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REVIEW ARTICLE

Ethnopharmacology of *Cannabis sativa:* Unveiling the Medicinal Heritage and Modern Applications

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Abstract

Cannabis sativa, a plant with deep historical and cultural significance, is receiving renewed attention due to its medicinal properties. *Cannabis* has demonstrated a wide range of ethnopharmacological effects. *Cannabis* has long been utilised as a natural treatment to support mental and physical balance in a variety of ancient cultures, including Chinese, Indian, Middle Eastern, and African communities. Its main bioactive ingredients, terpenes and Cannabinoids like *THC* (*tetrahydrocannabinol*) and *CBD* (*cannabidiol*), are primarily responsible for its medicinal potential. These substances have shown a variety of pharmacological advantages, such as neuroprotection, seizure control, pain alleviation, and anti-inflammatory actions. Since several nations have legalised medical *cannabis,* more studies are being done on how well it works to treat epilepsy and chronic pain. Genomic advances could lead to customised cannabis treatments that are based on each patient's unique genetic makeup, increasing effectiveness and reducing adverse effects. *Cannabis sativa* has the potential to gain more acceptance as a treatment for a number of ailments, such as neurodegenerative disorders like Alzheimer's and Parkinson's, anxiety, PTSD, chronic pain, and epilepsy. Future studies will probably concentrate on enhancing therapeutic use by resolving safety and regulatory issues, updating dosing guidelines, and making cannabis-based products more consistent. This strategy will help clinical studies define exact formulations, doses, and uses for the best results.

Major Findings: It exhibits therapeutic effects including neuroprotection, seizure control, pain management, and anti-inflammatory activity. Personalized cannabis treatments based on genetic makeup may improve therapeutic outcomes and reduce adverse effects.

Keywords: Cannabidiol, Cannabinoids, Ethnopharmacology, Neurodegenerative Disease, Modern Application, Traditional Medicine

1. Introduction

The *Cannabaceae* family includes *Cannabis sativa* L., also known as *cannabis*, which has been cultivated for thousands of years (Figure 1). Evidence of its use dates back to approximately 10,000 years ago. It is a multipurpose plant that has potential uses in medicine and pharmacology in addition to a range of agricultural and industrial purposes, such as the creation of paper, textiles, and fiber[1]. There is ongoing discussion on the classification of *Cannabis* species; according to some specialists, the genus contains three primary species: *C. sativa* L., *C. indica* Lam., and *C. ruderalis*. These species are distinguishable by their distinct morphological features[2,3]. To date, over 500 different phytochemicals have been identified in *C. sativa*[4]. Among these, compounds such as lignans, alkaloids, terpenoids, steroids, flavonoids, and cannabinoids are the most common. Cannabinoids, a group of terpenophenolic compounds unique to *Cannabis*, are the most studied and recognised secondary metabolites of the plant[5]. The most notable Cannabinoids include Cannabigerol (CBG), Cannabichromene (CBC), Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). The highest concentrations of Cannabinoids are found in the glandular trichomes and flowers of the plant[6]. There

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are numerous ways that Cannabinoids improve human health. In comparison to CBD, CBG, and CBC, which are non-psychoactive chemicals, THC is the psychoactive ingredient in *C. sativa*[7]. In addition to its antipsychotic, antinociceptive, anxiolytic, anti-inflammatory, and antioxidant properties, CBD. While THC acts as a bronchodilator, neuroprotective antioxidant, hunger stimulant, and pain and stiffness reducer, CBG and CBC are also said to possess antimicrobial properties [8]. The Cannabis plant is a dioecious annual herb with a maximum height of one to six meters[9]. One of the fastest-growing plants in the world, hemp is an annual with intricately arranged leaves[10]. In a single growth cycle, *cannabis* plants have the ability to remove up to 10 metric tons of carbon dioxide from the air, in addition to enhancing thermal balance, environmental effect, and air quality[11]. When it comes to yield, the *cannabis* plant is highly productive; on an equivalent plot of land, it may produce up to 250% more fiber than cotton and 600% more than flax. The advantages of the clothing made from the hemp market. Herbicides are not necessary while growing *Cannabis* plants since their dense canopies keep out weeds and minimise the amount of nematodes and fungi that live in the soil. Due to its deep root system, the *Cannabis* plant helps maintain the quality of the soil by halting nutrient runoff and erosion. By extracting contaminants like heavy metals from the soil and keeping them inside the plant, it also helps with phytoremediation. Leaves drop to the ground during the growing season, supplying a consistent amount of moist organic materials. Due to its ability to improve soil quality, the cannabis plant is a great choice for use in crop rotation plans that aim to increase the production of the main crop. It is anticipated that cannabis will be a viable and environmentally benign crop if growing is managed properly[12-14].



Figure 1. Image of *Cannabis sativa* plant.

2. Plant Profile

2.1 Nomenclature

Table 1. Terms used in Botany *Cannabis sativa's* taxonomic division are as follows

1	Kingdom	*Plantae* (Plant)
2	Subkingdom	*Tracheobionta* (vascular plants)
3	Superdivision	*Spermatophyta* (seed plants)
4	Division	*Magnoliophyta* (flowering plants)
5	Class	*Magnoliopsida* (Dicotyledons)
6	Subclass	*Hamamelidae*
7	Order	*Urticales*
8	Genus	*Cannabis*
9	Family	*Cannabaceae*
10	Species	*sativa*
11	Taxonomic authority abbreviation	L

2.2 Ethnobotanical Study of *Cannabis sativa*

One of the therapeutic plants, *Cannabis sativa* L., is well-known for its oil, fibre, and psychoactive and medical properties[15]. *Cannabis* is widely recognised for its medicinal and narcotic uses due to its many secondary metabolites, which include terpenoids, flavonoids, sterols, and phytocannabinoids[16-20]. Industrial *Cannabis sativa* (fibre type) stems yield very high-quality cellulosic and woody fibres; for the food and feed industries, seeds are a great source of fatty acids and proteins; and leaves and inflorescences are a treasure trove of secondary metabolites with a variety of medicinal uses. The primary medicinal cannabis product is the inflorescence (marijuana type). On female inflorescences, glandular trichomes are highly numerous and generate and collect hundreds of specific compounds with potential bioactivity.

2.3 Traditional Applications of *Cannabis sativa* Components[21-32]

The data provided in Table 1 shows that the analysis indicates that the seeds and leaves are the elements that are most frequently employed for treatment. The usage of *cannabis* seeds as nourishment has been documented in numerous studies. It is utilised in the making of pasta, beer, oil, and gluten-free flour with a nutty flavor[33,34]. Not only are the seeds utilised for human nutrition[21], but they are also used to treat hepatitis C, cancer, AIDS patients' nausea and vomiting, and other illnesses. Moreover, it is used as an analgesic, anxiolytic, antiepileptic, antiemetic, muscle relaxant, weight control aid, and pain reliever for neurological conditions[22]. Other cosmetic uses for these seeds include hair fortification via the external use of seed powder, primarily as a hair serum[23] (Table 2).

Cannabis sativa seeds, traditionally known for their applications in medicine and food, have recently been explored for their potential in addressing contaminated groundwater. Studies have shown that hemp seed protein powder is particularly effective at chelating "eternal chemicals," such as perfluoroalkyl and polyfluoroalkyl

Table 2. Traditional applications of *Cannabis sativa* components[21-32]

S. No.	Plant part used	Traditional uses	Administration	Dosage form
1	Seed	Nutrition	Oral	Powder
2	Seed	Narcotic, pain killer, and queasiness, emesis, appetite stimulant, anorexia in AIDS treatment, Chronic Hepatitis C, Nervousness, Convulsion and Spasmolytics.	Not define	Not define
3	Seed	Strengthening hair follicles	External	powder form
4	Seed	Pain Reliever, Joint protectant, Rheumatic pain reliever.	External	Oil
5	Leaf	Eczema	External	Powder form
6	Leaf	Abdominal distension, Throat clearing, and Phlegm.	Oral	Leaf extract
7	Leaf	Cerebrospinal system Gouty arthritis, Joint pain and Sedative	Oral	Powder form
8	Leaf	Schizophrenia Spectrum and Other Primary Psychotic Disorders	External	oil form
9	Leaf	Abdominal disorder	Not define	Not define
10	Leaf	Cardiovascular disorders, Dermatologic disorders, Acne, Sickle cell disease.	Not define	Powder, juice and paste
11	Inflorescence	Amoebic dysentery, Depressant, Reduced appetite, Watery stool.	Oral	Not define
12	Stem	Firebrand, Wood fuel	Not define	Raw
13	Stem, Flower	Hair care, Traditional uses	Not define	Not define
14	Stem	Building materials, Paper production, Textiles, Rope-making	Not define	Unprocessed
15	Root	Fever	External	Maceration
16	Root	Gout, Arthritis	External	Boiled root
17	Root	Joint discomfort	External	Tincture
18	Root	Skin irritation	External	Unprocessed decoction mixed with butter
19	Root	Inflammation	External	Boiled roots, Decoction
20	Root	Childbirth, Postpartum, Haemorrhage	Oral	Decoction
21	Root	Erysipelas, toxins	Oral	Decoction

substances, outperforming other plant-based protein sources in this regard[23]. It was discovered that the Cannabinoid proteins were also highly beneficial in treating soils tainted with salt[33]. The leaves are applied externally as a poultice to treat subcutaneous tissue disorders and eczema[22]. Additionally, locals take them orally to cure CNS issues such as gout, schizophrenia, arthritis, bloating, coughing, and mucus[22,25]. One of the most recognisable images of modern stoner culture is a cannabis leaf; the plant's recreational uses are often linked to the leaf's shape. Numerous studies have documented *Cannabis* leaves' traditional applications, which include treating a variety of illnesses like cancer, rheumatoid arthritis, hypertension, itching, poisoning from snakes and scorpions, as well as abnormalities of the digestive and circulatory systems[24-28]. Additionally, these leaves have been shown to have potent sedative, analgesic, and narcotic properties[76]. *Cannabis sativa* stem fibres are used in building, tools, clothing, paper, and rope production, according to numerous studies[21-23].

Defibration, which is essentially stem beating and grinding, is the method used to create these fibres. Chenevotte and *Cannabis* dust are the two byproducts that are produced in this method. It is crucial to emphasise that as plants mature, their fibres are coarser and tougher, resulting in a drop in fibre quality. The medicinal properties of the *Cannabis* plant extend to its roots in addition to its aerial portions. They are specifically used to treat erysipelas infection, joint pain, burns on the skin, inflammation, and vermin[30]. These roots are also taken orally as a juice to treat postpartum haemorrhage and childbirth-related problems[31]. The euphoric effect of *Cannabis sativa* is still the most commonly reported application. Inflorescences and leaves have been used as drugs in a variety of ways; for example, the leaves can be prepared or smoked, while the resin or inflorescences can be processed to make Charas, Attar, Hashish, Ganja, as well as plant powder. Additionally, beverages like Bhang, Thandai, and others can be made with the leaves, inflorescences, and shoots and Tandai, among others[24,35,36]. Documented the use of cannabis beverages for religious purposes. This plant preparation is widely drunk and is known as a traditional bhang drink for Indian holidays like Holi and Shivaratri[37]. The entire *Cannabis* plant was reported to be employed in certain ethnobotanical surveys. The majority of illnesses pertaining to the neurological system and mental problems are treated with the aerial portions. However, treating gastrointestinal diseases, diabetes, scarring, and asthma is the most common usage of those sections[32]. On the other hand, a few researchers mentioned the benefits of *Cannabis* inflorescences on appetite, dysentery, and diarrhoea, but they didn't address how to prepare or administer them[24]. Ethnobotanical research indicates that *Cannabis sativa* has been extensively utilised by various local populations, with some of its traditional uses being widespread across different countries, while others are specific to particular cultures. Its psychotropic, medicinal, and cosmetic applications are found globally, while religious uses of the plant have primarily been documented in Latin America and Asia. These diverse properties and activities are largely attributed to the existence of distinct chemically structured bioactive metabolites. The plant's Ethnobotanical significance has driven scientific interest in its chemical composition, leading to the isolation of the first compound, *cannabinol*, from *Cannabis* in the late 19th century[38].

2.4 Global Regulatory Guidelines

In many countries, the cultivation, distribution, and processing of *Cannabis* are prohibited. For example, in Morocco, cultivating cannabis is only permitted in certain regions, such as Ketama and Bani Khalid, with state authorisation. *Cannabis* was initially banned internationally through the International Opium Convention of 1912 and was subsequently added to the Schedule for the International Narcotics Control. Along with other highly addictive narcotics like heroin, it was later designated as a Schedule I substance under the 1961 Single Convention on Narcotic Drugs. Because of their restricted medicinal utility and potential for abuse, Schedule I drugs are tightly regulated. Additionally, cannabis was placed in Schedule IV of the 1961 Convention, which includes substances with little or no recognised medical value. On July 7, 2017, provisions related to drug addiction treatment, as well as the regulation of cannabis production for scientific and medical purposes, were introduced, ensuring that, so long as it complies with Articles 23 to 28 of the Single Convention, cannabis control for these objectives does not contravene responsibilities

under international treaties. As more nations amend their legal frameworks to allow for the medicinal or therapeutic use of *cannabis*, the worldwide discussion surrounding its regulation has accelerated in recent years. Many governments have enacted regulations that allow patients to access *Cannabis*-based treatments to alleviate symptoms, reduce pain, or enhance their overall well-being (Table 3).

2.4.1 *C. sativa's Biological Assessment and Potential*

From a biological standpoint, Cannabinoids such as Cannabidiol (CBD) and others are considered non-psychoactive. However, compounds like Δ9-tetrahydrocannabinol (THC), cannabinol (CBN), and Cannabidivarin (CBDV) are recognised as psychoactive Cannabinoids[52,53]. The primary psychoactive ingredient in *Cannabis* is THC, and

Table 3. *Cannabis* regulations and approvals worldwide[41-47,50,51]

Countries	Possession/ownership	Farming	Transport/sale
India	It is illegal on a federal level. Some states have legalised and allowed the usage of *Cannabis*, such as West Bengal, the Northeast, and Odisha.	It is forbidden on a federal level. Some states have legalised and allowed the usage of *Cannabis*, including West Bengal, the Northeast, and Odisha.	It is illegal at the federal level. West Bengal, the Northeast, and Odisha are among the states that have legalised and allowed the usage of *Cannabis*.
Argentina	Illegal (but not illegal if used for personal use and in tiny amounts)	Unlawful	Unlawful
Austria	It is not illegal to possess up to 5 g of *Cannabis*.	Unlawful	Unlawful
Australia	It is not illegal to possess up to five grams of *Cannabis*.	Unlawful	Unlawful
Finland	Unlawful (only for medical use)	Unlawful	Unlawful
Belgium	Unauthorised (non-criminal up to 3 g)	Unlawful (albeit not a crime if it's just one plant)	Unlawful
Bolivia	Unlawful (not criminal, but)	Unlawful	Unlawful
Brazil	Legal (The legalisation of CBD-based medications, such as THC and cannabis flower, is significant)	Unlawful	Unlawful
Canada	Invalid (legal for medical purposes)	Infraction (a small quantity of plants may be permitted)	Unlawful
Chile	Unlawful (not a crime)	Only for legitimate medical purposes	Unlawful
Colombia	Up to 22 grams are permissible for personal use.	Up to 22 grams are permissible for personal use.	Only scientific and medical uses are allowed.
United state	Although it is prohibited at the federal level, it is permitted in Alaska, California, Colorado, Nevada, and Washington.	In many states, it is legal to grow medicinal cannabis.	Legal for medicinal use, but illegal otherwise.
Costa Rica	Unlawful (not a crime)	Unlawful	Unlawful
Croatia	Unlawful (non-criminal)	Unlawful	Unlawful (except for therapeutic benefit)
Germany	Acceptable for use in medicine	Lawful	Lawful
Ireland	Acceptable for use in medicine	Unlawful	Unlawful
Mexico	Unlawful (not a crime)	Unlawful	Unlawful (not a crime)
Moldova	Unlawful (not a crime)	Unlawful	Unlawful

research on the toxicity of this metabolite has been done extensively[53,54]. The order in which its psychoactive component diminishes is as follows: The flower's inflorescence, leaves, seeds, roots, and stems[55]. Interest in the possible medical uses of cannabis and cannabinoids increased dramatically when the endocannabinoid (eCB) system in mammals was discovered in the 1990s[56]. Cannabinoids exert their physiological effects through the activation of various receptors, including adrenergic receptors, G-Protein Coupled Receptors (GPCRs) such as GPR55, GPR3, and GPR5, as well as *Cannabinoid* Receptors CB1 and CB2[55]. Historically, Pain, inflammation, and mental health issues have all been treated using different elements of the cannabis plant. For instance, the root has been suggested as a remedy for a number of ailments, including fever, inflammation, gout, arthritis, and joint pain. Additionally, it has been used for ailments like burns, tumours, postpartum hemorrhage, challenging labour, infections, gastrointestinal problems, and STDs[56]. *Cannabis* has been used to treat rheumatism, asthma, epilepsy, lethargy, glaucoma, insomnia, nausea, and pain in addition to being utilized as an appetite stimulant and digestive aid[55,53,57]. The inflorescence and leaves of *Cannabis* may contain sufficient levels of flavonoids, Mono- and Sesquiterpenoids, and Cannabinoids to be considered therapeutically beneficial, as concentrations above 0.05% are of pharmacological interest[53]. *Cannabis* contains terpenoids and flavonoids, including myrcene, limonene, pinene, β-caryophyllene, and *cannflavin* A, in addition to cannabinoids, which contribute to its pharmacological effects[55]. Research has shown that these compounds, found in the plant's above-ground parts, counteract the dysphoric effects of THC and enhance the anti-inflammatory properties of CBD[58]. Research has demonstrated that neutral Cannabinoids, such as *Cannabidiol* (CBD) and *Cannabidivarin* (CBDV), may be used therapeutically to treat epilepsy (focal seizures) and nausea and vomiting[59,60]. On the other hand, THC and CBN have been shown to effectively reduce intraocular pressure, making them potential treatments for glaucoma cases that do not respond to other therapies[61]. *Cannflavin* A and B are important

Table 4. An outline of the bioactivities of *Cannabis sativa*[63-80]

Separated bioactive substances	Uses and Bioactivity
THCA stands for tetrahydrocannabinolic acid	antiemetic, neuroprotective, Immunomodulatory, anti-inflammatory, and antineoplastic properties
CBDV (cannabidivarin)	Features that prevent seizures (anti-epileptic) and antiemetic qualities
Beta Myrcene	Analgesic and anti-inflammatory sedative
Dextrorotatory Limonene	powerful antidepressant and anxiolytic
Beta Ocimene	antifungal and anticonvulsant properties
Gamma Terpinene	antioxidant, anti-inflammatory, and anti-proliferative properties
Alpha Terpinene	An antioxidant
Alpha Pinene	Anxiolytic, bronchodilator, anti-inflammatory, and anti-microbial properties
THC, or tetrahydrocannabinol	Antioxidant, anti-inflammatory, and anti-pruritic properties
CBD (cannabidiol)	anti-inflammatory and anti-convulsive Antipsychotic, antioxidant, and immunosuppressive qualities
CBG, or cannabigerol	Effects against fungal infections, cancer, depression, moderate hypertension, pain relief, and arrhythmias
CBN, or cannabinol	Anti-inflammatory, anti-convulsant, and sedative
Tetrahydrocannabivarin THCV	Convulsant-preventing
Epifriedelanol	Antioxidant
Ligans	Antioxidant, anti-viral,anti-diabetic

flavonoids (prenylflavonoids) with anti-inflammatory, anti-cancer, antioxidant, neuroprotective, anti-parasitic, and antiviral activities, among other medical uses[62] (Table 4).

2.5 Utilised Plant Components and Preparation Techniques

The most commonly used portion of the *Cannabis sativa* plant is the leaf (53.8%), according to their intended use, the sections of *Cannabis* plants are arranged as follows: Root (23%), Seed (7.7%), flower, inflorescence, resin, and additional parts (3.8%). In traditional medicinal practices (FMPs), simple preparation methods are usually employed, rather than complex formulations. For severe cases, cannabis leaves are used to produce a vapour for inhalation, and an oil-based extract of the leaves is used in the treatment of schizophrenia[81]. The juice from cannabis leaves is consumed orally to alleviate bloating, coughing, and the production of phlegm[82] *Cannabis* leaves are used to eliminate dandruff. To treat fever, a mixture of macerated *Cannabis sativa* roots and leaves is consumed[83]. To reduce arthritis pain and serve as a CNS depressant, one teaspoon of powdered *Cannabis* leaves that have been crushed and dried is combined with water and consumed orally once a day[84]. Seed oil is beneficial for treating conditions such as rheumatism, cancer-related pain, and the side effects of cancer chemotherapy[85,86]. To treat ailments including phthisis, tetanus, menorrhagia, dysmenorrhea discomfort, and insanity, the root is ground into a paste with 25 black pepper and taken twice a day[87]. To alleviate the severe pains associated with dysentery and strangulated hernia, the dried female *Cannabis* flowering tips are introduced rectally[88].

3. Pharmacological Uses of *Cannabis sativa*

3.1 Diabetes

In 2012 analysis of data from Rajavashisth and colleagues discovered in the National Health and Nutrition Examination Survey that light marijuana users were less likely to have diabetes than heavy and ex-users. After adjusting for factors such as age, race, and alcohol consumption, they also found that both current and former marijuana users were less likely to be diagnosed with diabetes than non-users[89]. Delta-9-tetrahydrocannabinol (Δ9-THC), a compound derived from marijuana, has been shown to offer therapeutic or preventive benefits for individuals with diabetes[90]. In a study by Levendal and Frost (2006), rats treated with *Cannabis* exhibited lower blood glucose levels. However, when compared to the normal control group, the difference was not statistically significant[91].

3.2 Cancer

Cannabinoids have been demonstrated to impede the formation of new blood vessels, which are necessary to supply enough oxygen and nutrients to support the rapid development of cancer cells[92]. For a number of medicinal disorders, *Cannabis sativa* is prescribed and utilised. *Cannabis* is used to treat cancer patients' nausea and vomiting brought on by chemotherapy. Research has concentrated on how cannabinoid receptor agonists, specifically CB(1) and CB(2), can help treat breast cancer that lacks estrogen receptors[93]. Additionally, the Cannabinoids lower the possibility that cancer cells may invade nearby normal tissues and spread (that is, lessen the number of cancer cell colonies in numerous distinct tissues that are distant from the typical melanoma site). Additionally, it has been suggested that certain endocannabinoid activities may reduce the likelihood of mutations that could contribute to the development of cancer cells[94,95].

3.3 Parkinson's Disease

Cannabinoids have a notable receptor-mediated modulatory effect within the basal ganglia output nuclei, which may help alleviate some symptoms of Parkinson's disease. Additionally, recent research has revealed that certain cannabinoids act as powerful antioxidants, protecting neurons from damage and death, even without the involvement of cannabinoid receptors. It appears that marijuana may extend or even reverse the current dopaminergic degeneration of the mind, a process for which there is now no known cure. When used with already prescribed medications, cannabis would represent a qualitatively novel approach to Parkinson's disease treatment, enhancing it further[96].

3.4 HIV

Human Immunodeficiency Virus (HIV) patients have been treated with *Cannabis* to improve their appetite

and reduce pain during chemotherapy[97]. Clinical trials have shown that marijuana has some beneficial effects in a few conditions, including lowering intraocular pressure, reducing nausea and vomiting, stimulating bronchodilation, and lessening the effects of AIDS-related wasting syndrome. As a result, congeners of cannabinoids have been developed with potential therapeutic uses[98].

3.5 Glaucoma

Glaucoma is one of the main causes of blindness in the world today. The neuroprotective properties of cannabinoids efficiently Lower Intraocular Pressure (IOP). Cannabinoids may therefore be useful in the treatment of glaucoma[99].

3.6 Chronic Pain and Arthritis

Additionally, medical *Cannabis* is utilised to treat depression in patients, reduce neuropathic pain brought on by diabetes[100], arthritis, and chronic pain[101]. Experimental studies suggest that CB2 receptors are involved in the regulation of joint pain, including pain associated with arthritis[102,103].

3.7 Constipation

Studies have demonstrated the effectiveness of MaZiRenWan, a Chinese herbal preparation containing hemp, in addressing constipation. A single research team has conducted several randomised controlled trials that support its efficacy[104-106]. One investigation involved administering 7.5 g of MaZiRenWan capsules twice daily for eight weeks to individuals with functional constipation and excessive syndrome (characterised by overactivity in Traditional Chinese Medicine). When it came to increasing the frequency of complete spontaneous bowel movements, this herbal mixture, which included Semen *Cannabis sativa* (hempseed), Semen Pruni Armeniacae (bitter apricot seed), Radix Paeoniae Alba (white peony root), Fructus Immaturus Citri Aurantii (immature orange fruit), Cortex Magnoliae Officinalis (magnolia bark), and Radix et Rhizoma Rhei (rhubarb root and rhizome), proved greater results than a placebo. The benefits continued for eight weeks after treatment cessation. However, the study lacked a statistical sample size calculation and had a significant dropout rate, with 78.3% of the placebo group and only 70% of the therapy group completing the study, potentially introducing attrition bias[105,106]. Another multisite trial in China evaluated oral MaZiRenWan (7.5g twice daily) against a placebo and senna (15 mg daily). Results showed that MaZiRenWan was as effective as senna and better than placebo in relieving constipation symptoms. Patients receiving MaZiRenWan showed lasting improvements in bowel movements, straining, quality of life, and colonic transit, even eight weeks after treatment ended[104]. The anti-constipation effects of MaZiRenWan are believed to stem from active components such as emodin, amygdalin, albiflorin, honokiol, and naringin. These structurally related compounds significantly enhance colonic smooth muscle contraction in vitro. It's important to note, however, that none of these chemicals are present in hemp[107]. This observation reaffirms the notion that different chemicals in a herbal blend work in concert with one another[108]. Since there is just one sufficiently powered randomised controlled trial that has been published to date, mostly focusing on Chinese female patients, there are not enough papers to justify a meta-analysis and comprehensive review[104]. To fully understand how hemp contributes to this kind of synergism, more research must be done.

3.8 Anti-oxidant Activity

A substance that inhibits or decelerates the oxidation of molecules crucial to an organism's metabolism is known as an antioxidant. *Cannabis sativa* L. encompasses various antioxidant compounds. Numerous techniques have been extensively employed to evaluate the plant's antioxidant activity, ABTS (2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)), Ferric Reducing Ability of Plasma (FRAP), Oxygen Radical Absorbance Capacity (ORAC), phosphomolybdenum, and metal chelation techniques are a few examples. These approaches are well-documented in scientific literature. Research has demonstrated that *Cannabis sativa* seeds, leaves, and aerial parts exhibit antioxidant properties. The antioxidant activity of *Cannabis sativa* seeds has been the subject of extensive research. For example, *Manosroi et a*L.[109] utilised various assays, such as DPPH, chelating tests, and lipid peroxidation inhibition, to evaluate an ethanolic extract's antioxidant capacity. The findings, based on IC50 values (the concentration needed for 50% inhibition), revealed robust antioxidant activity in the seed extract, with

DPPH values of 14.5 mg/mL, chelating test values of 1.9 mg/mL, and lipid peroxidation inhibition values of 92.7 mg/mL. In a separate study, the methanolic extract of the seeds displayed moderate antioxidant activity against DPPH, with a 75% suppression at a concentration of 500 µL/mL[110]. The potent antioxidant effects are likely attributable to polyphenols and Cannabinoids in the seeds[111,112]. Besides polyphenols and cannabinoids, other metabolites found in cannabis seeds, such as lignamides[113] and proteins[114], show moderate antioxidant activity. However, their antioxidant effects are not as pronounced as those of polyphenols and cannabinoids. Extracts from these plant components have generally exhibited significant antioxidant properties, probably due to the high concentration of polyphenols in the leaves[115]. For example, a DPPH IC50 value of 2.7 mg/mL was found in a hydroalcoholic extract of the leaves[109]. This value is lower compared to the result from the seed DPPH test, indicating a stronger antioxidant potential in the leaves. Additionally, the plant's aerial portions showed a high level of antioxidant activity, with outcomes similar to those of the beneficial control[116]. As was previously noted, polyphenols are generally regarded as the main antioxidants in cannabis. They work by chelating metal ions, blocking lipoxygenase to stop oxidation, and neutralising free radicals that cause oxidative damage[117,118]. Furthermore, several volatile terpenes have potent antioxidant and anti-free-radical qualities[119]. This contributes to the explanation of the antioxidant activity of essential oils that have been isolated from the plant's aerial parts in a number of studies.

4. Modern Application of *Cannabis sativa*

4.1 Alzheimer Disease

Alzheimer's disease impacts nearly 5% of individuals aged 60 and older[120]. Key pathological features of the disease include reduced levels of choline acetyltransferase, the buildup of neurofibrillary tangles consisting of hyperphosphorylated tau protein and extracellular β-amyloid plaques[121]. While several Cannabinoids may interact with β-amyloid (Aβ), the relationship between CBD and THC is better understood[122]. In an *in vitro* study, THC demonstrated the ability to inhibit amyloid aggregation[123]. Additionally, various forms of THC were shown to influence the formation and aggregation of Aβ fibrils[124]. This *Cannabinoid* also reduced the inflammatory response and promoted the breakdown of intracellular Aβ[125]. THC was found to inhibit acetylcholinesterase activity[126], and when elderly mice were given a small dose of THC, their cognitive performance improved[127]. There have been reports highlighting the neuroprotective, anti-inflammatory, and antioxidant properties of CBD, along with its ability to prevent neurodegeneration in the cortex and hippocampus, and regulate the migration of microglial cells[128]. Unfortunately, the clinical trials conducted thus far have only lasted up to 14 weeks. For example, one trial demonstrated that a daily dose of 1.5 mg of THC improved patient mobility over two one-week periods, with no significant side effects. As a result, the overall impact of *Cannabis* on Alzheimer's Disease (AD) patients remains uncertain, with conflicting views on whether it is beneficial or harmful. To fully explore the therapeutic potential of each *Cannabinoid*, further preclinical and clinical studies are necessary.

4.2 Multiple Sclerosis

Although the precise origin of Multiple Sclerosis (MS) is unknown, a mix of environmental variables is thought to be responsible, such as smoking, Epstein-Barr virus infection, and poor nutrition, along with genetic predispositions. MS is a non-traumatic central nervous system disorder commonly affecting young adults, typified by demyelinating plaques in the brain and spinal cord's grey and white matter. Given that neurodegeneration is the primary driver of MS [129], Cannabinoids may offer potential treatments by providing neuroprotective effects. According to preclinical research, CBD effectively inhibits the onset and progression of multiple sclerosis. According to in vitro research, CBD may alter Th17 cell reactions, increasing IL-10 production while decreasing IL-17 and IL-6 levels[130]. Additionally, using the experimental autoimmune encephalomyelitis (EAE) model, CBD was shown to improve clinical outcomes and reduce cellular infiltration and tissue harm to the central nervous system[131]. Cannabigerol (CBG) has additionally been studied for its neuroprotective and anti-inflammatory properties. In cell cultures and mouse models of MS and EAE, CBG significantly reduced TNF-α levels and

improved symptoms of EAE. These findings suggest that both CBD and CBG may help in managing the neuroinflammatory and neurodegenerative aspects of MS.

4.3 Parkinson's Disease

The central nervous system is impacted by Parkinson's Disease (PD), a chronic degenerative neurological condition that causes both motor and non-motor symptoms. The disorder is typified by the buildup of misfolded α-synuclein proteins and the death of dopamine-producing neurons in the substantia nigra, which form fibrous inclusions known as Lewy bodies and Lewy neurites. Nevertheless, the precise biological pathways behind Parkinson's disease remain unclear; factors such as mitochondrial DNA damage, bioenergetic dysfunction, excessive Reactive Oxygen Species (ROS) production, and impaired calcium regulation contribute to increased neuronal death[132]. Pain is a prevalent and often under-recognised non-motor symptom of Parkinson's disease, for which there is currently no definitive treatment[133]. PD is thought to afflict about 4.1 million individuals globally, and by 2030, that figure is expected to double. Treatment strategies are gradually evolving from symptom management to slowing disease progression or potentially finding a cure. Currently, PD patients primarily receive treatments aimed at addressing motor dysfunction without targeting the underlying causes of the disease. Levodopa remains the most commonly prescribed medication for PD. While it is considered the most effective treatment[134], long-term use can lead to various complications and may become less effective over time[135]. Cannabinoids have shown some promise in treating PD, but they also come with a range of adverse side effects. Parkinson's disease is significantly influenced by the cannabinoid system, especially in the basal ganglia[136].

5. Future Directions

Because of its anti-inflammatory and neuroprotective qualities, cannabis has become a major focus of therapeutic research for ALS (Amyotrophic Lateral Sclerosis). Research suggests that marijuana may alter the immune system, which could prevent motor neuron degeneration[137]. Future research may include clinical trials that assess the safety and effectiveness of cannabis in managing ALS symptoms and potentially influencing the progression of the disease. Although cannabinoids have not been thoroughly studied in relation to Multiple System Atrophy (MSA), there is potential to investigate their capacity to alter immune responses[138], . Future studies could examine whether cannabinoids can improve autonomic function and reduce neuroinflammation in people with MSA, opening up new therapeutic intervention options. The scant study on cannabinoids in Frontotemporal Dementia (FTD) highlights their anti-inflammatory properties. Pointing to possible therapeutic uses. Future studies may investigate cannabis's potential to mitigate behavioral and cognitive symptoms of FTD by modulating immune responses in specific brain regions, potentially offering insights into novel treatment approaches. Moving forward, researchers recognised the importance of delving deeper into the mechanisms underlying cannabinoids' immunomodulatory effects. To develop more targeted and efficient therapies, it is crucial to explore the intricate signaling pathways and cell interactions involved. Furthermore, examining how cannabinoids impact various stages of neurodegenerative disorders and identifying disease-specific responses will be essential for tailoring treatment strategies. Moreover, the establishment of uniform protocols for cannabinoid administration and dosage is necessary to ensure consistent and reliable therapeutic outcomes, ultimately supporting evidence-based treatment methods[139].

7. Conclusion

In conclusion, the ethnopharmacology of *Cannabis sativa* provides a captivating insight into the plant's long-standing medicinal legacy, used across various cultures for centuries. Its therapeutic potential, from ancient healing practices to cutting-edge pharmacological innovations, remains undeniable. This review assembled and analysed new preclinical research on neurodegenerative illnesses that was prompted by the growing acceptability of cannabis. Through a variety of cellular and molecular mechanisms in neurodegenerative disorders, these studies illustrated the neuroprotective qualities of several cannabinoids. *Cannabis sativa* has the capacity

to address contemporary health issues and inspire novel therapeutic solutions.

8. Author Contribution

Vijaya Laxmi: Conceptualization, literature collection, original draft preparation, and graphical abstract creation. Jaya Martolia: Supervision, critical revision of the manuscript, final editing, and reference validation. Both authors have read and agreed to the published version of the manuscript.

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