Journal of Ayurveda and Integrative Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: elsevier.com/locate/jaim

Assessing effects of Cannabis on various neuropathologies: A systematic review

Suhrud Pathak [a], Jeyaram Bharathi Jeyabalan [a,b], Keyi Liu [a], Preston Cook [a], Bennett Lange [a], Shannon Kim [a], Rishi Nadar [a], Kiersten Ward [a], Courtney S. Watts Alexander [a], Ashwani Kumar [c], Kamal Dua [d,e], Timothy Moore [a], Jeyabalan Govindasamy [f,*], Muralikrishnan Dhanasekaran [a]

[a] Harrison College of Pharmacy, Auburn University, Auburn, AL, 36849, USA
[b] Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Nilgiris, Ooty, Tamil Nadu, 643 001, India
[c] Patanjali Herbal Research Department, Patanjali Research Foundation, Haridwar, 249405, India
[d] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW, Australia
[e] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, NSW, Australia
[f] Alwar Pharmacy College, Alwar, Rajasthan, 301030, India

ARTICLE INFO

Keywords:
Cannabis
Cannabis congeners (Δ9-Tetrahydrocannabiorcol-THC
Cannabidiol-CBD
Cannabigerol-CBG)
Neuropathologies
Neuroprotection
Neurotoxicity
Neurological disorders

ABSTRACT

Natural bioactives possess a wide range of chemical structures that can exert a plethora of pharmacological and toxicological actions, resulting in neuroprotection or neurotoxicity. These pharmacodynamic properties can positively or negatively impact human and animal global healthcare. Remarkably, Ayurvedic botanical Cannabis has been used worldwide by different ethnicities and religions for spiritual, commercial, recreational, nutraceutical, cosmeceutical, and medicinal purposes for centuries. Cannabis-based congeners have been approved by the United States of America's (USA) Food & Drug Administration (FDA) and other global law agencies for various therapeutic purposes. Surprisingly, the strict laws associated with possessing cannabis products have been mitigated in multiple states in the USA and across the globe for recreational use. This has consequently led to a radical escalation of exposure to cannabis-related substances of abuse. However, there is a lacuna in the literature on the acute and chronic effects of Cannabis and its congeners on various neuropathologies. Moreover, in the post-COVID era, there has been a drastic increase in the incidence and prevalence of numerous neuropathologies, leading to increased morbidity and mortality. There is an impending necessity for a safe, economically viable, multipotent, natural bioactive to prevent and treat various neuropathologies. The ayurvedic herb, Cannabis is one of the oldest botanicals known to humans and has been widely used. However, the comprehensive effect of Cannabis on various neuropathologies is not well established. Hence, this review presents effects of Cannabis on various neuropathologies.

1. Introduction

Between 2500 and 500 BC, the Ayurvedic philosophy emphasizing the healthy way of life emerged and flourished. Ayurveda literally means "science of life" ("Ayu" = life, "Veda" = science) because the ancient Indian system of health treatment focused on humans and their ailments. It is stated that pleasant health implies a metabolically well-balanced human [1]. The practice of Ayurveda therapeutics consists of plants and natural bioactives. Natural bioactives are a comprehensive term for various biologically active compounds produced by organisms such as bacteria, fungi, animals, and plants. In addition to being minimally toxic, natural bioactives are considered to have a wide variety of chemical structures, leading to extensive pharmacological and biological activities [2,3]. Due to their structural and pharmacodynamic features, natural bioactives are utilized prophylactically and therapeutically in treating different pathologies, including various diseases and disorders related to the central and peripheral nervous system. Notably, for centuries, natural bioactives have been applied in treating neurodegenerative and neurological disorders by various ethnic populations globally.

Peer review under responsibility of Transdisciplinary University, Bangalore.
* Corresponding author.
E-mail address: Jeyabalan2001@gmail.com (J. Govindasamy).

https://doi.org/10.1016/j.jaim.2024.100911
Received 31 August 2023; Received in revised form 12 January 2024; Accepted 19 February 2024

The source of information on the use of naturally obtained cannabis (known as *Vijayā* in the Ayurvedic system of Indian Medicine and synonymously known as *Bhanga* in Hindi) for the management of a wide range of medical conditions by the traditional Indian medicinal practitioners' dates back to early 6000BC in the *Vedas*, 1500BC to 600AD in *Samhitās* and 800AD to 1900AD in *Samgraha Granthās* (Compendia of Ayurveda) [4,5]. The ancient lore of the use of this Vijayā in Indian system of medicine is also recorded from the medieval period and many extensive literature reviews of the natural bioactive compound also traces the accumulation of extensive evidences reported in the classical texts of Ayurveda [6–8].

Cannabis has a complex mixture of phytoconstituents ranging from cannabinoid and non-cannabinoid phenols, flavonoids to stilbenoids and alkaloids while more than five hundred chemical constituents are isolated and reported from the cannabis plant [9]. Cannabinoids are the principal bioactive compounds in cannabis. These compounds are further divided as endocannabinoids, phytocannabinoids and synthetic cannabinoids. There are two major active compounds; psychoactive compound Δ-9-tetrahydrocannabinol (THC) and non-psychoactive compound cannabidiol (CBD) [10]. Recent evidences suggest that the therapeutic potential of cannabis is not solely attributed to individual cannabinoids but involves a synergistic interaction known as the entourage effect [11]. This phenomenon implies that the combined action of various cannabinoids, terpenes, and flavonoids may enhance the overall therapeutic efficacy of cannabis extracts.

Due to its rich distribution of phytochemicals and secondary metabolites results to its wide range of cosmeceutical, nutraceutical, and pharmaceutical applications [12]. Cannabis was extensively used as a potential medication in the treatment of an extensive array of diseases and conditions targeting the potential systems of the human body [13–16] including the central nervous system (anxiety, insomnia, seizures, pain, paralysis, and mental disorders), reproductive system (erectile dysfunction, decreased libido), gastrointestinal system (diarrhea, indigestion, hernia), respiratory system (cough, asthma, wound tuberculosis) and gynecological disorders (dysmenorrhea, menorrhagia and expedite delivery).

Many prevalent neurological and neurodegenerative diseases that afflict humans occur due to aging, genetic variation, neurotoxin exposures, inflammation, excitotoxicity, mitochondrial dysfunction, excessive calcium influx, apoptosis, necrosis, autophagy, and oxidative stress. Unfortunately, many of these neuropathologies do not currently have a complete cure. This demands an in-depth focus on etiopathological identification, prevention of disease progression, and effective pharmacotherapeutic approaches with minimal adverse effects, including hypersensitivity or other allergic manifestations. Prophylactic and therapeutic strategies include decreasing inflammation, oxidative stress, apoptosis, or other neurodegenerative pathways. Inflammation in the central nervous system (CNS) is a protective response that occurs due to the insult caused by different environmental and biological factors. Unfortunately, inflammation can lead to reversible and irreversible neuropathologies if the cytokines persist for a longer duration. Cytokines exert their action in the CNS by binding to receptors and altering enzyme activities [17]. Astrocytes (star-shaped glial cells) utilize cytokines in immune responses to surge inflammation [18]. Brain trauma, tau-phosphorylation, endogenous and exogenous neurotoxins, and other natural body functions can induce inflammation throughout a lifetime that can selectively affect physiological function. Similar to inflammation, oxidative stress, and mitochondrial dysfunction have been strongly implicated as critical factors behind the declining ATP content resulting in attenuated neuronal functions (neurophysiology) and the neuroanatomical changes resulting in neurodegeneration and neuronal death. Increased pro-oxidants and/or decreased antioxidants have been positively correlated with the increased generation of pro-oxidants, such as reactive oxygen species (ROS).

In addition to inflammation, oxidative stress, and mitochondrial dysfunction, excitotoxicity and apoptosis are evidently indicated in the neurotoxic signaling pathways related to the major prevalent neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS). It should be noted that apraxia and aphasia, both considered disorders in their own right, are also frequently observed as symptoms of the above neurodegenerative disorders. A greater consumption of antioxidants has been shown to reduce the neurotoxic effects of ROS on the body's neurons, alleviating oxidative stress [3]. Fibromuscular dysplasia (FMD) is a neurological disorder in which natural bioactives can have a potential therapeutic action. Injections of the neurotoxin produced by the *Clostridium botulinum*, onabotulinumtoxin A, commercially known as Botox®, have been known to relieve the chronic severe migraines accompanying FMD [19,20]. Similar to FMD, epilepsy is another neurological disease where natural bioactives (flavonoids, alkaloids, and terpenoids) are evidenced to be effective and safe [21].

Cannabis neurotransmission can be increased or decreased by precisely altering the precursors, synthetic enzymes, cofactors, release, calcium influx, post-synaptic receptor, reuptake (transporters), degrading enzymes, and pre-synaptic receptors, which can lead to central and peripheral disease prevention or treatment strategies. Currently, the ligands that are related to cannabis neurotransmissions are broadly classified as endogenous cannabinoids (anandamide, 2-arachidonoylglycerol), phytocannabinoids (cannabidiol, cannabigerol, and tetrahydrocannabinol), and synthetic cannabinoids (nabilone and dronabinol).

CBD is a phytocannabinoid (*Cannabis sativa, Cannabis indica, Cannabis rudralis*) that is imperative in modern healthcare research for non-psychoactive and potent anti-inflammatory properties [22,23]. CBD can cross the blood-brain barrier (BBB) through passive diffusion and can bind to the cannabinoid receptors, mostly through the CB_2 receptor [24]. Interstingly, the CB_2 receptor is found in the hippocampus and almost all immune cells. CBD has a low affinity for CB_1 due to molecular geometry but can still bind in certain circumstances. CBD can significantly alter IL-4, IL-5, IL-6, IL-13, TNF-α, COX-2, and iNOS expression and activities [25,26]. Furthermore, the importance of CB_2 receptor-mediated neuroprotective action was proved by knocking out this receptor, which led to augmented inflammation and neurotoxic insult [27]. Like CBD, THC is an anti-inflammatory bio-active that can significantly reduce inflammation. THC significantly decreases myeloid immune cell infiltration and contact allergic ear swelling [28]. The major difference between CBD and THC in exerting pharmacodynamic actions is associated with the interaction with CB_1 and CB_2 receptors and the agent's psychoactive potential. Unlike CBD, THC's anti-inflammatory effects are carried by its interaction with both the CB receptors [29]. THC is lipophilic and exerts anti-inflammatory effects by inhibiting the IFN-γ, CCL2, CCL8, and CCL10 production [28]. The other major bioactive in cannabis natural bioactive pathways is cannabigerol (CBG). Compared to the other bioactives, CBG is less studied and not very popular. Similar to THC and CBD, CBG is lipophilic and passively diffuses across the BBB [30,31]. Additionally, CBG contains many of the positive pharmacodynamic effects that CBD possesses, including the anti-inflammatory effects on IL-1β, IFN-γ, and TNF-α and minimization of macrophage-associated apoptosis by Caspase-3 suppression [32].

Supplementary to the anti-inflammatory action, the neuroprotective substance's subsequent important pharmacological neuroprotective quality can be its ability to possess antioxidant capabilities by decreasing the pro-oxidants and/or increasing the antioxidants. Over time, the human body, especially the brain, must scavenge naturally occurring toxic reactive free radicals. These compounds are highly reactive and can interfere with proteins, nucleic acids, and carbohydrates, and thus interfere with the ability of the neurons to function normally. Many diseases like AD, CTE, and PD are due to the eventual buildup of these neurotoxic ROS, pro-inflammatory & pro-apoptotic cytokines, leading to reduced ATP production, excitotoxicity, and consequential irreversible neuronal damage. To combat this, natural and synthetic neuroprotectants can be used to prevent and treat neuronal insult. Antioxidants are molecules with increased electrons

that can be donated to ROS, preventing ROS from bonding or interfering with the CNS functions. CBD acts directly as an antioxidant [31] and, therefore, can scavenge ROS and terminate neurotoxicity. Furthermore, CBD affects protein transcription, where the nuclear erythroid 2-related factor (Nrf2) is activated, which targets cytoprotective genes, including the formation of several endogenous antioxidants [33]. Thus, CBD can both directly and indirectly act as an antioxidant, leading to neuroprotection. THC was found to be comparable to CBD in exerting its antioxidant effects [34]. However, CBG possesses the strongest phytocannabinoid antioxidant activity [35]. CBG exerts its neuroprotective antioxidant activity through its interaction with the PPAR-γ receptor and affects superoxide dismutase (SOD-1) [36]. Cannabinol (CBN), cannabigerolic acid (CBGa), and cannabidiolic acid (CBDA) are other cannabis bioactives with antioxidant capabilities [35]; Due to their antioxidant and anti-inflammatory effects, the cannabis bioactives have been shown to protect against beta-amyloid-induced neurotoxicity [37].

Neurological disorders are rampant globally and are incompletely curable. Immediate prophylactic measures must be taken to prevent these diseases, reducing morbidity and mortality and suppressing the global healthcare burden. Natural, easy-to-procure, and cheap neuroprotective bioactives must be identified and incorporated into routine care. Cannabis meets the above criteria and synergistically has been shown to exhibit potent neuroprotective properties with minimal adverse effects. However, the general effect of Cannabis on various neuropathologies is unknown. Hence, this study extensively assessed the overall impact of Cannabis on different neuropathologies.

Uses of Cannabis and Cannabis Products in the Ayurveda Medication System:

The history of cannabis as an Ayurvedic medicine is deeply rooted in ancient Indian traditions and has been documented in various modern day research works. Cannabis has played a dual role in ancient Indian culture, serving both sacred and medicinal purposes. It is considered one of the "Five Kingdoms of Herbs" with potent medicinal properties in Ayurveda [38]. Ayurvedic research works have provided detailed information about the pharmacological properties of cannabis, categorizing it based on its taste (*Rasa*), potency (*Virya*), post-digestive effect (*Vipaka*), and specific actions on the body (*Karma*). The recognition of cannabis as having diverse properties contributed to its integration into various Ayurvedic formulations used in the treatment of an array of medical [39] as conditions.

Pain Management (Shoola): Cannabis has been historically used in Ayurveda for its analgesic properties to alleviate pain, especially in conditions such as arthritis and rheumatism. It is believed to have a calming effect on the nerves and may provide relief from various types of pain [40].

Anti-Inflammatory (Shotha): Ayurvedic practitioners may use cannabis to address inflammatory conditions. The anti-inflammatory properties are thought to be beneficial in conditions like inflammatory joint disorders [41].

Appetite Stimulation (Vitakara): Cannabis has been traditionally employed to stimulate appetite, making it potentially useful in cases of anorexia or other conditions where appetite enhancement is desired [42].

Digestive Disorders (Grahani): Ayurveda recognizes cannabis for its potential in addressing digestive disorders. It is used to alleviate symptoms such as nausea, vomiting, and indigestion [43].

Mental Health (Unmada): In Ayurveda, cannabis is associated with the treatment of certain mental health conditions. It is used cautiously to address symptoms of anxiety, insomnia, and stress [44].

Asthma and Respiratory Conditions (Shwasa): Cannabis has been historically employed in Ayurveda to address respiratory conditions such as asthma. It is believed to have bronchodilator effects that may help in managing respiratory symptoms [45].

Aphrodisiac (Vajikara): Some Ayurvedic texts suggest the use of cannabis as an aphrodisiac, potentially enhancing sexual vitality and performance [46].

Epilepsy (Apasmara): Cannabis has been mentioned in Ayurveda for its potential anticonvulsant properties, and it may be considered in the management of certain types of epilepsy [47].

While cannabis has continued to be used in traditional Ayurvedic medicine, its broader use has faced challenges due to legal and regulatory considerations. Over the time, changes in societal attitudes and legal regulations have influenced the perception of cannabis in India and globally. In recent years, there has been a resurgence of interest in exploring the medicinal properties of cannabis, leading to scientific research validating some of its traditional uses. Studies have investigated the cannabinoids present in cannabis and their interactions with the endocannabinoid system, shedding light on the mechanisms underlying its therapeutic effects. The evolving legal landscape and ongoing scientific research present both challenges and opportunities for the integration of cannabis into modern healthcare globally. Hence, standardization, quality control, and responsible use are crucial for the continued exploration of cannabis in Ayurveda.

2. Materials and methods

2.1. Literature search

The current study used an advanced search option to manually scan the PubMed (NIH) database for published publications through the second week of August 2023. The terms "cannabis and neuropathologies" are a few crucial search terms. We searched the CDC, NIH, and WHO databases for relevant clinical data and the categorization of neuropathologies. We also manually examined the references of the publications associated with and relevant to the current literature search. All languages were used to search for articles, and no filter limits were utilized (Fig. 1).

2.2. Study selection and inclusion/exclusion criteria

Clinical studies, journal publications, meta-analyses, randomized control trials, reviews, and systematic reviews were considered to understand the relationship between Cannabis and neuropathologies. The current study has included more than two hundred and fifty neuropathologies. The various common and rare neuropathologies are [48]: Absence of the Septum Pellucidum; Acid Lipase Disease; Acute Disseminated Encephalomyelitis; Adrenoleukodystrophy; Agenesis of the Corpus Callosum; Agnosia; Aicardi Syndrome; Aicardi-Goutières Syndrome; AIDS and HIV; Alexander Disease; Alpers Disease; Alzheimer's Disease; Amyotrophic Lateral Sclerosis (ALS); Anencephaly; Angelman Syndrome; Antiphospholipid Syndrome; Aphasia; Apraxia; Arachnoid Cysts; Arachnoiditis; Arteriovenous Malformations (AVMs); Ataxia and Cerebellar or Spinocerebellar Degeneration; Ataxia Telangiectasia; Atrial Fibrillation and Stroke; Attention Deficit Hyperactivity Disorder; Autism Spectrum Disorder; Back Pain; Barth Syndrome; Batten Disease; Behcet's Disease; Bell's Palsy; Benign Essential Blepharospasm; Binswanger's Disease; Brachial Plexus Injury; Brain and Spinal Cord Tumors; Brown-Sequard Syndrome; CADASIL; Canavan Disease; Carpal Tunnel Syndrome; Central Cord Syndrome; Central Pain Syndrome; Central Pontine Myelinolysis; Cerebellar Degeneration; Cerebellar Hypoplasia; Cerebral Aneurysms; Cerebral Arteriosclerosis; Cerebral Atrophy; Cerebral Cavernous Malformations; Cerebral Hypoxia; Cerebral Palsy; Cerebro-Oculo-Fascio-Skeletal (COFS) Syndrome; Charcot-Marie-Tooth Disease; Chiari Malformations; Chorea; Chronic Inflammatory Demyelinating Polyneuropathy (CIDP); Coffin-Lowry Syndrome; Colpocephaly; Coma; Complex Regional Pain Syndrome; Congenital Myasthenia; Congenital Myopathy; Corticobasal Degeneration; Craniosynostosis; Creutzfeldt-Jakob Disease; Cushing's Syndrome; Cytomegalovirus; Dandy-Walker Syndrome; Deep Brain Stimulation for Movement Disorders; Dementia, Multi-Infarct; Dementias; Dermatomyositis; Developmental Dyspraxia; Diabetic Neuropathy; Dravet Syndrome; Dysautonomia; Dysgraphia; Dyslexia; Dyssynergia Cerebellaris

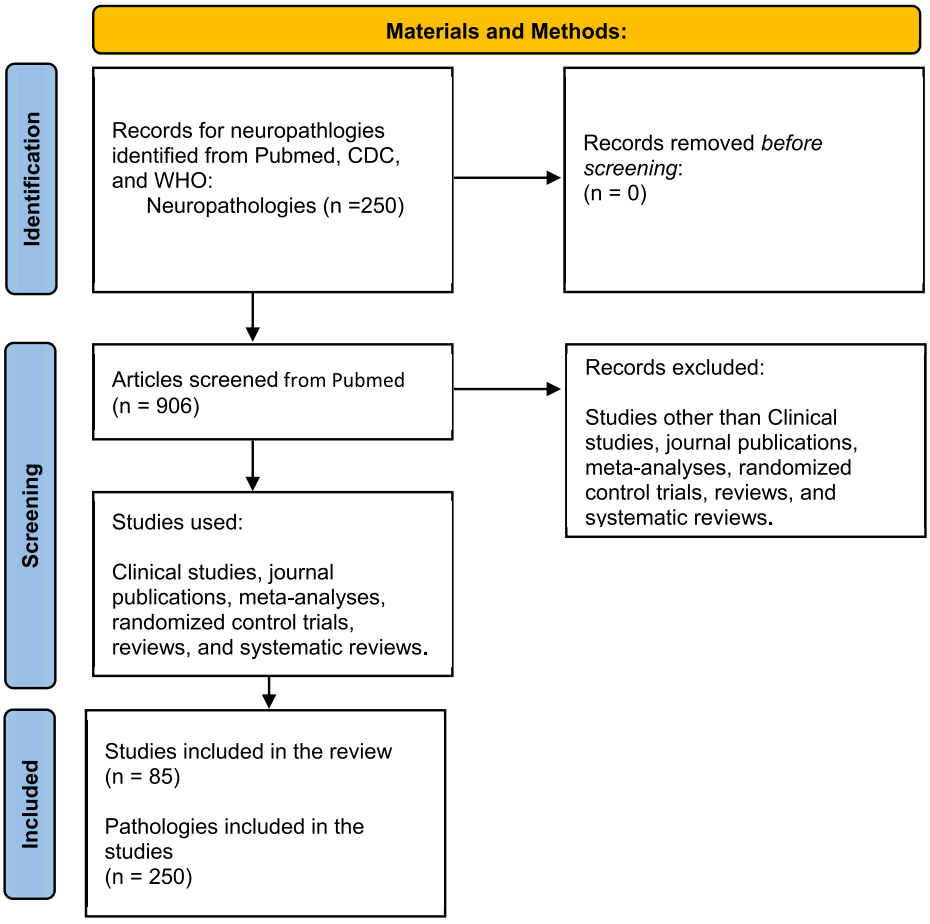

Fig. 1. The PRISMA systematic reviews flow diagram.

Myoclonica; Dystonia; Empty Sella Syndrome; Encephalitis; Encephalitis Lethargica; Encephaloceles; Epilepsy and Seizures; Essential Tremor; Fabry Disease; Fahr's Syndrome; Familial Periodic Paralyses; Farber's Disease; Febrile Seizures; Fibromuscular Dysplasia; Foot Drop Syndrome; Friedreich Ataxia; Frontotemporal Disorders; Functional Neurologic Disorder; Gangliosidoses; Gaucher Disease; Gerstmann's Syndrome; Gerstmann-Straussler-Scheinker Disease; Giant Axonal Neuropathy; Guillain-Barré Syndrome; Headache; Hemicrania Continua; Hemifacial Spasm; Hereditary Neuropathies; Hereditary Spastic Paraplegia; Herpes Zoster Oticus; Holmes-Adie Syndrome; Holoprosencephaly; HTLV-1-Associated Myelopathy (HAM)/Tropical Spastic Paraparesis (TSP); Huntington's Disease; Hydranencephaly; Hydrocephalus; Hydromyelia; Hypersomnia; Hypertonia; Hypotonia; Hypoxic Ischemic Encephalopathy; Inclusion Body Myositis; Incontinentia Pigmenti; Infantile Neuroaxonal Dystrophy; Infantile Spasms; Inflammatory Myopathies; Iniencephaly; Isaacs Syndrome; Joubert Syndrome; Kearns-Sayre Syndrome; Kennedy's Disease; Kleine-Levin Syndrome; Klippel-Feil Syndrome; Klippel-Trenaunay Syndrome; Klüver-Bucy Syndrome; Krabbe Disease; Kuru; Lambert-Eaton Myasthenic Syndrome; Landau-Kleffner Syndrome; Learning Disabilities; Leigh Syndrome; Lennox-Gastaut Syndrome; Lesch-Nyhan Syndrome; Leukodystrophy; Lewy Body Dementia; Lipid Storage Diseases; Lipoid Proteinosis; Lissencephaly; Locked-In Syndrome; Lupus; Lyme Disease; Megalencephaly; Melkersson-Rosenthal Syndrome; Meningitis; Menkes Disease; Meralgia Paresthetica; Metachromatic Leukodystrophy; Microcephaly; Migraine; Miller Fisher Syndrome; Mitochondrial Myopathies; Moebius Syndrome; Monomelic Amyotrophy; Motor Neuron Diseases; Moyamoya Disease; Mucolipidoses; Mucopolysaccharidoses; Multifocal Motor Neuropathy; Multiple Sclerosis; Multiple System Atrophy; Muscular Dystrophy; Myasthenia Gravis; Myoclonus; Myotonia; Myotonia Congenita; Narcolepsy; Neuroacanthocytosis; Neurodegeneration with Brain Iron Accumulation; Neurofibromatosis; Neuroleptic Malignant Syndrome; Neuromyelitis Optica; Neuronal Migration Disorders; Neurosarcoidosis; Neurosyphilis; Neurotoxicity; Niemann-Pick Disease; Normal Pressure Hydrocephalus; Occipital Neuralgia; Ohtahara Syndrome; Olivopontocerebellar Atrophy; Opsoclonus Myoclonus; Orthostatic Hypotension; Pain; Paraneoplastic Syndromes; Paresthesia; Parkinson's Disease; Paroxysmal Choreoathetosis; Paroxysmal Hemicrania; Parry-Romberg Syndrome; Pelizaeus Merzbacher Disease; Peripheral Neuropathy; Periventricular Leukomalacia; Pervasive Developmental Disorders; Pinched Nerve; Piriformis Syndrome; Pituitary Tumors; Polymyositis; Pompe Disease; Porencephaly; Post-Polio Syndrome; Postural Tachycardia Syndrome [49]; Primary Lateral Sclerosis; Progressive Multifocal Leukoencephalopathy; Progressive Supranuclear Palsy (PSP); Prosopagnosia; Pseudotumor Cerebri; Rasmussen's Encephalitis; Refsum Disease; Repetitive Motion Disorders; Restless Legs Syndrome; Rett Syndrome; Reye's Syndrome; Sandhoff Disease; Schilder's Disease; Schizencephaly; Septo-Optic Dysplasia; Shaken Baby Syndrome; Shingles; Sjögren's Syndrome; Sleep Apnea; Sotos Syndrome; Spasticity; Spina Bifida; Spinal Cord Infarction; Spinal Cord Injury; Spinal Muscular Atrophy; Spinocerebellar Ataxias including Machado-Joseph Disease; Stiff-Person Syndrome; Striatonigral Degeneration; Stroke; Sturge-Weber Syndrome; Subacute Sclerosing Panencephalitis; SUNCT Headache; Swallowing Disorders; Sydenham Chorea; Syncope; Syringomyelia; Tabes Dorsalis; Tardive Dyskinesia; Tarlov Cysts; Tay-Sachs Disease; Tethered Spinal Cord Syndrome; Thoracic Outlet Syndrome; Thyrotoxic Myopathy; Todd's Paralysis; Tourette Syndrome; Transient Ischemic Attack (TIA); Transmissible Spongiform Encephalopathies; Transverse Myelitis; Traumatic Brain Injury (TBI); Tremor; Trigeminal Neuralgia; Troyer Syndrome;

Tuberous Sclerosis Complex; Vasculitis in the Nervous System; Von Hippel-Lindau Disease (VHL); Wallenberg's Syndrome; Wernicke-Korsakoff Syndrome; Whiplash; Whipple's Disease; Williams Syndrome; Wilson Disease; Zellweger Syndrome.

Based on our previous published study [50], this study has been categorized as: "Not reported" (Zero reports available as of date), "Minimally reported" (1–10 reports available as of date), "Moderately reported" (11–100 reports available as of date), "Well reported" (101–500 to Five hundred available reports as of date) and "Significantly reported" (501+ reports available as of date). Moreover, we also assessed the specific impact (Positive or Negative, Protective or Toxic) of Cannabis on "moderately reported", "well reported", and "significantly reported" neuropathologies.

3. Results

The effects of Cannabis was searched against the above-mentioned neuropathologies and then categorized into five groups. A total of 48% of neuropathologies are not yet reported, and 32%, 14%, 4%, and 2% are minimally, moderately, well, and significantly reported, respectively, addressing the impact of Cannabis

Our current findings on Cannabis focused on its neuroprotective therapeutic ability and the negative impact (toxic effects) on various neuropathologies. Cannabis showed neuroprotective effects against most neuropathologies and exhibited a negative impact or elevated the risk of a few neuropathologies (Supplementary data Table 1; Table 1 and 2). In supplementary data Table 1 the list of neuropathologies, with a "Not reported" and "minimally reported" impact of Cannabis were shown. Neuroprotective effects of cannabis were identified for the following neuropathologies: Dravet Syndrome, Migraine, Hypertonia, Dementias, Alzheimer's Disease, Headache, Parkinson's Disease, Peripheral Neuropathy, Spasticity, Multiple Sclerosis, Functional Neurologic Disorder, Epilepsy and Seizures, AIDS and HIV, Pain, which has "well reported" and "signifcantly reported" (Table 2) Hypotonia, Meningitis, Cerebral Palsy, Lupus, Narcolepsy, Restless Legs Syndrome, Tuberous Sclerosis Complex, Diabetic Neuropathy, Hypersomnia, Infantile Spasms, Motor Neuron Diseases, Chorea, Sydenham Chorea, Repetitive Motion Disorders, Wilson Disease, Primary Lateral Sclerosis, Todd's Paralysis, Amyotrophic Lateral Sclerosis (ALS), Dystonia, Central Pain Syndrome, Pervasive Developmental Disorders, Huntington's Disease, Spinal Cord Injury, Ataxia and Cerebellar or Spinocerebellar Degeneration, Traumatic Brain Injury (TBI), Lennox-Gastaut Syndrome, Tremor, Tourette Syndrome, Autism Spectrum Disorder, which has "moderately reported" (Table 1). Conversely, a toxic effect of Cannabis was identified for Stroke, Attention Deficit Hyperactivity Disorder, which has "well reported" and "signifcantly reported" (Table 2) Orthostatic Hypotension, Transient Ischemic Attack (TIA), Syncope, Tuberous Sclerosis Complex, Encephalitis, Sleep Apnea, Learning Disabilities, Developmental Dyspraxia, Cerebral Atrophy, and Coma, which has "moderately reported" (Table 1). Thus, our current study clearly identifies a current void in the literature associated with the impact of Cannabis on various neuropathologies.

Table 1
Neuropathologies, with a 'moderately reported' specific pharmacodynamic effects of Cannabis)

Neuropathologies	Pharmacodynamic Effect
Meningitis	Protective effect [51]
Cerebral Palsy	Protective effect [52]
Lupus	Protective effect [53]
Orthostatic Hypotension	Toxic effect [54]
Transient Ischemic Attack (TIA)	Toxic effect [55]
Narcolepsy	Protective effect [56]
Restless Legs Syndrome	Protective effect [57]
Syncope	Toxic effect [58]
Tuberous Sclerosis Complex	Protective effect [59]
Diabetic Neuropathy	Protective effect [60]
Hypersomnia	Protective effect [61]
Infantile Spasms	Protective effect [62]
Motor Neuron Diseases	Protective effect [63]
Chorea	Protective effect [64]
Sydenham Chorea	Protective effect [65]
Repetitive Motion Disorders	Protective effect [29]
Encephalitis	Toxic effect [66]
Wilson Disease	Protective effect [66]
Primary Lateral Sclerosis	Protective effect [67]
Todd's Paralysis	Protective effect [68]
Sleep Apnea	Slightly toxic effect [69]
Learning Disabilities	Toxic effect [70]
Atrial Fibrillation	Toxic effect [71]
Amyotrophic Lateral Sclerosis (ALS)	Protective effect [72]
Developmental Dyspraxia	Toxic effect [73]
Dystonia	Slightly protective effect [74]
*Central Pain Syndrome	Protective effect [75]
Cerebral Atrophy	Slight Toxicity [76]
Pervasive Developmental Disorders	Protective Effect [77]
Huntington's Disease	Protective Effect [78]
Coma	Toxic Effect [79]
Spinal Cord Injury	Protective Effect [80]
Ataxia and Cerebellar or Spinocerebellar Degeneration	Protective Effect [81]
Traumatic Brain Injury (TBI)	Protective Effect [82]
Lennox-Gastaut Syndrome	Protective Effect [83]
Tremor	Protective Effect [84]
Tourette Syndrome	Protective Effect [85]
Autism Spectrum Disorder	Protective Effect [86]

Table 2
The list of neuropathologies, with a "well reported" and "significantly reported" impact of Cannabis (with specific pharmacodynamic effects).

Neuropathologies[a]	Pharmacodynamic Effect
Dravet Syndrome	Protective Effect [83]
Migraine	Protective Effect [88]
Hypertonia	Protective Effect [90]
Dementias	Protective Effect [92]
Alzheimer's Disease	Protective Effect [94]
Headache	Protective Effect [96]
Parkinson's Disease	Protective Effect [97]
Peripheral Neuropathy	Protective Effect [98]
Stroke	Toxic Effect [99]
Attention Deficit Hyperactivity Disorder	Toxic Effect [100]
Spasticity	Protective Effect [101]
Neuropathologies[b]	**Pharmacodynamic Effect**
Multiple Sclerosis	Protective Effect [87]
Functional Neurologic Disorder	Protective Effect [89]
Epilepsy and Seizures	Protective Effect [91]
AIDS and HIV	Protective Effect [93]
Pain	Protective Effect [95]

[a] Neuropathologies with a "well reported" impact of Cannabis.
[b] Neuropathologies with a"significantly reported" impact of Cannabis.

4. Discussion

Though many natural bioactives exist and have displayed medicinal value against various disorders for centuries, one notable therapeutic natural bioactive used in treating numerous pathologies is Cannabis [37, 102–106]. There are three different types of cannabis congeners: endogenous, phyto, and synthetic cannabinoids. These endogenous and exogenous ligands act by binding to two different cannabinoid receptors, CB_1 and CB_2. Cannabis congeners act as an agonist on the cannabinoid receptors and activate the cannabinoid receptors leading to the cannabinoid neurotransmission. CB_1 activation results in downstream activation of the p38 and c-Jun NH2-terminal kinase (JNK), mitogen-activated protein kinases (MAPK) signaling pathways, triggering oxidative stress and inflammatory response and leading to cell death. Contrarily, CB_2 is typically found in CNS and immune cells and cells generated from the immune system, and unlike CB_1 activation, CB_2 activation appears to have anti-inflammatory properties.

Neuropathologies are generally classified based on anatomical deficits (structural disorders) and physiological alterations (functional changes). The WHO also classifies the neuropathologies based on the features distressing the whole nervous system (CNS and PNS), which is based on the neuronal insult in the brain, spinal cord, autonomic nervous system, somatic nervous system (skeletal muscle or neuromuscular junction), cranial nerves, peripheral nerves, and nerve endings. The burden of morbidities and mortalities caused by neuropathologies is drastically escalating and is being recognized as a global public health challenge, and concerningly, the burden associated with neuropathologies is set to rise during the next few decades due to the population aging [107]. Hence, there is an imminent need for a valid and safe natural bioactive with neuropharmacological effects and neuroprotective properties with minimal adverse effects to diagnose, prevent, and treat various neuropathologies.

Cannabis has been shown to exert neuroprotection against mental, movement, and memory-related neuropathologies [108]. Cannabis has significantly reduced the neuronal hyperarousal associated with its neuroprotective effects in Dravet syndrome (epileptic encephalopathy), epilepsy, seizures, and Lennox-Gastaut syndrome. With regard to the neuroprotective abilities against neurodegenerative diseases, Cannabis exerted neuroprotection in various dementias, AD, PD, ALS, HD, and cerebellar or spinocerebellar degeneration. Cannabis also exerted neuroprotection against various movement disorders (PD, spasticity, restless legs syndrome, dystonia, HD, tremors, infantile spasms, motor neuron diseases, chorea, Sydenham chorea, repetitive motion disorders, ataxia, Tourette syndrome, hypertonia, hypotonia, spinal cord injury), sleep disorders (hypersomnia, narcolepsy) and pain-related diseases (migraine, headache, central pain syndrome, peripheral neuropathy, multiple sclerosis) and neurodevelopment disorders (autism spectrum disorder).

5. Conclusion

Cannabis is a thought-provoking contemporary healthcare topic of global research and interest, due to its inherent potent and multi-pharmacological activities and common recreational use. For centuries, botulin was considered a potent poison or toxin known to induce severe toxicity; however, in more recent history, it has been approved for treating migraines and spasticity and for the prevention of age-related wrinkles. Similarly, despite its prevalent and continuous ongoing religious use, recreational consumption, and medical value, Cannabis has been prevalently regarded as a substance of abuse and a "bane & curse" to modern society. Nevertheless, historical evidence and recent systematic animal and clinical studies have shown Cannabis to have potent medicinal benefits. The current study suggests the neuroprotective prophylactic and therapeutic impact of Cannabis and also described the negative effects of Cannabis on neuropathologies.

Sources of Funding

None

Author contributions

S.P. and M.D.: writing original draft conceptualization, designing, analyzing and interpreting the data; J.B.J., K.L., P·C., S·K., R.N., K. W., C·S.A., A.K., and K.D.: screening, analyzed and interpreted the data; T. M. and J.G.: analyzed, visualized, supervised and interpreted the data.

All authors were involved in drafting and revising the manuscript.

Declaration on generative AI in scientific writing

All the authors declare no use of AI in scientific writing.

Conflict of interest

All the authors declare no conflict of interest.

Acknowledgements

We would like to thank the Department of Drug Discovery and Development for providing us with the resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2024.100911.

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