannabis [26].

Cannabigerol (CBG), Cannabichromene (CBC), Cannabicyclol (CBL), Cannabielsoin (CBE), Cannabinodiol (CBND), Δ9-THC, cannabidiol (CBD), Cannabitriol (CBT) and cannabinol (CBN) are some of the cannabinoid constituents of cannabis plant (Elsohly and Slade, 2005) with Δ9-THC, cannabidiol (CBD) and cannabinol (CBN) being the most prevalent natural cannabinoids [8, 27]. The figure below shows the structure of some cannabinoids.

Cannabigerol (CBG) type was the first cannabinoid identified, and its precursor cannabigerolic acid (CBGA) was shown to be the first biogenic cannabinoid formed in the plant. Propyl side-chain analogs and a monomethyl ether derivative are other cannabinoids of this group [12, 14].

Cannabidiol (CBD) (figure 2) was isolated in 1940, but its correct structure was first elucidated in 1963 by Mechoulam and Shvo. Cannabidiol (CBD) is a major constituent of medical cannabis.

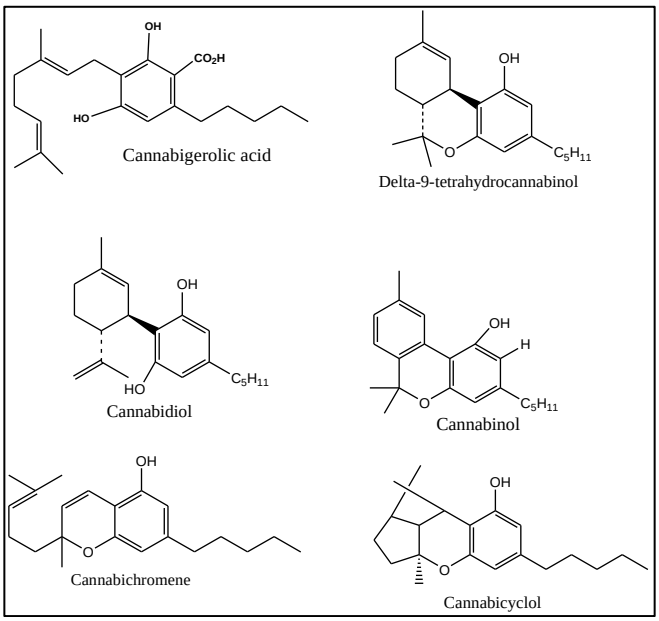


Fig 2: Structures of common cannabinoids [2].

The structure of tetrahydrocannabinol was unknown until Gaoni and Mechoulam in1964 isolated D9-THC and used NMR to assign the double bond position and the *trans* configuration [14].

CBN-type cannabinoids are the fully aromatized derivatives of THC, and although they have been isolated from different cannabis extracts they are thought of as artifacts. The concentration of CBN in cannabis products (marijuana, hashish and hash oil) increases during storage of these materials while the D9-THC concentration decreases, but at a different rate [14].

Cannabinoids exist mainly in the plant as their carboxylic precursors (D9-tetrahydrocannabinolic acid [THCA] and cannabidiolic acid [CBDA]) and are decarboxylated by light or heat while in storage or when combusted [26]. The strength of cannabis is measured by how rapidly the body takes up the chemicals and the user feels their effects. Anyone who has used cannabis multiple times has likely encountered "strong stuff." Typically, that refers to cannabis that gets you high faster or has a stronger effect [20]. It is usually measured in terms of the percentage of its key psychoactive ingredient, Δ9-tetrahydrocannabinol (Δ9-THC or simply THC), but THC is only one of over 80 different cannabinoids found in the cannabis plant, key among these being cannabidiol (CBD). The many other cannabinoids present in cannabis are less well understood but their relative proportions may also have subtle influences on the variable effects of different strains.

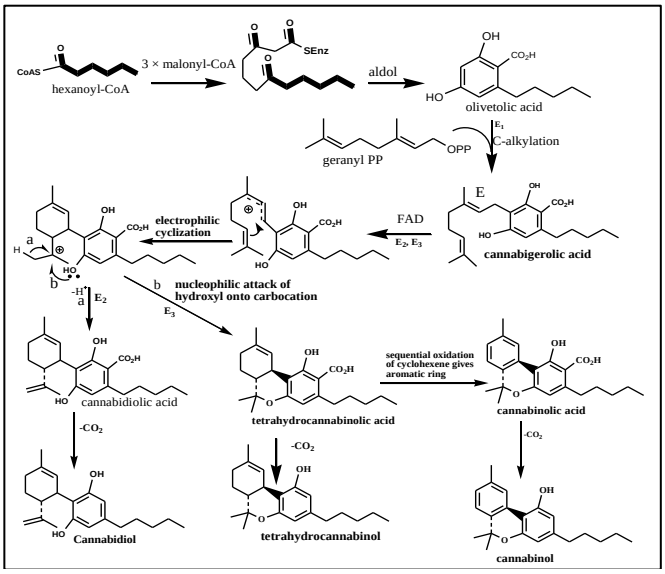
Lower-strength, outdoor-grown cannabis tends to be less than 10%THC, while indoor-grown, 'premium' cannabis varieties are predominantly in the10-20% range. The potency of lower-quality and premium-grade resin has historically been roughly the same as this in European markets, although newer techniques such as butane or carbon dioxide extractions have produced oils and other concentrates, such as butane hash oil (BHO, the semi-solid forms sometimes known as 'wax' or 'glass'), that have extremely high potencies, some reaching concentrations of over 80% THC [28].

3.2 Biosynthesis of Cannabinoids

Cannabinoids are biosynthesized in an acidic form, among which the most abundant are cannabidiolic acid (CBDA) and Δ9-tetrahydrocannabinolic acid A (THCA-A). However, these acidic cannabinoids are not stable since they may decompose

in the presence of light or heat. Overall, acidic cannabinoids are decarboxylated to their neutral homologues, as in the case of tetrahydrocannabinolic acid (THCA), which is decarboxylated to tetrahydrocannabinol [6].

As shown on figure 3 all the cannabinoid structures contain a monoterpene C_{10} unit attached to a phenolic ring that carries a C_5 alkyl chain. The aromatic ring/C_5 chain originates from hexanoate and malonate, cyclization to a polyketide giving olivetolic acid, from which cannabigerolic acid can be obtained by *C*-alkylation with the monoterpene C_{10} unit geranyl diphosphate. Cyclization in the monoterpene unit necessitates a change in configuration of the double bond, and this involves an oxidative step in which FAD is a cofactor. It may be rationalized as involving the allylic cation, which will then allow electrophilic cyclization to proceed. Cannabidiolic acid is then the result of proton loss, whilst tetrahydrocannabinolic acid is the product from heterocyclic ring formation via quenching with the phenol group. CBD and THC are then the respective decarboxylation products from these two compounds; decarboxylation is non-enzymic and facilitated by the adjacent phenol function. The aromatic terpenoid-derived ring in cannabinolic acid and CBN can arise via a dehydrogenation process. The PKS for olivetolic acid formation has yet to be characterized; a related type III PKS system from *Cannabis* catalyzed the formation of the decarboxylated derivative olivetol instead of olivetolic acid [2].



E_1: Olivetolate geranyl transferase **E_2:** Cannabidiolic acid (CBDA) synthase

E_3: Tetrahydrocannabinolic acid (THCA) synthase

Figure 3: Biosynthesis of cannabinoids [2].

4. Quality control of cannabinoids

Medicinal cannabis cultivated without government control, basic Good Production Practices like GAP, GMP, GLcP and GDP producers do not necessarily apply. This is even more prominent in case of seized cannabis for medical use. This has consequences for the safety and efficacy of the medicinal cannabis:

- There can be considerable batch- to- batch variation in strength and the qualitative composition of the medicine, resulting in varying effectiveness.
- Cannabis is known for containing *Aspergillus fumigatus L.*, a fungus that can infect the user and produces toxins that may provoke a psychosis. A Dutch study compared illegal cannabis batches with medicinal cannabis produced under state control. Some samples of the former contained up to 480,000 CFU/gram, while the latter was produced with very low levels of the fungus and then sterilized.
- Contamination can also derive from pesticides used during production or from heavy metals in the substrate [32].

Quality and safety testing protects consumers from the health risks associated with adulterated or contaminated cannabis, and from the risks of consuming cannabis of unknown or unreliable potency. It should therefore be a strict licensing condition for producers.

Despite passing laws to legalize cannabis for medical use, most states have not followed up with legislation requiring testing for levels of pesticide, mould, bacteria or other microorganisms that can be harmful to health. Washington's regulations, for example, oblige every licensed cannabis producer and processor to submit representative samples of their cannabis and cannabis-infused products to an independent, state-accredited third-party testing laboratory on a schedule determined by the state liquor control board. If these samples do not meet standards adopted by the board, the entire lot from which the sample was taken must be destroyed. Producers are also required to make provisions for testing in order to establish the potency (THC concentration) of all their products, and this must be clearly marked on all packaging [28].

4.1 Identification and quantification of cannabinoids

Identifying a plant sample as *Cannabis sativa L.* is the first step [12]. Different methods are reported for identification of cannabis and cannabinoids. These include:

4.1.1 Microscopy

The botanical identification of plant specimens consists of physical examination of the intact plant morphology and habit (leaf shape, male and female inflorescenses, etc.) followed by the microscopical examination of leaves for the presence of cystolith hairs; the very abundant trichomes, which are present on the surface of the fruiting and flowering tops of Cannabis, are the most characteristic features to be found in the microscopic examination of Cannabis products (not liquid Cannabis, hashish oil). Sometimes microscopic evidence is still available in smoked Cannabis residues.

4.1.2 Chromatographic Techniques

4.1.2.1 Thin-Layer Chromatography

One- and two-dimensional TLC is suited for the acquisition of qualitative cannabinoid profiles from plant material. Fast blue salt B or BB are used for visualization and result in characteristically colored spot patterns. For quantitation, instrumental TLC coupled to densitometry is necessary.

4.1.2.2 Gas Chromatography, Gas Chromatography/Mass Spectrometry

GC with flame ionization or MS detection is now the best established method for the analysis of Cannabis and its products. Derivatization is necessary (e.g., silylation or methylation) when information about cannabinoid acids, the dominating cannabinoids in the plant is required. The total cannabinoid content is determined when the GC analysis is performed without derivatization. GC/MS is the method of choice for creating Cannabis profiles and signatures (chemical fingerprints), a tool for attributing the country of origin, the conditions of cultivation.

4.1.2.3 High-Performance Liquid Chromatography

High-performance liquid chromatography makes possible the simultaneous determination of neutral and acidic phytocannabinoids without derivatization. Reversed phase columns and preferably solvent programmed gradient systems are required for the separation of major and minor cannabinoids and their corresponding acids. Detection is usually performed by UV and diode array photometers, as well as by fluorescence, electrochemically and, recently, MS [12].

5. Traditional uses of *Cannabis sativa L*.

Afghanistan: Hot water extract of the resin is taken orally to induce abortion [24]

China: cannabis fibre was used in as decoration, to make clothes, ropes, fishing nets, paper, and food plant and was originally considered one of China's five cereal grain.

India: In special festivities such as weddings, it was said that a father must bring bhang to the ceremonies to prevent evil spirits from hanging over the bride and groom. Bhang was also a symbol of hospitality. "A host would offer a cup of bhang to a guest as casually as we would offer someone in our home a glass of beer. A host who failed to make such a gesture was despised as being tightfisted and misanthropic.

Jamaica: Ganja became a predominant symbol in the Rastafarian movement and its use became a religious sacrament. Even today, it is believed that ganja is a holy herb and when inhaled, it allows the Rastafarian to 'loosen up' his head and truly perceive himself as a Black person without the pre-conditioned forces of European society. This in turn permits the revelation that Haile Selassie is truly their God and Ethiopia, the home of the Blacks.

Ethiopia: *C. sativa* is used as an intelligence booster. It is also a component of multi-herb preparations used to treat various illnesses including wound healing and others [25].

6. Modern uses of Cannabis and Cannabinoids as Medicine

In the United States cannabis is now classified as a schedule-I drug, regarded as having high potential for abuse, and to be unsafe to take without medical supervision. Recently, several states have legalized the medical use of cannabinoids [27].

Cannabinoids are implicated in a variety of physiological and pathological conditions including inflammation, immunomodulation, analgesia, cancer and others [16]. Agents that increase the endocannabinoid system activity are likely to be used as potential hypnotics, analgesics, antiemetics, antiasthmatics, antihypertensive, immunomodulatory drugs, anti-inflammatory and neuroprotective agents, antiepileptics, drugs for treatment of glaucoma, spasticity and other "movement disorders", eating disorders, or alcohol withdrawal [19].

6.1 Chemotherapy induced nausea and vomiting

In many countries, cannabis and individual cannabinoids are approved for relief and prevention of nausea and vomiting caused by anti-cancer and anti-HIV chemotherapy. This action is exerted through the endocannabinoid system [20].

Among the cannabinoid medications, nabilone and dronabinol were initially approved in 1985 for nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional antiemetic treatments [26].

Studies have documented the superior efficacy of THC over placebo and prochlorperazine. THC is effective against mild and moderate emetogenic chemotherapy but not high dose cisplatin chemotherapy. This action is exerted though stimulation of CB1 receptors [30].

6.2 Appetite stimulation

Cannabis and cannabinoids are also approved for stimulation of appetite in AIDS patients with a severe loss of body weight. However this action, exerted through CB1 receptors, mainly increases intake of carbohydrates, not of protein, and is therefore not very effective for restoration of tissue mass [5].

In animals, CB1 receptor antagonism decreases motivation for palatable foods. CB1 receptors were found to be preferentially involved in the reinforcing effects of sweet, as compared to a pure fat, reinforcer [22].

6.3Alzheimer's disease

Alzheimer's disease is a neurological disorder of unknown origin that is characterized by a progressive loss of memory and learned behavior. A review of the recent scientific literature indicates that cannabinoid therapy may provide symptomatic relief to patients afflicted with AD while also moderating the progression of the disease. Additional cannabinoids were also found to reduce the inflammation associated with Alzheimer′s disease in human brain tissue in culture [23].

THC competitively inhibits acetyl cholinesterase and prevents AChE-induced amyloid beta-peptide aggregation, the key pathological marker of AD. THC treatment also decreased severity of disturbed behavior, and this effect persisted during the placebo period in patients who had received THC [22, 23] thus, THC and its analogues may provide an improved therapeutic option for Alzheimer′s disease, simultaneously treating both the symptoms and the progression of disease [23].

6.4 Effects in Patients with multiple sclerosis

Multiple Sclerosis is an autoimmune inflammatory disease that affects the central nervous system (CNS) including the presence of axonal degeneration and focal lesions in the white matter Cannabis has proven ability to manage pain associated with MS. In a clinical trial conducted on humans in 2005, cannabis based medicine delivered in the form of a sublingual spray was demonstrated to be significantly more effective than placebo at reducing pain and sleep disturbances in MS sufferers [7].

According to randomized, placebo-controlled trial conducted by John Zajicek *et al* on 630 participants with stable multiple sclerosis and muscle spasticity at 33 UK centres with oral cannabis extract (n=211), Δ9- tetrahydrocannabinol (Δ9THC); n=206), or placebo (n=213) for a total 15 weeks period improvement in spasticity reported in 61%, 60%, and 46% of participants on cannabis extract, Δ9-THC, and placebo, respectively [34].

6.5 Glaucoma

Glaucoma is an irreversible eye disease characterized as a group of eye conditions that can produce damage to the optic nerve and result in a loss of vision due to progressive loss of the retinal cells. It is the second leading cause of blindness in the world. It is now known that the endocannabinoid system is present throughout most ocular tissues and it is also known that the intraocular pressure can be lowered by use of cannabinoids [10].

In about 65% of both normal subjects and patients with glaucoma, THC has been shown to reduce the IOP, and both oral THC and smoked cannabis are effective. After smoking marijuana, the fall in IOP reaches its peak in about 2 h and is

gone by 3 to 4 h. The therapeutic objective of preventing retinal and optic nerve damage in glaucoma requires a continuously sustained fall in IOP. To produce such a sustained effect with marijuana, it would be necessary to smoke it eight to 10 times a day. The effect of oral THC is more prolonged, and fewer doses a day would be required, but it is still not possible to avoid the psychoactive effects at THC doses that would provide a useful reduction of IOP [21].

According to a prospective double- blind study conducted by Trans. Ophthalmologic Society on fifteen volunteer paid young male adults with marijuana and marijuana placebo being given on alternate experimental days it was observed that a marked reduction in the IOP after smoking marijuana [16].

THC, CBN, and nabilone were active in lowering intraocular pressure in rabbits, while CBD was inactive. The effect on IOP of 2-AG was biphasic; an initial increase in IOP followed by a reduction [21].

The IOP reducing effect does not seem to be related to a systemic reduction of arterial blood pressure. However, a direct effect on the ciliary processes, and specifically a reduction in capillary pressure, leading to changes in aqueous humour dynamics, has been proposed. Green *et al* showed that Δ9-THC decreased the secretion of ciliary processes and led to a dilatation of the ocular blood vessels through a possible b adrenergic action. In addition, Sugrue indicated that cannabinoids may inhibit calcium influx through presynaptic channels and in this way reduce the noradrenaline release in the ciliary body, leading to a decrease in the production of aqueous humour [27].

7. Health risks of medicinal cannabis

- **Lack of evidence for safety of cannabis and cannabinoids, particularly regarding long term effects:**

An obvious fear regarding cannabis/cannabinoid usage is that long term health effects may impact on users. According to The Barnes report, there is mixed evidence of residual effects on users of cannabis, with some studies indicating such effects and some indicating none, but THC is likely to be the main driver of any potential long term negative impacts; other cannabinoids have not been implicated. It is also important to note that most evidence of long term damage from cannabis usage comes from recreational, not medicinal, users of the drug–controlled usage in tandem with medical supervision may not pose the same level of risk [18].

- **Mood**

The main feature of the recreational use of cannabis is that it produces a euphoria effect or 'high'. The high can be induced with doses of THC as low as 2.5 mg in a herbal cigarette and includes a feeling of intoxication, with decreased anxiety, alertness, depression and tension and increased sociability. The high comes on within minutes of smoking and then reaches a plateau lasting 2 hours or more, depending on dose. It is not surprising that the overwhelming reason for taking cannabis given by recreational users is simply 'pleasure' [9].

Recent studies of cannabis users in the unintoxicated state evidenced that long-term heavy cannabis use is associated with impaired memory function. The evidence suggests impaired encoding, storage, manipulation and retrieval mechanisms [15].

- **Effects on cognition and psychomotor performance**

Cannabis impairs cognitive and psychomotor performance. The effects are similar to those of alcohol and benzodiazepines and include slowing of reaction time, motor incoordination, and specific defects in short-term memory, difficulty in concentration and particular impairment in complex tasks which require divided attention. The effects are dose-related but can be demonstrated after relatively small doses (5-10 mg THC in a joint), even in experienced cannabis users, and have been shown in many studies across a wide range of neurocognitive and psychomotor tests. These effects are additive with those of other central nervous system depressants [9].

According to Health Canada, impairment of cognitive function can be linked to levels of THC after smoking. Psychoactive cannabinoids increase risk of traffic accidents and risk of psychotic symptoms among vulnerable persons. Most of these effects are dependent on dose and route of administration and are attributable to a modulation of endocannabinoid system in the brain, via specific interactions with their receptors [15, 9].

- **Dependence**

A tendency for people to develop a dependence upon cannabis is often cited as a reason to avoid usage. According to the Barnes Report, the generally accepted dependence rate of users of cannabis is 9%, but this is based off recreational usage and is likely to be smaller in medicinal usage [18]

- **Variability risk due to dosage and composition inconsistencies:**

Unless supply of cannabis is strictly regulated with consistent growth conditions, it is possible that patients could be consuming unknown quantities of cannabinoids, which could present health risks [18].

8. Future directions

Despite historically used as medicinal agents for treating a variety of conditions, including fever, inflammation; roots are still largely ignored in scholarship and in medical practice. Therefore future research should compare the phytochemistry of hemp roots with those from various drug chemovars to determine if there are differences in active compounds.

There are various traditional methods of preparing cannabis root for therapeutic use. The raw cannabis roots can be prepared by pounding and crushing the fresh root to extract its juices. Future studies will also have to determine the best methods of preparing cannabis roots and best methods to administer cannabis roots for various conditions.

Despite ample theoretical evidences on the therapeutic uses of cannabinoids in management of glaucoma there are limited clinical evidences on long term management. Thus, future clinical investigations should be carried out on clinical effectiveness of these phytocannabinoids to be marketed as management alternatives for glaucoma.

9. Conclusion

There is renewed interest in pharmacotherapy with cannabis flowers and their extracts, stems, and leaves. The phytocannabinoids, including THC and CBD, have been the major focus of attention for medicine and are found in the glandular resin heads, which are most concentrated in flowers and bracts. It has been advanced that whole plant cannabis can be used for multiple therapeutic purposes. Pure tetrahydrocannabinol and several analogues have shown significant therapeutic benefits in the relief of nausea and vomiting, and stimulation of appetite in patients with wasting syndrome. Recent evidence clearly demonstrates analgesic and antispasticity effects that will probably prove to be clinically useful. Whilst there is a good theoretical basis for the use of cannabis and cannabinoids in the treatment of

glaucoma there are no satisfactory studies of longer term use. There are a number of single dose studies confirming that the cannabinoids can reduce intraocular pressure. Thus at the present time there is only some evidence of efficacy in glaucoma. Even though cannabis has the aforementioned medicinal uses, the majority of the youth in Ethiopia uses the plant for the recreational values leading addiction and dependence of the majority of the users. Hence cannabis is produced in areas without government control makes quality control and assurance leading to contamination of the product resulting toxicities for the end users.

10. Recommendations

1. Health professionals should be encouraged to identify, and offer help to people dependent on cannabis. The health departments should consider making recommendations for combining cannabis treatment programs with those of tobacco, alcohol and other substances.
2. Even though, cannabis is produced in different parts of Ethiopia, lots of cannabis is imported by different means from abroad. Thus, strict control should be maintained through these lines.
3. Recreational use of cannabis in many areas of Ethiopia by the youth leads to addiction of the productive man power. Therefore, FMHACA should provide strict laws on the use of cannabinoids and should work on the enforcement of these laws.

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