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Cannabis sativa: One-Plant-One-Medicine for Many Diseases-Therapeutic Uses-A Review of Evidence

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Abstract: This present review highlights the efficacy and therapeutic uses of Cannabis on the basis of ongoing and proven clinical trials. Since from 5,000 years ago the parts of cannabis plant was used by medicinal practitioners from India and regularly used to cure various diseases, syndromes and disorders. Nabilone is a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy. Cannabidiol (CBD) and its metabolite 7-OH-CBD, but not THC or other congeneric cannabinoids tested, potently block SARS-CoV-2 replication in lung epithelial cells. Cannabis has a bronchodilator effect on the airways and might have an anti-inflammatory effect, yet there are many harmful effects on the lungs of asthmatic patients. Cannabis sativa-based cream on Cutaneous leishmaniasis (CL) associated skin lesions promoted the healing process. Cannabis oil was used as a body lotion for controlling monkeypox viral disease. However, there are some adverse reactions and insignificant effect of medical Cannabis and hemp was also noticed in the treatment of diseases. Cannabis and Cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear. Furthermore, the clinical results remained controversial and warranted further investigation.

Key Words: Ayuverda, Cannabis, Cancer, Sativex, Nabilone, Migraine, Lennox-Gastaut Syndrome (LGS)

I. Introduction

Cannabis sativa L. belongs to the family *Cannabiaceae* was used as a medicine before the Christian era in Asia**,** mainly in India**,** China, Bhutan, Nepal, Afghanistan, Pakistan and Iran, and Persians (1-20). Cannabis has been used for thousands of years for recreational, medicinal, or religious purposes (254-270). Cannabis is also a wild noxious weed with notorious psychoactive principle (THC) found growing in all the parts of India. Cannabis has a long history in India, recorded in legends and religion. It was found in various habitats ranging from sea level to the temperate and alpine foothills of the Indian Himalaya Region from where it was probably spread over the last 10,000 years (250-275). Many historians believed that Indian Himalayan Region was the centre of origin of *Cannabis sativa* L. and *Cannabis indica* L. (250-275). Tribal people in the Himalayan region used Cannais as a home made herbal medicine for many diseases. During, Covid-19, the infusion of Cannabis flower with a morning cup of tea has saved the life of many people. Cannabis oil was used as dengue mosquito repellnt for controlling dengue viral fever, bacterial infections and fungal diseases (250-275). Cannabidiol (CBD) and Cannabinol (CBN) can alter the functional activities of the immune system (1-300). Many inflammatory conditions are associated with dysfunction of the immune system. Cannabis has been used for centuries as a medicine in the treatment of a variety of inflammatory disorders including rheumatic arthritis (RA),

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gastrointestinal (GI) diseases such as Crohn's disease (CD) and inflammatory bowel disease (IBD), and other GI problems such as anorexia, emesis, abdominal pain, diarrhea, and diabetic gastroparesis (1-300).

According to Ayuverda in India, the medicinal value of the Cannabis plants was well documented more than 5,000 years ago (250-274). This was the first Indian evidence to support the medicinal value of Cannabis plants which was well documented in Ayuverda in India (1-300). The earliest written reference to Cannabis in India may occur in the *Atharvaveda*, dating to about 3000 BCE (250-280). In the traditional pharmacopeia of human history, both recreational and medicinal uses of the Indian *Cannabis sativa* L. have been described for several centuries (250-270). Introduced into Western medicine by William O'Shaughnessy in 1838 to treat a variety of conditions, including rheumatic pain and epilepsy, the use of Cannabinoids (CBs) in clinical practice entered a period of latency and oblivion due to political barriers and problems in establishing quality control (250-270, 328).

Cannabis was (re) introduced into British medical practice in the early 1840's by Irish physician Dr. William O'Shaughnessy, an army surgeon serving in Calcutta, India (250-274, 328). In the Victorian period, Cannabis was widely used for a variety of ailments, including muscle spasms, menstrual cramps, rheumatism, the convulsions of tetanus, rabies, and epilepsy, and as a sedative (250-275, 328). Cannabis extracts were typically administered orally in the form of an alcoholic tincture and were commonly incorporated in proprietary medicines (250-274, 328). With the introduction of synthetic drugs, herbal remedies were increasingly viewed as unpredictable and many of them, including cannabis extracts and tinctures, were removed from the British Pharmacopoeia of 1932 but retained in the British Pharmaceutical Codex of 1949 (250-275, 328).

Cannabis has been long used since ancient times for both medical and recreational use (Figure-1). Past research has shown that Cannabis can be indicated for symptom management disorders, including cancer, chronic pain, headaches, migraines, and psychological disorders (anxiety, depression, and post-traumatic stress disorder). Active ingredients in Cannabis that modulate patients' perceptions of their conditions include Δ9-tetrahydrocannabinol (THC), Cannabidiol (CBD), flavonoids, and terpenes (1-303). These compounds work to produce effects within the endocannabinoid system to decrease nociception and decrease symptom frequency. There is a worldwide growing interest and investments in using medical cannabinoids for the treatment of numerous diseases (1-315).

Cannabis sativa L., is classified into two types as Industrial *Cannabis sativa*, hemp or Medical *Cannabis sativa* L.(drug or marijuana) based on its THC content (1-300). Medical *Cannabis sativa* (drug or marijuana) contains very high levels of THC (above 0.3 to 38% of dry weight). On the other hand Industrial *Cannabis sativa* L. (Hemp) contains very low levels of THC (0 to 0.3% of dry weight) (1-300). However, due to the presence of psychoactive molecules, Λ9-tetrahydrocannabinol (Λ9-THC) and Λ8-tetrahydrocannabinol (Λ8-THC), Cannabis cultivation and its use is restricted/regulated in many countries (1-300). The official discovery of Δ9-tetrahydrocannabinol (THC) is commonly attributed to Dr. Raphael Mechoulam affectionately referred to as the Godfather of Cannabis Science (250-275). Δ9-tetrahydrocannabinol (THC) was discovered in 1964 by Dr. Raphael Mechoulam and his colleagues at Israel's Weizmann Institute of Science (250-275). The credit of the discovery of Cannabidiol (CBD) in 1963 and Δ9-tetrahydrocannabinol (THC) in 1964 isolated from Cannabis sativa attributed to Dr. Raphael Mechoulam and his team (250-275).

The *Cannabis sativa* L. plant contains more than 560 chemicals, of which 200 are known as Cannabinoids (1-300). The most studied cannabinoids are Δ9 -tetrahydrocannabinol (THC), which produces the majority of its psychopharmacological and other effects through two cannabinoid receptors, CB1 (localized mainly in the brain) and CB2 (localized mainly in the periphery), and Cannabidiol (CBD), a non-psychoactive cannabinoid. The endogenous cannabinoids, known as the endocannabinoid system (ECS), consist of the endogenous lipid ligands N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonylglycerol (2-AG), their biosynthetic and degradative enzymes, and the CB1 and CB2 receptors that they activate (1-300).

The legalization of Cannabis for medical and recreational purposes has become increasingly prevalent in many countries for example, USA, Canada, UK, Italy and other countries (1-300). The increasing legalization of *Cannabis* for recreational and medicinal purposes in the United States has spurred renewed interest in the therapeutic potential of Cannabinoids (CBs) for human disease (1-315). Accordingly, interest in therapeutic applications for cannabinoids (CBs) has skyrocketed, with 55% of dermatologists reporting a patient-initiated conversation about cannabinoids in the past year (1-300). The medical Cannabis market in the USA is expected to grow to US $ 12.5 billion by 2025. Thus the iron is hot to strike with impactful research on the therapeutic applications of CBs for human skin disease (1-300).

Cannabinoids can be administered orally, sublingually, or topically, they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol, or manufactured synthetically. Prescribed cannabinoids include dronabinol capsules, nabilone capsules, and the oromucosal spray nabiximols. Some countries have legalized medicinal-grade Cannabis for chronically ill patients. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal Cannabis.

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Numerous diseases, such as chronic pain, asthma, rheumatoid arthritis (RA), wound healing, constipation, multiple sclerosis (MS), cancer, inflammation, glaucome, neurodegenerative disorders (Epilepsy-seizure disorder, Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette's syndrome, Dystonia, Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS)), Obesity, weight loss, anorexia, and emesis, osteoporosis, schizophrenia, cardiovascular disorders, sleep disorders, Traumitic brain injury (TBI), Post traumetic stress injury, drug addiction (Marijuana), AIDS Wasting syndrome, Amyotrophic lateral sclerosis (ALS), depression and anxiety, diabetes, migraine (headache disorder), Covid-19 (SARS-CoV-2), Leishmaniasis (Kala-Azar), and metabolic syndromerelated disorders, to name just a few, are being treated or have the potential to be treated by Cannabinoid agonists/ antagonists/cannabinoid-related compounds (1-315).

In the following section the ongoing and completed clinical trials of the Cannabinoid compunds, THC, CBD and others cannabinoids used as a medicine/ adverse effects has been highlighted and updated.

Figure-1: Warning sign for Cannabis sativa L.

1) Chronic Pain

Although Cannabis was used therapeutically for millennia in India, China, Nepal, Bhutan, Pakistan, Afghanistan and other Asian countries, Cannabis has been a prohibited substance worldwide for most of the 20th Century (1-55). With the revision of prohibitive regulations in many jurisdictions during the past 2 decades, Cannabis is increasingly available to patients as a potential treatment option for various symptoms (1-55). Pain relief, sleep promotion and alleviation of distress, depression and anxiety are the most common reasons for Cannabis use (1-55). The renewed interest in the therapeutic effects of Cannabis emanates from the movement that began 25 years ago to make Cannabis available as a medicine to patients with a variety of conditions (1-55).

Cannabis has been used for millennia as a pain-relieving substance (1-22). Evidence suggests that cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways (1-22). When Δ9-Tetrahydrocannabinol (THC) was given to a patient with familial Mediterranean fever, with chronic relapsing pain and gastrointestinal inflammation, a highly significant reduction in pain was noted (1-22). The administration of single oral doses of Δ9-Tetrahydrocannabinol (THC) to patients with cancer pain demonstrated a mild analgesic effect (1-22). Patients who suffered from pain also tend to self-medicate with marijuana (1-45). In an anonymous cross-sectional survey, (35%) of chronic non-cancer pain patients reported having used Cannabis for relieving pain (1-22). Cannabis-treated AIDS patients reported improved appetite, muscle pain, nausea,

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anxiety, nerve pain, depression, and paresthesia (1-22). Not only Δ9-Tetrahydrocannabinol (THC) but also other Cannabinoids can potentially affect different types of pain (1-22).

Relief from chronic pain is by far the most common condition cited by patients for the medical use of Cannabis (1-22). For example, Light et al. (2014) reported that 94 percent of Colorado medical marijuana ID cardholders indicated "severe pain" as a medical condition (1-22). Likewise, Ilgen et al. (2013) reported that 87 percent of participants in their study were seeking medical marijuana for pain relief (1-22). In addition, there is evidence that some individuals are replacing the use of conventional pain medications (e.g., opiates) with Cannabis (1-23). For example, one recent study reported survey data from patrons of a Michigan medical marijuana dispensary suggesting that medical Cannabis use in pain patients was associated with a 64 percent reduction in opioid use (1-24). Similarly, recent analyses of prescription data from Medicare Part D enrollees in states with medical access to Cannabis suggested a significant reduction in the prescription of conventional pain medications (1-25). Combined with the survey data suggesting that pain is one of the primary reasons for the use of medical Cannabis (1-23). These recent reports suggested that a number of pain patients are replacing the use of opioids with Cannabis, despite the fact that Cannabis has not been approved by the U.S. Food and Drug Administration (FDA) for chronic pain (1-24).

Nabilone is a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy (1-22). In Canada, the United States, and the United Kingdom, Nabilone is marketed as Cesamet (1-22). A significant decrease in disabling spasticity-related pain of patients with chronic upper motor neuron syndrome (UMNS) was found with Nabilone (1-22). Another cannabinoid, Ajulemic acid (AJA), was effective in reducing chronic neuropathic pain, although cannabinoid side effects (tiredness, dry mouth, limited power of concentration, dizziness, sweating) were noted (1-22). The combination of Δ9-Tetrahydrocannabinol (THC) with the nonpsychotropic Cannabis constituent Cannabidiol (CBD) has a higher activity than THC alone (1-22).

The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS) (1-22). Chronic neuropatic pain can also be treated with Cannabis extracts containing THC, or CBD, or with Sativex (1-22). The latter was also effective in reducing sleep disturbances in these patients and was mostly well tolerated (1-22). Sativex is the first Cannabis-based medicine to undergo conventional clinical development and be approved as a prescription drug (1-25). It is efficacious and well tolerated in the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain (1-22). Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada (1-24).

Current Cannabis research has shown that medical cannabis is indicated for symptom management for many conditions not limited to cancer, chronic pain, headaches, migraines, and psychological disorders (anxiety and post-traumatic stress disorder). Δ9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are active ingredients in Cannabis that modulate a patient's symptoms (1-40). These compounds work to decrease nociception and symptom frequency via the endocannabinoid system (ECS) (40). Research regarding pain management is limited within the USA as the Drug Enforcement Agency (DEA) classifies it as a schedule one drug (1-25). Few studies have found a limited relationship between chronic pain and medical Cannabis use (40). One of the study demonstrated that medical Cannabis use provides adequate pain management (1-40). Patients suffering from chronic non-malignant pain may benefit from medical Cannabis due to its convenience and efficacy (1-40).

Patients often seek medical consultations most commonly because of having intolerable chronic pain (40). Medications such as NSAIDs or opioids are being used to relieve such pain (1-40). However, long-term use of these medications can also cause adverse effects on health (40). Several studies have been done regarding Cannabis as an alternative for chronic pain (1-40). Some patients were reported to get relief from Cannabis consumption through various routes, and the use of it has been legalized, too, in some states in the USA and countries like Germany. Italy, the Netherlands, UK, Australia, Uruguay, Brazil, Colombia, Chile, Thailand, and Jamaica (1-40). Compared with opioids, studies showed that Cannabis use has lesser adverse effects, and it could even lessen opioid dependence (1-40). As clinicians, it is good to determine the primary purpose of using Cannabis before prescribing to the patients to determine the advantages and disadvantages (1-40).

2) Asthma

Asthma is defined as a chronic inflammatory disease of the airways (22, 25). The chronic inflammation is associated with airway hyper-responsiveness (an exaggerated airway-narrowing response to specific triggers such as viruses, allergens and exercise) that leads to recurrent episodes of wheezing, breathlessness, chest tightness and/or coughing that can vary over time and in intensity (22, 25-33). Asthma is a chronic disease of the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus (25). Although asthma is often believed to be a disorder localized to the lungs, current evidence indicated that it may represent a component of systemic airway disease involving the entire respiratory tract, and this is supported by the fact that asthma frequently coexists with other atopic disorders, particularly allergic rhinitis (22, 25).

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In most patients, however, control can be achieved through the use of avoidance measures and appropriate pharmacological interventions. Inhaled Corticosteroids (ICS) represented the standard of care for the majority of patients (22, 25). Combination ICS/long-acting beta2-agonist inhalers are preferred for most adults who failed to achieve control with ICS therapy (22, 25). Allergen-specific immunotherapy represented a potentially disease-modifying therapy for many patients with asthma, but should only be prescribed by physicians with appropriate training in allergy (22, 25-33).

Cannabis has a bronchodilator effect on the airways and might have an anti-inflammatory effect on asthmatic patients (22, 25-33). However, harmful effects on the lungs are mainly attributed to smoking and include airway irritation and the development of chronic bronchitis symptoms (22, 25-33). In humans, habitual smoking of marijuana may cause mild, but significant, functional lung impairment (22, 25-33). However, a mild and inconstant bronchodilatory action was found for THC (22, 25-33). In other clinical trials, smoking marijuana or ingesting THC were found to increase airway conduction (22, 25-33). Other plant cannabinoids did not provide effective bronchodilation (22, 25-33). In another study, salbutamol and THC significantly improved ventilatory function (22, 25-33). Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective (22, 25-33). In one of the study reported that no cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were not detected by radioimmunoassay (22, 25-33). The mode of action of THC differed from that of sympathomimetic drugs (22, 25-33). Cannabis has some benefit, yet there are many harmful effects on the lungs. Additional research is needed to determine the harmful effects of vaporizers as well as inhalers (22, 25-33).

Inhaling Cannabis is least safe for people with asthma. As noted previously, inhaling Cannabis by smoking or vaping should be avoided by those with asthma. For anyone using Cannabis, particularly those with a chronic illness, safety is paramount and comes first (34-35). A small number of studies have shown that the use of Cannabis increased the risk of bronchial asthma (34-35). There is, however, a paucity of longitudinal studies which are able to control for known risk factors of bronchial asthma (34). This suggested that Cannabis is a risk factor for bronchial asthma or use of asthma medication even when known risk factors are taken into consideration. Intake of Cannabis through smoking should be avoided in persons at risk (34-35). The study strengthens earlier findings and suggested that current use of Cannabis is a risk factor for precipitating asthma, even when other known risk factors for asthma are taken in to consideration (34-35). No previous studies have used asthma medication as an outcome (34-35). These findings are important in the light of the changes in legislation being considered in many countries (34-35). Those who opt taking Cannabis may need to find out the alternatives to smoking. The ongoing measurement of respiratory function amongst cannabis users is advisable (34-35).

Therefore, the association between marijuana smoking and asthma remains controversial, and the inconsistency among different studies may be attributed to the variations in study design and sample characteristics (34-35). Recent studies have raised the concern on the risk of asthma in marijuana smokers. However, the results remain controversial and warranted further investigation (34-35). With a growing number of marijuana smokers, examining the association between marijuana smoking and asthma and quantifying such association through meta-analysis have important implications for public health and clinical decision-making (34-35).

3) Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that affects around 1% of the general population (39). It is characterized by autoantibody and pro-inflammatory cytokine production, which eventually leads to the activation of resident synovial fibroblasts (SF) (39). Rheumatoid arthritis (RA) synovial fibroblasts (RASF) produce large amounts of interleukin (IL)-6, but they also engaged in matrix degradation by the synthesis of several matrix metalloproteinases (MMPs) such as MMP3 (39). RASF are activated by Tumour Necrosis Factor (TNF), a major cytokine involved in the pathogenesis of rheumatoid arthritis (RA) (39).

Cannabidiol (CBD) is a non-intoxicating phytocannabinoid from *Cannabis sativa* that has demonstrated anti-inflammatory effects in several inflammatory conditions including arthritis (36). However, Cannabidiol (CBD) binds to several receptors and enzymes and, therefore, its mode of action remains elusive (36). In one of the study reported by Lowen et al., (2020) (36) showed that Cannabidiol (CBD increases intracellular calcium levels, reduces cell viability and IL-6/IL-8/MMP-3 production of rheumatoid arthritis synovial fibroblasts (RASF) by activating transient receptor potential ankyrin (TRPA1) and mitochondrial targets (36).

Cannabidiol (CBD reduced cell viability, proliferation, and IL-6/IL-8 production of RASF (36). Moreover, CBD increased intracellular calcium and uptake of the cationic viability dye PoPo3 in RASF, which was enhanced by pre-treatment with TNF (36). In addition, an inhibitor of the mitochondrial permeability transition pore, cyclosporin A, also blocked the effects of Cannabidiol (CBD on cell viability and IL-8 production (36). Thus, Cannabidiol (CBD) possesses anti-arthritic activity and might ameliorate arthritis via targeting synovial fibroblasts under inflammatory conditions (36).

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Cannabidiol (CBD) and Λ9-tetrahydrocannabinol (THC) are the most prevalent, pharmacologically active phytocannabinoids found in the *Cannabis sativa* L. plant (37). THC has well-established effects on pain but is associated with psychoactive effects, which may hinder its application in the pain-reduction setting (37). In contrast, Cannabidiol (CBD) lacks the psychoactive properties of Λ9-tetrahydrocannabinol (THC) but has anti-infammatory, antinociceptive, and antioxidant effects, making it an intriguing target for the treatment of pain and inflammatory conditions, including the numerous manifestations of arthritis (37). Previous studies have identified the potential for cannabinoids to directly modulate pain within synovial joints (37).

Since its medical legalization, Cannabis preparations containing the major phytocannabioids (Cannabidiol (CBD) and Λ9-tetrahydrocannabinol (THC) have been used by patients with rheumatoid arthritis (RA) to alleviate pain and inflammation (39). However, minor cannabinoids such as Cannabigerol (CBG) also demonstrated anti-inflammatory properties, but due to the lack of studies, they are not widely used (39). Cannabigerol (CBG) binds several cellular target proteins such as cannabinoid and α2-adrenergic receptors, but it also ligates several members of the transient potential receptor (TRP) family with TRPA1 being the main target (39). Therefore, modulation of TRPA1 signaling by Cannabigerol (CBG) might be used to modulate disease activity in rheumatoid arthritis (RA) since this autoimmune disease is accompanied by oxidative stress and subsequent activation of pro-inflammatory pathways (39).

Rheumatoid synovial fibroblasts (RASF) were stimulated or not with tumour necrosis factor (TNF) for 72 h to induce TRPA1 protein (39). Cannabigerol (CBG) increased intracellular calcium levels in TNF-stimulated RASF but not un-stimulated RASF in a TRPA1-dependent manner (39). In addition, PoPo3 uptake, a surrogate marker for drug uptake, was enhanced by CBG (39). RASF cell viability, IL-6 and IL-8 production were decreased by CBG (39). In peripheral blood mononuclear cell cultures (PBMC) alone or together with RASF, CBG-modulated interleukin (IL)-6, IL-10, TNF and immunoglobulin M and G production which was dependent on activation stimulus (T cell-dependent or independent) (39). As Cannabigerol (CBG) is non-psychotropic, it might be used as add-on therapy in RA to reduce IL-6 and autoantibody levels (39).

Cannabidiol (CBD) and Cannabigerol (CBG) has been studied for its potential anti-inflammatory properties with regards to inflammatory conditions, but with conflicting and limited research surrounding rheumatoid arthritis (RA) (38). The reviewed studies highlighted no significant adverse reactions from the use of the Cannabidiol (CBD) therapeutics in the varying dosages and routes of Cannabidiol (CBD) administration (38). From these four studies there is evidence to suggest that there are benefits of Cannabidiol (CBD) as a therapeutic in terms of inflammation. Furthermore, three of the studies specifically found a reduction in the inflammatory marker TNF-α caused by rheumatoid arthritis (RA) after administration of the various therapeutic interventions and dosages (38). There is a requirement for more human clinical trials to determine the anti- inflammatory properties, the safety, dosage, route of administration and efficacy of Cannabidiol (CBD in humans with rheumatoid arthritis (RA) (38).

Cannabidiol (CBD) is a non-psychoactive cannabinoid that has shown promise in preclinical studies to reduce inflammation and pain associated with arthritis (37). One of the study found associations between Cannabidiol (CBD) use and improvements in patient's arthritis symptoms and reductions in other medications (37). Future research should focus on exploring the benefits of Cannabidiol (CBD) use in this patient population with clinical trials (37).

4) Wound Healing

A wound is defined as the breakage in the continuity of the skin (54). Wound may also be defined as an interruption within the continuity of the epithelial lining of the skin or mucosa that occurs as a result of physical or thermal damage (54). In general, wound healing is classified with four specific stages of hemostasis, inflammation, proliferation, and maturation (54). Different wound dressings containing antibiotics and antibacterial agents, nanoparticle based wound dressings prevent bacterial infection and bio film formation in the wound bed (54). However, the use of antibiotics, allopathic drugs and antibacterial nanoparticles in wound healing has some limitations since most of these antibacterial agents have side effects such as cytotoxicity (54). Furthermore, there is no efficient evidence-based therapy available for specific chronic wounds (54). Another problem is wound healing and wound management is very expensive health care, which poor people cannot afford to bear expenditure (54). There are a variety of herbal plants that have wound healing properties (54). Plant-based constituents have been extensively used for the treatment and management of different types of wounds (54). Folklore cultures employ a significant number of plants to treat cuts, wounds, and burns (54). Addition to this, the use of natural plant derived substances are considered safe compared to synthetic molecules and can be much cheaper than conventional therapies (54).

Wound-related pain is the result of primary factors such as tissue necrosis, ischemia, inflammation, edema, and infection (41-53, 55). The secondary factors also include peripheral and secondary neural sensitization, and peri-wound tissue pathology (41- 55). Wound-related pain is divided into two categories: baseline pain and breakthrough pain, as reported by patients (41-53, 55). Baseline pain is constant and continuous pain (41-53, 55). In comparison, breakthrough pain is characterized as an intensified pain with rapid onset, whose existence is independent of baseline pain (41-53, 55).

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Most of the studies suggested that the application of topical cannabinoids would be beneficial for wound healing (41-53, 55). The skin has its own Endocannabinoid system (ECS) which is a key regulator of various homeostatic processes, including those necessary for normal physiologic wound healing (41-53, 55). The use of topical Cannabinoids (CBs) for wounds minimizes the possibility of negative side effects; indeed, most topical cannabinoid formulations have negligible systemic absorption within commonly used carriers (eg lotions, creams, oils) which should assuage concerns about systemic side effects (41-53, 55). Cannabidiol (CBD) in particular is attractive due to its lack of psychotropic effects and added ability to modulate pain (41-53, 55). Data on the use of Cannabinoids (CBs) for wound healing are scarce (41-53, 55). Compelling pre-clinical evidence supporting the therapeutic potential of Cannabinoids (CBs) to improve wound healing by modulating key molecular pathways has been reported and reviewed (41-53, 55).

Topical Cannabidiol (CBD) has already been used safely in two small case series of orphaned diseases (Epidermolysis Bullosa [EB] and Pyoderma Gangrenosum) wherein patients reported decreased pain and, for the EB group, subjective decreases in healing time (41-53, 55). A topical Cannabinoids (CBs) formulation containing Cannabidiol (CBD), Λ9-tetrahydrocannabinol (THC) and various terpenes and flavonoids has also been successfully used in a small cohort of two patients with biopsy proven-calciphylaxis; clinically significant analgesia and closure were achieved in 0.6 and 2.5 months, respectively (41-53, 55). These few studies suggested that Cannabinoids (CBs) hold great promise for the treatment of classically difficult or recalcitrant wound subtypes (41-53, 55). Topical Cannabis-Based Medicines (TCBM), applied to both wound beds and peri-wound tissues, represented a promising novel, non-invasive, and safe treatment option for NUC leg ulcers (41-53, 55). The ease and simplicity of its application also allowed for potential self-application and self titration by patients (41-53, 55).

Another preclinical research has shown that the dominant chemical classes derived from the Cannabis plant, cannabinoids, terpenes, and flavonoids, interact with the integumentary ECS to promote wound closure and analgesia (41-53, 55). This is a prospective open label cohort study involving two elderly Caucasian females with recalcitrant NUC leg ulcers of greater than 6 months duration (41-53, 55). Topical Cannabis-Based Medicines (TCBM) composed of cannabinoids, terpenes, and flavonoids were applied daily to both the wound bed and peri-wound tissues until complete wound closure was achieved (41-53, 55). Complete wound closure was achieved in a mean of 76.3 days (53). Additionally, no analgesics were required after a mean of 63 days (53). The treatments were well tolerated with no adverse reactions (41-53, 55).

Cannabis-based medicine is capable of improving healthcare outcomes for patients suffering from wound-related pain, while simultaneously reducing the use of the current analgesics that caused adverse side effects and inhibit wound healing (41-53. 55). Current and ongoing research suggested that Cannabis-based medicines are very potential and promising candidate as a novel approach for treating wound-related pain (41-53, 55). These discoveries have been made possible by the global shift toward the legalization of medical Cannabis and the elucidation of the Endocannabinoid system (ECS) (41-53, 55).

For instance, a 2017 case study documented rapid onset of pain relief in a patient with a malignant oral-buccal wound after implementing topical Cannabidiol (CBD), and Λ9-tetrahydrocannabinol (THC) oils with vaporized Cannabis flower (41-53, 55). Another study involving 3 cases of pyoderma gangrenosum implemented topical Cannabidiol (CBD), and Λ9-tetrahydrocannabinol (THC) oil and reported not only rapid pain relief, but opioid-sparing effects after using the Cannabis-based medicine (41-53, 55). A 2020 clinical trial employed topical Cannabis-based medicine containing congeners of all three chemical classes to a cohort of patients with non-uremic calciphylaxis wounds (41-53, 55). Complete wound closure was observed in a mean of 2.5 months and zero utilization of all anaglesics was possible at a mean of 2.1 months (41-53, 55).

Cannabis-based medicine extends the possibility for improved pain relief, safer methods with less harm and fewer iatrogenic risks, self-titration and the reinstatement of personal agency, and enhanced wound healing (41-53, 55). The use of Cannabis-based medicine in a creative manner (i.e. multiple routes of administration and in combination with reduced dosages of status quo adjuvant analgesics) has improved overall relief of wound-related pain, improved quality of life, and reduced burdens and harm to patient and society (41-53, 55). Further research into Cannabis-based medicine is necessary to evaluate optimal dosages, protocols, and applications (41-53, 55).

As Cannabis use has become increasingly prevalent, surgeons must be aware of its potential effects in the peri-operative setting, particularly as these related to wound healing and cardiovascular, pulmonary, and hematologic function (41-53, 55). Several studies have explored the effects of Cannabis on peri-operative pain, but little is known about its effects on wound healing, or cardiovascular, pulmonary, or hematologic physiology(41-53, 55). Much of the literature examining the effects of Cannabis is limited by inconsistent formulation, route, and timing of administration (41-53, 55). Further research is needed to elucidate the effects of route of administration (eg, topical, ingestible, inhalational), dose/duration, and timing of Cannabis use among surgical patients, and other potential side effects of Cannabis (41-53, 55).

5) Constipation

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Constipation is a common functional gastrointestinal disorder that affects patients of all ages (56-65). Constipation could be resulted in the unsatisfying defecation, infrequent stools, difficult stool passage or both with pain and stiffness (56-65). Acute constipation may cause closure of the intestine, which may even requires surgery (56-65). Constipation refers to a situation where bowel movements are hard or become infrequent or difficult stool passage leading to Irritable Bowel Syndrome (IBS) (56-65). They may need to spend more time in the toilet as passing stools becomes a difficult process (56). Some people experienced a feeling of an incomplete bowel movement and feel a blockage (56-65). When the stools are too hard, there is more strain on the muscles in the rectum (56-65). Constipation, characterized by dry stools, prolonged defecation cycle, and defection difficulty, is one of the most common gastrointestinal disorders diagnosed in clinical practice, with a prevalence of 12%–19% worldwide (56-65). Constipation decreases quality of life as patients often suffer from both physical symptoms and psychological distress (56-65). Chronic constipation is a complicated condition among older individuals, which is characterized by difficult stool passage (56-65).

Common causes of constipation in the elderly people are linked to several factors including lack of normal bowel movements or aging, lack of proper diet, low-fiber food consumption, lack of adequate fluid intake, lack of adequate physical activity, illness or the use of drugs (56-65). Occasional episodes of constipation can also be occurred due to the consumption of food that is difficult to digest (56-65). Constipation episodes may even occur as a side effect of taking certain medications (56-65).

Constipation leading to three bowel movements a week, stools are dry, hard and/or lumpy, stools are difficult or painful to pass, stomach ache or cramps, and feel bloated and nauseous (56- 65). Constipation happens because colon absorbs too much of water from waste (stool/poop), which dries out the stool making it hard in consistency and difficult to push out of the body (56-65). Food normally moves through the digestive tract, nutrients are absorbed (56-65). The partially digested food (waste) that remains moves from the small intestine to the large intestine, also called the colon (56). The colon absorbs water from this waste, which creates a solid matter called stool (56-65). In case of diabetic patients with constipation, food may move too slowly through the digestive tract (56). This gives the colon more time to absorb water from the waste. The stool becomes dry, hard, and difficult to push out (56-65).

Conventional treatment includes the use of laxatives to remove stools (56-65). The regular use of such chemical-based drugs can imbalance body metabolism and affect the digestive system (56-65). Natural plant products rich in fiber, melatonin and anthraquinones are important for the prevention and treatment of gastrointestinal disorders (56-65). Ayurveda recommends a holistic approach to treat constipation. The Ayurvedic treatment for constipation required the use of herbal formulations (56-65). Medicinal plants possess a significant laxative potential and support their folklore (56-65). In addition to natural laxatives, an Ayurvedic diet, exercise, and massage are key elements of maintaining a healthy digestive system (56-65).

Cannabidiol (CBD) oil has emerged as a popular natural remedy for a variety of health issues including digestive problems and constipation (56-65). Cannabidiol (CBD) oil is used for the treatment of constipation relief (56-65). Cannabis seed oil is nutritious. The seeds are rich in essential fatty acids: the omega-3 fatty acids, alpha-linolenic acids (ALA) and the omega-6 fatty acid gamma-linolenic acid (GLA) (56-65). Seeds also contain natural vitamin E and protein. Cannabinoids are antispasmodic. Sedate when there is irritation. Relax the smooth muscles. The relaxing effects of Λ9-tetrahydrocannabinol (THC) can help the intestines pass bulk bowel movements much easier and more quickly because the Λ9-tetrahydrocannabinol (THC) relaxes the nerves in the intestinal wall (56-65). There is a theory that THC helps the stomach to digest and process foods more easily (56-65). Cannabis has been subject to fairly widespread use regarding digestive issues, in both clinical and non-clinical contexts (56-65). The science is limited; however, studies have so far pitched THC against symptoms of inflammatory bowel disease and the frequency of diarrhoea (56-65). There is also research into Cannabidiol (CBD), impact on the speed at which waste passes through the intestines (56-65). Furthermore, Cannabis is being studied for its potential to indirectly address stomach issues arising from using other types of drugs. Opioids are often prescribed for pain relief and are known to cause constipation (56-65). Medical Cannabis is currently being trialled for its potential to help reduce opioid use (56-65). Therefore, it could potentially limit the effects of the latter in causing side effects such as constipation (56-65). Cannabis is also widely appreciated for its ability to put people in a relaxed state (56-65). One of the many therapeutic applications of Cannabis is relief from constipation (56-65). Stomach pain and bowel problems can often be eased with marijuana (56-65).

Although the endogenous cannabinoid system modulates bowel function, the understanding of the impact of recreational medical Cannabis-marijuana (MJ) use on bowel motility is limited (56-65). One of study examined the effect of medical Cannabis- marijuana (MJ) on self-reported bowel function among a large cohort of US adults (62-65). Overall, constipation prevalence was lower among those with recent marijuana (MJ) use compared with those with past/never use (7.5% vs 10.2%, P = 0.03) (62-65). Recent marijuana (MJ) use was associated with a 30% decreased odds of constipation (crude odds ratio: 0.71 [0.56–0.98], P = 0.005), which persisted after stepwise adjustment for age and other demographic factors including sex, ethnicity, education, body mass index, and socioeconomic status (AOR: 0.64 [0.49–0.83], P = 0.001); comorbidities, substance use

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(alcohol, tobacco, heroin, and cocaine), constipating medications, general health condition, rigorous physical activity, and emotional disturbances (AOR: 0.68 [0.48–0.93], *P* = 0.016); and diet (AOR: 0.68 [0.52–0.89], *P* = 0.006) (62-65). There was no association between recent marijuana (MJ) use and diarrhoea (56-65). In a nationally representative sample of community-dwelling US adults, recent marijuana (MJ) use was associated with decreased odds of constipation, counter to the known physiologic effects of cannabinoids on colonic motility (62-65).

Hemp is used for constipation in the form of Chinese medicine pill MaZiRenWan has been documented in several randomised controlled trials conducted by the same group of researchers (62-69). MaZiRenWan (MZRW) is the most frequently used Traditional Chinese Medicine formula to treat chronic constipation and Cannabis sativa L. is regarded as a monarch drug in MZRW (62-69). However, the targets of *Cannabis sativa* L. that enhance colonic motility and improved constipation symptoms remain unknown (62-69). This study was designed and investigated the laxative effect and underlying mechanism of the Water extract of Cannabis sativa L. (WECSL) using a loperamide-induced constipation mouse model (62-65). This study reported that WECSL treatment significantly improved intestinal motility and water electrolyte metabolism, decreased inflammatory responses, prevented gut barrier damage, and relieved anxiety and depression in constipated mice (62-69). WECSL also structurally remodeled the composition of the gut microbiota and altered the abundance of bacteria related to inflammation, specifically Butyricicoccus and Parasutterella (62-69). Moreover, WECSL failed to relieve constipation symptoms following intestinal flora depletion, indicating that WECSL alleviates constipation symptoms depending on the gut microbiota (62-65). This research also provides a basis for WECSL to be further investigated in the treatment of constipation from the perspective of modern medicine (62-69).

6) Multiple Sclerosis

Multiple sclerosis (MS) is known as an autoimmune disease that damages the neurons in the central nervous system (22, 70-98). Multiple sclerosis (MS) is characterized by its most common symptoms of spasticity, muscle spasms, neuropathic pain, tremors, bladder dysfunction, dysarthria, and some intellectual problems, including memory disturbances (22, 70-98). Multiple sclerosis (MS) is a multifactorial disease and it is widely accepted that CNS neuroinflammation is responsible for demyelination (70-98). This demyelinated disease leads to severe impairment of nerve signal transmission between the brain and spinal cord that causes a loss of myelin sheath (22, 70-98). The only use of cannabinoids in neurological disorders and the only complementary medicine intervention with high-level evidence for efficacy in MS is pharmaceutical cannabinoids for spasticity (22, 70-98). Several clinical studies have been conducted and investigated the effects of Cannabis on the relief of these symptoms in Multiple sclerosis (MS) patients (22, 70-98).

Spasticity continues to be a very prevalent, highly invalidating, and difficult-to-manage symptom in patients with multiple sclerosis (MS) (22, 70-98). One of the study demonstrated that adding the THC:CBD sprays have been shown to be more effective in treating MS spasticity than optimizing the dose of first-line antispastic drugs in selected responders patients (22, 70-98).

Multiple sclerosis (MS), a chronic demyelinating autoimmune disease of the central nervous system (CNS), is a leading cause of non-traumatic neurologic disability in young adults (22, 70-98). Medical cannabis (MC) has recently generated interest as a therapy for neurologic disorders, including MS (70-98). Medical Cannabis varies widely in composition and includes pharmacologically active cannabinoids (22,98).

MS patients manifest a range of symptoms as a result of motor, sensory, autonomic, and psycho-behavioral dysfunction including fatigue (75–90%) and mobility impairment (90%), gait difficulties, paresthesia, vision problems, speech impairments, dizziness and vertigo, urinary bladder dysfunction, neurogenic bowel dysfunction, sexual dysfunction, chronic neuropathic pain (85%), cognitive deficits in information processing, speed, episodic memory, complex attention and executive function, physical disability, anxiety and depression, and sleep disturbances that correlated with fatigue and depression (22, 70-98).

The Cannabis plant contains up to 200 cannabinoids, though Δ9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) have been the primary focus of medical investigation (22,70-98). THC has psychoactive effects, such as cognitive impairments, psychosis, dysphoria, and anxiety, whereas CBD is non-intoxicating and has anti-inflammatory, analgesic, and antipsychotic properties, and can counter several unwanted side effects of THC (22,70-98). A significant number of people with multiple sclerosis (MS) are using or considering using Cannabis for a range of symptoms (70-98). Recent studies have indicated that there is a wide acceptance of Cannabis within the MS community, with 20–60% with multiple sclerosis currently using cannabis, and 50–90% would consider usage if it were legal and more scientific evidence was available (70-98).

The efficacy of *Cannabis sativa* L. in the management of MS outcomes such as spasticity, pain, tremors, ataxia, bladder functions, sleep, quality of life, and adverse effects were assessed (22,70-98). Most clinical studies showed the positive effects of cannabinoids with their different routes of administration, such as oromucosal spray and oral form, in reducing most MS symptoms (70-96). The oromucosal spray Nabiximols demonstrated an improvement in reducing MS spasticity, pain, and quality

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of life with a tolerated adverse effect (70-98). Oral cannabinoids are significantly effective for treating MS pain and spasticity, while the other symptoms indicated slight improvement and the evidence is quite inconsistent (70-98). Oromucosal spray and oral Cannabis are mainly used for treating patients with MS and have positive effects on treating the most common symptoms of MS, such as pain and spasticity, whereas the other MS symptoms indicated slight improvement, for which further studies are needed (22, 94-98).

Nabiximols, an oromucosal spray of a whole Cannabis plant extract with a 1:1 ratio of THC to Cannabidiol (CBD), was initially licensed and approved in Europe, the United Kingdom, and Canada for the treatment of pain and spasticity associated with multiple sclerosis (GW Pharmaceuticals, 2016) but it continues to undergo evaluation in Phase III clinical trials in the United States (22, 94-98). Efforts are under way to develop targeted pharmaceuticals that are agonists or antagonists of the cannabinoid receptors or that modulate the production and degradation of the endocannabinoids, although such interventions have not yet demonstrated safety or effectiveness (22, 94-98).

The consistency, efficacy, and safety of Cannabis-based medicines have been demonstrated in humans, leading to the approval of the first Cannabis-based therapy to alleviate spasticity and pain associated with multiple sclerosis (MS) (22, 70-98). Indeed, the evidence supporting the therapeutic potential of Cannabinoids for the management of pathological events related to this disease is ever increasing (95-98).

Cells in the immune and nervous system express the machinery to synthesize and degrade endocannabinoids, as well as their CB1 and CB2 receptors, each mediating different intracellular pathways upon activation (95). Hence, the effects of cannabinoids on cells of the immune system, on the blood-brain barrier (BBB), microglia, astrocytes, oligodendrocytes and neurons, potentially open the way for a plethora of therapeutic actions on different targets that could aid the management of MS (70-98). As such, cannabinoids could have an important impact on the outcome of MS in terms of the resolution of inflammation or the potentiating of endogenous repair in the central nervous system (CNS) (95-98). In MS and other neurodegenerative diseases, the neuroprotective effects of Cannabinoids have been attributed to stimulation of CB1R, the most abundant GPCR in the brain, whereas CB2R, the non-psychotropic cannabinoid receptor, has almost exclusively been associated with immunomodulatory effects (70-98).

Another recent study by Rainka et al., (2023) (97) showed that medical Cannabis may helped to decrease chronic pain, muscle spasticity, and sleep disturbances in patients with MS, and patients may also be able to reduce opioid use during MC treatment (97-98). Users of medical Cannabis may required individualized therapy to balance efficacy and AEs (97). Prospective studies of the effects of medical Cannabis on MS symptoms and opioid use would be beneficial, and, ultimately, could influence future legislation as it pertains to the legalization of medical Cannabis in the United States (97). Medical Cannabis may be an effective and well-tolerated adjunctive therapy for patients with multiple sclerosis with chronic pain and muscle spasticity (97). Medical Cannabis treatment may allow for dose reduction or discontinuation of opioid analgesics in patients with multiple sclerosis. Cost is a barrier to medical Cannabis treatment for many patients (70-97). Future research will be necessary to identify the precise mechanisms triggered by cannabinoid signaling in order to regulate key homeostatic pathways in the brain (22, 70-98).

7) Cancer

Cancer is a broad term used to describe a wide range of related diseases that are characterized by an abnormal, unregulated division of cells. Cancer is a biological disorder that often resulted in tumour growth (99-103). Cancer cells are descendants of a single cell in which genetic errors or mutations, have occurred. These errors may occur spontaneously or randomly when cells divide or they may present themselves as a result of exposure to environmental toxins (Carcinogens). Cancer occurs when these abnormal cells continue to grow at a uncontrolled rate. As these abnormal cells divide, they can eventually form a solid mass called tumour (99-103). A malignant (Cancerous) tumour will continue to grow at an uncontrolled rate and may eventually harm other areas of the body. Therefore, the definition of cancer is the abnormal, and uncontrolled growth of cells. The immune system will recognize damaged cells and kill them before tumorus can form and cause problems. Therefore, because of all these factors, cancers are not thought to be the result of the single event (99-103). Cancer is among the leading causes of mortality throughout the world, there will be an estimated 1.7 million new cancer diagnoses (22, 99-103). The coronavirus disease 2019 (COVID-19) pandemic caused delays in the diagnosis and treatment of cancer because of health care setting closures, disruptions in employment and health insurance, and fear of COVID-19 exposure. There is evidence to suggest that Cannabinoids (and the endocannabinoid system more generally) may play a role in the cancer regulation process (22, 99-103). Therefore, there is interest in determining the efficacy of Cannabis or cannabinoids for the treatment of cancer (99-103). The anti-proliferative action of cannabinoids on cancer cells was first noticed in the 1970s (99-103). Since then Cannabinoids were found to act on various cancer cell lines, through various mechanisms (22, 99-103). Cannabinoids were also found to be suppressors of angiogenesis and tumour invasion (22, 99-103).

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There is moderate-certainty evidence that oromucosal nabiximols and THC are ineffective in relieving moderate-to-severe opioid-refractory cancer pain (102). There is low-certainty evidence that nabilone is ineffective in reducing pain associated with (radio-) chemotherapy in people with head and neck cancer and non-small cell lung cancer (102). There is low-certainty evidence that a single dose of synthetic THC analogues is not superior to a single low-dose morphine equivalent in reducing moderate-to-severe cancer pain (102). There is low-certainty evidence that CBD does not add value to specialist palliative care alone in the reduction of pain in people with advanced cancer (102).

As the endocannabinoid system has been shown to play a role in tumour development and growth, it has been suggested that Cannabis products may be used because of their cytostatic effect against specific tumours in which cannabinoid receptors are highly expressed (103). Application of Cannabis products for this purpose should only be performed on the basis of tumour characterisation and profiling (103). Nevertheless, the application of Cannabis products alone to treat cancers has not shown convincing results so far (103). Cannabinoids may inhibit efflux transporters and drug-metabolising enzymes, possibly inducing pharmacokinetic interactions with anticancer drugs being substrates for these proteins. This may enhance the cytostatic effect and/or drug-related adverse effects (103). Similar interactions are likely with drugs used for symptom management treating pain, nausea, vomiting and anorexia (103). Cannabis products are usually well tolerated and may improved the quality of life of patients with cancer (although not unambiguously proven) (103). The combination with immunotherapy seems undesirable because of the immunosuppressive action of Cannabinoids (103). Further clinical research is warranted to scientifically support (refraining from) using cannabis products in patients with cancer (103-104).

Future clinical research is absolutely warranted to scientifically underpin positive preclinical and/or anecdotal data obtained with Cannabis products in patients with cancer. Pilot studies investigating anticancer effects should be undertaken to demonstrate possible antitumour efficiency, which should most reasonably be performed in patients who are in a palliative setting and for whom have no other treatment opportunities (103). Such pilot studies may form a basis for larger trials. Based on the outcome of such studies, the potential and limitations of Cannabis products for the clinic can be more objectively determined (103). In glioma patients, the results obtained with Cannabis products seem hopeful, but larger randomised clinical trials should be undertaken to demonstrate efficiency (103-104). In principle, Cannabis products may modulate the pharmacokinetic profile of anticancer drugs by interfering with drug transporters and with metabolic enzymes (103, 104). A very important, yet in many studies neglected, aspect here is the qualitative and quantitative composition of the Cannabis products used, the route of administration and the exposure (dose, frequency and duration of treatment) (103). The translation of preclinical data to clinical applications of Cannabinoids and medicinal Cannabis however remains challenging (99-104). Additionally, the use of Cannabis products in combination with anticancer drugs may resulted in more non-serious adverse events, possibly due to overdosing. The claimed advantages of applying Cannabis products for symptom management and relief in patients with cancer remain controversial (103).

8) Glaucoma

Glaucoma is a group of eye diseases that cause progressive damage of the optic nerve at the point where it leaves the eye to carry visual information to the brain (104-113). If left untreated, most types of glaucoma progress, without warning or obvious symptoms to the patient, towards gradually worsening visual damage and could eventually lead to blindness (99-112). And if sight is lost to glaucoma, the visual damage is mostly irreversible (99-112**).** This is why glaucoma has also been labelled as the "Silent Blinding Disease" or the "sneak thief of sight (104-112). Glaucoma is an optic neuropathy characterized by the loss of retinal ganglion cells and subsequent progressive degeneration of the optic nerve (104-112). It is the most common cause of irreversible blindness in the world (99-112). The most significant modifiable risk factor is the control of intraocular pressure (IOP) (99-112). There are several types of glaucoma. Some may occur as a complication of other visual disorders (the so-called "secondary" glaucomas), but the vast majority is "primary", i.e. they occur without a known cause (104-112). Glaucoma is an optic neuropathy characterized by the loss of retinal ganglion cells and subsequent progressive degeneration of the optic nerve (99-112). The most significant modifiable risk factor is the control of intraocular pressure (IOP) (104-112). Glaucoma is an irreversible disease and a worldwide leading cause of blindness (99-113).

Cannabis plants and their derivatives Λ(9)-tetrahydrocannabinol (THC) and Cannabidiol (CBD) have been evaluated for the treatment of many disorders, including lowering intraocular pressure (IOP) (104-112). THC has been identified as the metabolite relevant to IOP-lowering, and this potential to treat glaucoma has been the subject of research over the past five decades (99-112). CB1 and CB2 receptors have been identified widely in the eye (99-113). More recently, Cannabis primary psychoactive component Λ (9)-tetrahydrocannabinol (THC) and its major non-psychoactive ingredient Cannabidiol (CBD) have been used for the treatment of sleep disorders, pain, skin disorders, and lowering of intraocular pressure (IOP) (99-112). Control of IOP is the most significant modifiable risk factor for glaucoma, an optic neuropathy that causes irreversible blindness (104-113).

9) Parkinson's disease

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Parkinson's disease (PD) is a serious neurodegenerative condition impacting many individuals worldwide (114-119). Parkinson's disease is a brain disorder that causes unintended or uncontrollable movements, such as shaking, stiffness, and difficulty with balance and coordination (114-119). Symptoms usually begin gradually and worsen over time. As the disease progresses, people may have difficulty in walking and talking (114-119). They may also have mental and behavioural changes, sleep problems, depression, memory difficulties, and fatigue (114-119). Parkinson's has four main symptoms: Tremor in hands, arms, legs, jaw, or head (114-119). Muscle stiffness, where muscle remains contracted for a long time, slowness of movement, impaired balance and coordination (114-119). Depression and other emotional changes, difficulty in swallowing, chewing, and speaking, urinary problems or constipation, and skin problems (114-119). Symptoms often begin on one side of the body or even in one limb on one side of the body (114-119). As the disease progresses, it eventually affects both sides (114-119). However, the symptoms may still be more severe on one side than on the other (114-119). People with Parkinson's disease often develop a parkinsonian gait that includes a tendency to lean forward; take small, quick steps; and reduce swinging their arms (114-119).

The main therapy for Parkinson's disease is Levodopa (114-119). Nerve cells use levodopa to make dopamine to replenish the brain's dwindling supply (114-119). Usually, people take Levodopa along with another medication called Carbidopa. Carbidopa prevents or reduces some of the side effects of levodopa therapy such as nausea, vomiting, low blood pressure, restlessness and reduces the amount of levodopa needed to improve symptoms (114-119). Therefore, anyone could be at risk for developing Parkinson's, disease. Most of the research studies suggested that this disease affects more men than women and nne clear risk is age (114-119). Early-onset forms of Parkinson's are often, but not always, inherited, and some forms have been linked to specific alterations in genes (114-119). The most prominent signs and symptoms of Parkinson's disease occurred when nerve cells in the Basal Ganglia, an area of the brain that controls movement, become impaired and/or die (114-119). Normally, these nerve cells, or neurons, produce an important brain chemical known as Dopamine (114-119). When the neurons die or become impaired, they produce less dopamine, which causes the movement problems associated with the disease (114-119). Scientists still do not know what causes the neurons to die (114-119).

People with Parkinson's disease also lose the nerve endings that produce norepinephrine, the main chemical messenger of the sympathetic nervous system, which controls many functions of the body, such as heart rate and blood pressure (114-119). Many brain cells of people with Parkinson's disease contain Lewy bodies, unusual clumps of the protein alpha-synuclein (114-119). Some cases of Parkinson's disease appear to be hereditary, and a few cases can be traced to specific genetic variants (114-119).

There is a need for new non-invasive treatments of Parkinson's disease (PD). Cannabinoids in the form of Cannabidiol (CBD) and Λ-9-tetrahydrocannabinol (THC) may offer utility as treatment, and there are clinical evidence for the efficacy and safety of cannabinoids in treating Parkinson's disease (PD) (114-119). Medical Cannabis (MC) has recently garnered interest as a potential treatment for neurologic diseases, including Parkinson's disease (PD) (114-119). The Medical Cannabis (MC) may improve motor and non-motor symptoms in patients with Parkinson's disease (PD) and may allowed for the reduction of concomitant opioid medication use (114-119). Large, placebo-controlled, randomized studies of medical Cannabis (MC) use in patients with Parkinson's disease (PD) are required. Over the 1–3 years of follow-ups, the medical Cannabis (MC) treatment regimens appeared to be safe (114-119). Medical Cannabis (MC) did not exacerbate neuropsychiatric symptoms and had no detrimental effects on disease progression (114-119). Cannabinoids have been shown to safely offer important potential in treating motor symptoms in Parkinson's disease (PD) and some non-motor symptoms (114-119). More large-scale randomized control trials for specific forms of Cannabinoid treatments are required to determine their overall efficacy (114-119). Published research publications provided scientifically sound evidence in the evaluation of Cannabidiol (CBD) as a potential pharmacotherapeutic tool for the treatment of mood disorders such as anxiety and depression and diseases such as Alzheimer's and Parkinson's in animal and human studies (114-119). Furthermore, a wide variety of methodologies, ranging from novel analytical and computational techniques to a medical case, also cast light on Cannabidiol (CBD) underlying action mechanisms, therapeutic monitoring, and potential side effect profile (114-119).

Endocannabinoids of the ECS act at Cannabinoid receptor type 1 (CB1) receptors to modulate the activity of dopamine and other neurotransmitters in the Basal ganglia, rendering the ECS a potential target for pharmacological intervention in Parkinson's disease (PD) (114-119). The ECS itself implicated in the pathology of Parkinson's disease (PD) (114-119).

Cannabinoids offer both anti-parkinsonian and neuroprotective properties as therapeutic mechanisms in Parkinson's disease (PD) treatment (114-119). Pre-clinical studies have demonstrated cannabinoids act to suppress excitotoxicity, glial activation, and oxidative injury that cause degeneration of dopaminergic neurons (114-119). Cannabinoids are divided into three categories: endogenous, plant-derived phytocannabinoids and synthetic. The most studied endogenous endocannabinoids are AEA and 2-arachidonoylglycerol, and Δ9-THC, the latter being the psychoactive component of Cannabis (114-119). The principal phytocannabinoids responsible for the therapeutic effects of Cannabis are Δ9-tetrahydrocannabidiol (Δ9-THC) and

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Cannabidiol (CBD) (114-119). Common Cannabis preparations vary in their ratio of Cannabidiol (CBD) to the synthetic cannabinoids approved for use by Health Canada are Nabiximols and Nabilone (114-119).

10) Alzheimer's disease (Dementia)

Alzheimer's disease (AD) is the most common form of dementia, a serious brain disorder that impacts daily living through memory loss and cognitive changes (20-124). Alzheimer's disease is characterized by the profound memory loss affecting daily routine life (120-124). Memory impairment (short memory loss) is the hallmark symptom of Alzheimer's disease (120-124). Alzheimer's disease is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906 (120-124). Alzheimer's disease is also age related neurodegenerative disorders caused by progressive loss of structure or function of neurons, resulting in neuronal cell death (120-124). Alzheimer's patients have an Acetylcholine deficiency. Stressful conditions, free radicle scavanging and oxidation are often associated with loss of memory and cognitive functions, which may lead to threats of schizophrenia and Alzheimer's disease (120-124). However, the use of allopathic drugs has resulted in the adverse side effects on the human body and thus limits the use of such drugs (120-124). Herbal cognitive enhancer drugs have shown their potent effect in Alzheimer's disease due to their antioxidant and neuropharmacological actions (120-124). The use of natural cognitive enhancers evidenced to improve mental functions such as cognition, memory, intelligence, motivation, attention and concentration (120-124). Traditional *Ayurvedic* herbal system of medicine is fundamentally preventive, protective, nutritive, curative and less expensive (120-127). Therefore, the use of herbal medicine for the treatment of Alzheimer's disease is a novel approach without any side effects (120-124).

There is currently no cure for Alzheimer's disease and approved treatments do not halt or slow disease progression, highlighting the need for novel therapeutic strategies (125). Importantly, the Endocannabinoid system (ECS) is affected in Alzheimer's disease (AD) (120-125). Phytocannabinoids, including Cannabidiol (CBD) and Λ9- tetrahydrocannabinol (THC), interact with the ECS, have anti-inflammatory, antioxidant, and neuroprotective properties, can ameliorate amyloid-β and NFT-related pathologies, and promoted neurogenesis (120-125). Thus, in recent years, purified CBD and THC have been evaluated for their therapeutic potential. CBD reversed and prevented the development of cognitive deficits in Alzheimer's disease rodent models, and low-dose THC improved cognition in aging mice (125). Importantly, CBD, THC, and other phytochemicals present in *Cannabis sativa* interact with each other in a synergistic fashion (the "entourage effect") and have greater therapeutic potential when administered together, rather than individually (125). Thus, treatment of Alzheimer's disease (AD) using a multi-cannabinoid strategy (such as whole plant cannabis extracts or particular CBD:THC combinations) may be more efficacious compared to cannabinoid isolate treatment strategies (120-125).

Phytocannabinoids, including Cannabidiol (CBD) and Λ9-tetrahydrocannabinol (THC) have gained attention as a potential therapeutic strategy for dementia including AD (125). CBD (non-intoxicating) and THC modulate the ECS, are neuroprotective, anti-inflammatory, and antioxidant, and emerging evidence suggests that they have therapeutic-like effects on Aβ accumulation and tau hyperphosphorylation (125).

The management of behavioural symptoms and rigidity in patients with dementia constitutes a significant challenge (120-126). Short-term studies suggested an interest in the use of medical Cannabis, but long-term data are lacking (120-126). A long-term THC/CBD (1:2) medication can be administered safely and with overall positive clinical improvement to poly medicated older adults with severe dementia and associated problems (126). The results must be confirmed in a randomized trial (120-126). The natural Cannabis oil has a THC: CBD proportion of 1:2, where CBD possibly reduces the THC psychoactive properties and other side effects previously reported with synthetic THC formulations (120-126). The dosages used in this study were significantly higher than the ones reported in other studies, even if the safety limits proposed for other pathologies were respected (120-126). Also, the pharmacological profile was favorable and did not provide evidence of critical drug–drug interactions. The interest in medical Cannabis is rising. Based on the results of this study, this new approach might represent a valid, feasible, and safe alternative for patients with dementia (120-126). Numerous *Cannabis sativa* L.-prevalent phytochemicals were found to have promising efficacy in the treatment of neurodegenerative diseases, with Alzheimer's disease (AD) serving as an example (120-127). Moreover, many phytocannabinoids and terpenes, as well as some selected flavonoids, exhibited neuroprotection that was offered through an array of molecular and cellular pathways (120-127). These pathways could be Cannabinoid receptor-mediated, amyloid β, or direct anti-aggregatory and antioxidant against the pathological toxic hallmark protein in Alzheimer's disease (AD) (120-127).

However, further investigations, and in particular, clinical studies, are required to determine optimal dose and ratio of cannabinoids for treatment of behavioural, cognitive, and pathological symptoms of Alzheimer's disease (AD) (125). Thereby also considering other Cannabinoids in addition to the current focus on THC and CBD (most Cannabis extract studies did not profile Cannabinoid content beyond those two phytocannabinoids) (120-125). Importantly, all relevant studies reviewed were carried out in one sex/gender only (125). Given that sex-specificity is evident in Alzheimer's disease (AD) transgenic mouse

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models and gender differences are seen in dementia as well as in the ECS and the response to Cannabis, it is pertinent that these future investigations consider both sexes (12-125).

Finally, there are no research studies that proved Cannabis, or products such as Cannabis oil (CBD oil), can stop, slow, reverse or prevent the Alzheimer's disease (AD) that cause dementia (120-129). Some studies suggested that Cannabis could help to manage a few behavioural symptoms of dementia, such as agitation and aggression. But more research is needed to understand the long-term effects of taking Cannabis, and whether it is an effective and safe way to tackle dementia symptoms (120-129). Therefore, it is also a caution to physicians, people with dementia and families that need to do more research before to recommend cannabinoids to treat agitation. Researchers need more studies to replicate findings and investigated anticipated side effects associated with Cannabinoids, such as sedation and worsening memory (120-127). More research will go a long way in clearing the air around the potential benefits and drawbacks of medical Cannabis, and supported informed guidelines, policies and standards (120-129).

11) Obesity, Weight Loss, Anorexia, and Emesis

Overweight, insulin resistance and obesity emerged as leading health concerns all over the world (22, 128-141). The above mentioned disturbances are characterized by excessive or abnormal fat accumulation, and are major risk factors for a number of chronic diseases, such as cardiovascular diseases, diabetes, and cancer (22, 128-141). Currently, the non-psychotropic component of *Cannabis sativa*—CBD is in the center of interest, due to its well-established anti-inflammatory, anti-oxidant, anti-convulsant, anti-psychotic and potential anti-obesity properties (22, 128-141). Cannabidiol (CBD) has the promising potential as a therapeutic agent and might be effective in alleviating the symptoms of insulin resistance, type 2 diabetes and metabolic syndrome (128-141). Many studies have indicated that Cannabidiol (CBD) affects both lipid and glucose metabolism through the action on various receptors as well as several metabolites (22, 128-141). Cannabis has been known for centuries to increase appetite and food consumption (22, 128-141). Obesity and coexisting disorders such as insulin resistance, hypertension, and hypertriglyceridemia lead to the development of metabolic syndrome and type 2 diabetes (22, 128-141).

Rimonabant leads to significant weight loss in obese human subjects (22, 128-141). In clinical trials Rimonabant, a Cannabinoid-1 receptor blocker was found to cause a significant mean weight loss, reduction in waist circumference, increase in HDL cholesterol, reduction in triglycerides, and increase in plasma adiponectin levels (22, 128-141). Surprisingly, the US Food and Drug Administration has declined to approve rimonabant, primarily due to its slight potential to enhance anxiety and suicidal thoughts (22, 128-141).

The other side of the same coin is anorexia (22). Anorexia is a potentially life-threatening eating disorder characterized by an abnormally low body weight, intense fear of gaining weight, and a distorted perception of weight or shape (22). People with anorexia use extreme efforts to control their weight and shape. People with binge-eating disorder regularly eat too much food (binge) and feel a lack of control over their eating. On the other hand the Emesis is nothing but reflex act of ejecting the contents of the stomach through the mouth or vomiting. They may eat quickly or eat more food than intended, even when not hungry, and may continue eating even long after they are uncomfortably full (22). While in obese populations weight loss is the main goal, in other populations, such as patients with cancer or AIDS, it is an immense problem (22, 128-141). Dronabinol (synthetic THC, known as Marinol, approved for the treatment of nausea and vomiting in cancer and AIDS patients) is associated with consistent improvement in appetite (22, 128-141). It was found to be safe and effective for anorexia associated with weight loss in patients with AIDS, and is associated with increased appetite, improvement in mood, and decreased nausea (22, 128-141). In clinical trials, weight was stable in dronabinol patients, while placebo recipients lost weight (22, 128-141). Dronabinol was found to be safe and effective for the treatment of HIV wasting syndrome, as well as in patients with Alzheimer's disease and with advanced cancer (22, 128-141).

Cannabidiol (CBD) is considered as a potential therapeutic agent due to its anti-inflammatory, anti-oxidant, anti-tumor, neuroprotective, and potential anti-obesity properties (128-141). Cannabis-derived therapies are gaining popularity in the medical world. More and more perfect forms of Cannabinoids are sought, which could be used in the treatment of many common diseases, including metabolic syndrome, whose occurrence is also increasing (22, 128-141). The research results on the use of Cannabidiol in obesity are contraindicatory (22, 128-141). When it comes to glucose homeostasis, it appears that Cannabidiol (CBD) maintains it, sensitises adipose tissue to insulin, and reduces fasting glucose levels, so it seems to be a potential target in this kind of metabolic disorder, but some research results are inconclusive. Cannabidiol (CBD) showed some promising results in the treatment of various lipid disorders. Some studies have proven its positive effect by decreasing LDL and increasing HDL as well (22, 128-141). Despite their probable efficacy, Cannabidiol (CBD) and its derivatives will likely remain an adjunctive treatment rather than a mainstay of therapy. Studies have also shown that Cannabidiol (CBD) in patients with hypertension has positive effects, even though the hypotensive properties of cannabidiol are small (22, 128-141).

12) Huntington's disease

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Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), represent a significant global health challenge (142-149). Huntington's disease (HD) is a progressive brain disorder caused by a defective gene (142-149). The defective gene was identified in 1993 causes virtually all Huntington's disease (142-149). The defective gene codes the blueprint for a protein called huntingtin (142-149). This protein's normal function is not yet known, but it is called "huntingtin" because scientists identified its defective form as the cause of Huntington's disease (142-149). Defective huntingtin protein leads to brain changes that caused abnormal involuntary movements, a severe decline in thinking and reasoning skills, and irritability, depression and other mood changes (142-149). This disease caused changes in the central area of the brain, which affect movement, mood and thinking skills (142-149). These conditions are characterized by the progressive deterioration of neurons in the central nervous system, leading to debilitating symptoms and a decline in cognitive and motor functions (142-149).

The hallmark symptom of Huntington's disease is uncontrolled movement of the arms, legs, head, face and upper body (142-149). Huntington's disease also causeed a decline in thinking and reasoning skills, including memory, concentration, judgment, and ability to plan and organize (142-149). Huntington's disease brain changes lead to alterations in mood, especially depression, anxiety, and uncharacteristic anger and irritability (142-149). Another common symptom is obsessive-compulsive behavior, leading a person to repeat the same question or activity over and over (142-149). Very severe symptoms of Huntington's disease include alterations in movement, mood, and cognition with an estimated prevalence of approximately 3 cases per 100,000 (142-149). Cardinal features of Huntington's disease include neuronal death and neuro-inflammation in the striatum, globus pallidus, substantia nigra, and cerebral cortex with advanced stages of Huntington's disease exhibiting wide spread neuronal death among the cerebellum, hippocampus, and brain stem (142-149). There is currently no cure for Huntington's disease and no way to slow or stop the brain changes it causes and treatments focus on managing symptoms (142-149).

Cannabinoids possess various properties that show potential for the treatment of neurodegenerative disorders like Huntington disease, and cannabinoid administration has shown efficacy in the treatment of like Huntington disease (142-149).

A 2009 randomized controlled trial assessing the use of a synthetic cannabinoid (Nabilone) in 44 patients with Huntington disease (HD) demonstrated behavioural and symptomatic improvements in patients (142-149). Two more recent human trials, both involving the use of plant-cannabis extracts (Sativex), have shown mixed results (142-149). While one study identified no significant changes in patients' motor subscores on the Unified Huntington's Disease Rating Scale, patients participating in a second study did showed motor score improvements following the initiation of Cannabis therapy (142-149). The majority of studies showed statistically significant results favouring the use of medical marijuana, especially for improving motor symptoms and quality of sleep and further human trials are warranted (142-149).

One small scale pilot study has indicated potential therapeutic capacity of nabilone in Huntington disease (HD), having observed improvements to motor skills and participant cognition (22, 142-149). A case report also observed that medicinal Cannabis and nabilone were able to improve patient motor function and cognitive behavior (142-149). In contrast, clinical trials have observed either no significant difference in motor function and cognition with Nabiximols compared to placebo controls, failure to provide symptomatic protection with CBD, or significant increases in involuntary movements with nabilone (142-149).

Despite extensive research, effective treatments that can halt or reverse Huntington disease (HD) disease progression remain elusive (142-149). In recent years, there has been increasing interest in exploring the potential role of Medical Cannabis sativa (drug or marijuana) in the management and treatment of neurodegenerative diseases (142-149). Interestingly, emerging evidence suggests that marijuana and its constituents possess neuroprotective properties (142-149). Cannabinoids, through their interaction with the endocannabinoid system, have demonstrated anti-inflammatory, antioxidant, and anti-excitotoxic effects, which may help to combat the underlying mechanisms of neurodegeneration (142-149). The potential role of marijuana in neurodegenerative diseases is a topic that warrants careful consideration and further investigation (142-149). While the current scientific evidence is promising, more research, including well-designed clinical trials, is needed to establish marijuana's efficacy, safety, and optimal usage in the treatment of neurodegenerative conditions (142-149). Collaborative efforts between researchers, healthcare professionals, regulatory bodies, and patients are crucial in advancing our understanding and exploring the full potential of marijuana-based therapies (142-149).

Cannabinoids, including those found in Cannabis, have shown promise as potential therapeutics for numerous health issues, including pathological pain and diseases that produce an impact on neurological processing and function (22, 142-149). Thus, Cannabis use for medicinal purposes has become accepted by a growing majority. However, clinical trials yielding satisfactory endpoints and unequivocal proof that medicinal Cannabis should be considered a frontline therapeutic for the most examined central nervous system indications remains largely elusive (22, 142-149).

13) Epilepsy (Seizure disorder)

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Epilepsy is also known as a seizure or a brain disorder that causes recurring seizures (150-167). Epilepsy can be a therapeutic challenge and there are many types of epilepsy (150-167). Epilepsy is considered to be one of the most common non-communicable neurological diseases especially in low to middle-income countries (150-167). Approximately one-third of patients with epilepsy have seizures that are resistant to anti-epileptic medications (150-167). A seizure is a sudden, uncontrolled burst of electrical activity in the brain (150-167). It can cause changes in behaviour, movements, feelings and levels of consciousness (150-167). In patients with seizures, the normal electrical pattern is disrupted by sudden and synchronized bursts of electrical energy that may briefly affect their consciousness, movements or sensations (150-167). Having two or more seizures at least 24 hours apart that do not have a known cause is considered to be epilepsy (150-167). There are many types of seizures, and they have a range of symptoms and severity (150-167). Seizure types vary by where they begin in the brain and how far they spread and the most seizures last from 30 seconds to two minutes (150-167). A seizure that lasts longer than five minutes is a medical emergency and seizures can happen after a stroke or a head injury (150-167). Most of the seizure disorders can be controlled with medicine. However, managing seizures can affect daily life (150-167).

Symptoms vary based on the type of seizure (150-167). They also can range from mild to severe. Seizure symptoms may include: Temporary confusion, a staring spell, jerking movements of the arms and legs that can not be controlled, loss of consciousness or awareness, cognitive or emotional changes, fear, anxiety or a feeling that have already lived this moment (150-167). About one-third of the patients suffering from epilepsy have drug-resistant epilepsy (150-167). Drug-resistant epilepsy is associated with reduced quality of life, serious psychosocial consequences, and cognitive problems (150-167).

The off-label use of *Cannabis sativa* plant in treating seizures is known since ancient times (150-167). The active ingredients of this plant are Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD), the latter considered safer and more effective in treating seizures, and with less adverse psychotropic effects (150-167). There is an increasing interest in developing Cannabis preparations for the treatment of drug-resistant epilepsy as they are observed to be more efficacious with less side effect profile (150-167).

In one of these studies, Cannabidiol (CBD) was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome (150-167). For the first time, there is now class 1 evidence that adjunctive use of Cannabidiol (CBD) improved seizure control in patients with specific epilepsy syndromes (150-167). Another study established the feasibility of whole-plant medical Cannabis as an effective and well-tolerated medicine for reducing seizure frequency in children suffering with intractable epilepsies (166).

Approximately one third of epilepsy patients do not become seizure free with anti-seizure medications (167). This treatment gap motivates research for new therapeutic options, such as Cannabidiol (CBD) (150-167). CBD differs from other Cannabis derivatives because of its consistent efficacy and lack of a psychoactive effect (150-167). The most common adverse effects (AEs) are drowsiness, reduced appetite, diarrhea, and vomiting (150-167). The combination of Cannabidiol (CBD) and Clobazam may increase both the effectiveness and the risk of adverse effects associated with these drugs (150-167).

Cannabidiol (CBD) is a cannabinoid that lacks psychoactive effects. It has a more consistent antiepileptic efficacy than THC (167). The use of cannabis and other THC-rich products is not appropriate because of its dubious effect on seizure control and negative psychotropic effects (167). The role of Cannabidiol (CBD) in the treatment of drug-resistant epilepsy is adjuvant and often overstated. Adverse effects are usually mild, and the discontinuation rate is low (167).

14) Dravet and Lennox-Gastaut syndromes (Childhood Epilepsy)

Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS) are rare epileptic disorders classified as epileptic encephalopathies (150-186). Epileptic encephalopathies represented a group of devastating epileptic disorders that appear early in life (150-186). Therefore, Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS) are known as childhood eplepsis (150-186). It is characterized by a triad of signs, which include multiple seizure types, slow spike-wave complexes on electroencephalographic (EEG) recordings, and impairment of cognitive function (150-186).

Dravet Syndrome (DS) is an intractable pediatric epilepsy syndrome that begins in early childhood. It is characterized by frequent, prolonged seizures, developmental delay, speech impairment, ataxia, hypotonia, sleep disturbances, and other health problems (150-186). In addition to the severe comorbid conditions associated with these diseases, Dravet Syndrome (DS) has one of the highest rates of mortality due to sudden unexpected death in epilepsy, among other forms of childhood-onset epilepsy (150-186). Pharmacological treatment for both disorders is complex. Treatment options for patients with Lennox-Gastaut Syndrome (LGS) are limited because of the resistance of seizures to pharmacological treatment (150-186).

Cannabidiol (CBD), a substance extracted from the *Cannabis sativa* plant, is one of the treatments currently used for Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS) (150-186). The efficacy and safety of add-on Cannabidiol (CBD)

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in these syndromes has been demonstrated in large multicenter, randomized, double-blind, placebo-controlled clinical trials, showing a reduction in seizure frequency and a good overall tolerability (150-186).

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) currently present a therapeutic challenge. A pharmaceutical Cannabidiol (CBD) specialty (Epidyolex®) has been approved by the FDA and European Medicines Agency (EMA) for the treatment of seizures in these syndromes (150-186). However, in Italy, the use of galenic formulations versus the pharmaceutical Cannabidiol (CBD) has not been clearly regulated (150-186). The use of a pharmaceutical Cannabidiol (CBD) in Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) patients is useful for both seizure treatment and quality of life (QoL) improvement (150-186). However, further studies are needed to confirm the improvement in quality of life and the best strategy for switching from a galenic formulation to pharmaceutical Cannabidiol (CBD) (150-186).

In 2018, a plant-based pharmaceutical formulation of purified Cannabidiol (CBD) in oral solution (Epidyolex®, GW Pharmaceuticals) has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an add-on therapy, in adjunction to Clobazam, for seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients aged 2 years and over, and as add-on therapy for seizures associated with Tuberous Sclerosis Complex (TSC) in patients aged 2 years and over (150-186). This is the only approved Cannabidiol (CBD) medicine complying with the three fundamental pharmaceutical pillars of safety, quality, and efficacy, which underpin the international regulatory standards (150-186). However, currently in Italy, the use of Cannabidiol (CBD) galenic formulations in treating Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS), and other drug-resistant epilepsies is still quite widespread (150-186).

Cannabidiol (CBD) oral solution is a new AED class and the first plant-derived cannabidiol agent approved for two of the most severe and difficult-to-treat forms of childhood epilepsy, DS and LGS (150-186). Clinical benefits of the agent include a significant reduction from baseline in the frequency of convulsive seizures when compared to placebo (150-186). CBD oral solution is a strawberry-flavoured, clear-to-yellow solution supplied in a 105-mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution (100 mg cannabidiol/mL) (186). Two 5-mL calibrated oral-dosing syringes and a bottle adapter are packaged in a carton with CBD oral solution (186). The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day) and can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day) after the first week (186). If further reduction of seizures is needed, the dose may be increased to the maximum recommended maintenance dose of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily as tolerated (186).

Another study highlights that CBD has an antiseizure effect comparable to other antiseizure medications with a positive safety profile independent of the epilepsy subtype. Comedication with clobazam was not associated with a better outcome (182). Higher doses to achieve seizure frequency reduction were safe, particularly in children (182). Cannabidiol (CBD) is approved for treatment of Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) (182). Several studies suggested antiseizure effects also beyond these three epilepsy syndromes (182).

The interest in the medical use of plant-based cannabidiol (CBD), a nonpsychotropic phytocannabinoid, is high given its multiple reported effects. Several studies have highlighted its antiseizure effect in children with drug-resistant epilepsy (DRE) (182). Phase III studies of CBD reported promising effects on seizure frequency and associated problems in Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) and tuberous sclerosis complex (TSC) (182). Due to FDA, Epidyolex is approved for those epilepsy subtypes over an age of 1 year and above. Overall, CBD seems to have a good safety profile (150-182-186). CBD is considered effective in the reduction of the frequency of seizures and the improvement of neuropsychological functions, as well as vigilance and participation, resulting in an improved patients' Quality of Life (150-186). Moreover, the pharmaceutical CBD approved by a regulatory body is safer than a galenic formulation, in terms of concentration of the active compound (150-186).

15) Tourette syndrome (Tics)

Tourette syndrome is a neurodevelopmental disorder characterized by the presence of chronic motor and vocal tics (sudden, repetitive movements or sounds that are difficult to suppress and can only be delayed with difficulty) (187-194). Tourette syndrome is characterized by chronic motor and vocal tics (187-194). Onset is generally in childhood or adolescence with an estimated prevalence of 1% (187-194). Tics may persist into adulthood and individuals with persisting tics experience adversity, including discrimination and unemployment, as well as reduced quality of life (187-194). Tourette syndrome is a neurological disorder characterized by sporadic movements or vocalizations commonly called tics (187-194). Symptomatic management of tics includes drugs (e.g., a 2- adrenergic agonists or dopamine antagonists) and behavioural therapy (187-194). Effective therapies with acceptable side-effect profiles for tics are therefore needed (187-194). Tourette syndrome affects about one per cent of the population and is four times more common in men than women (187-194).

While there is currently no cure for Tourette syndrome, recent efforts have explored whether Cannabis may be effective in reducing symptoms commonly associated with the disorder (187-194). There is preliminary evidence of benefit from Cannabis products containing Λ9-tetrahydrocannabinol (THC) and that co-administration of Cannabidiol (CBD) improved the side-effect

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profile and safety (187-194). One of the study reported that severe Tourette syndrome, treatment with Λ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) reduced tics and may reduced impairment due to tics, anxiety, and obsessive-compulsive disorder (187-194). Cannabinoids are a biologically plausible therapy for tics because of their capacity to modulate the "endocannabinoid" system. The predominant endocannabinoid receptor in the central nervous system, the cannabinoid CB1 receptor (CB1R), is densely concentrated in the basal ganglia, believed to be the pathobiological nexus of Tourette syndrome (187-194). Uncontrolled observational studies have reported an association with Cannabis use and reduction in tic severity, although, until recently, only two small, randomized, placebo-controlled trials have been conducted at a single center (187-194). Both involved ingestion of capsules containing Λ9-tetrahydrocannabinol (THC), resulting in modest improvements in the frequency and severity of tics (187-194). In a recent placebo-controlled study, a single vaporized dose of Λ9-tetrahydrocannabinol (THC) was associated with a non-significant trend toward a reduction in a video-based rating of tic severity; this study was underpowered, however, because it included only nine participant (187-194).

The results of one of the study of a placebo-controlled, double-blind, crossover study investigated the effects of repeated dosing of an oral oil containing 5 mg/ml of THC and 5 mg/ml of CBD (187-194). This study adds to a small body of literature suggesting that oral 1:1 THC:CBD is an effective treatment for tics and psychiatric comorbidity associated with severe Tourette syndrome (187-194). Furthermore, the adverse-effect profile, including both sedation and increased appetite (among some participants), is similar in nature to adverse effects commonly reported with antipsychotic agents (187-194). Larger and longer trials taking the adverse-effect profile of these agents into consideration are warranted (187-194).

16) Dystonia

Dystonia is a disorder characterized by sustained or repetitive muscle contractions which resulted in abnormal fixed postures or twisting, repetitive movements (195-207). Oral pharmacological agents are generally ineffective, with repeated injections of botulinum toxin being the most effective current therapy (195-207). Stimulation of the cannabinoid receptors has been postulated as a way to reduce dystonia (195-207). Anecdotal reports have suggested that Cannabis may alleviate symptoms associated with dystonia (195-207). In a 1986 preliminary open pilot study in which five patients with dystonic movement disorders received cannabidiol, dose-related improvements were observed in all five patients (195-207).

While Cannabis-based medicine (CBM) is being commonly used in patients with movement disorders, there is a scarcity of publications regarding the effect of Cannabis on dystonia (195-207). A subset of dystonia patients who used medical Cannabis under clinical observation reported significant subjective improvement during 30 months of use in average (195-207). Further prospective randomized controlled trials are required to examine the effectiveness of Cannabis in dystonia (195-207). One of the study indicated that Λ9-tetrahydrocannabinol (THC)-containing medical Cannabis products may be a promising starting point for further research into the therapeutic benefits of Cannabis based-medicine (CBM) for dystonia in patients with widespread symptoms (195-207). However, more randomized, placebo-controlled studies are necessary to determine the most effective THC dose, with or without the addition of Cannabidiol (CBD) and other Cannabinoids (195-207).

17) Sleep Disorders

Sleep is a biological necessity that enables restorative functions that are essential for normal daytime function (208-225). Approximately 30% of the general population report poor sleep, which may be attributed to lifestyle choices, environmental factors, and/or the presence of an untreated sleep disorder or other medical complaints such as pain (208-225). The behavioural interventions such as cognitive behavioural therapy for insomnia (CBT-I) are the mainstay of treatment pharmaceutical sleep aids such as benzodiazepines and Z-drugs (208-225). However, such drugs are often associated with undesirable side effects and should not be used long term, leading to an upsurge of interest into alternative treatments (208-225). Sleep disorders are the third most common indication for the prescription of medical Cannabis products in Australia, after pain and anxiety (208-225). While the use of cannabis for medical purposes is growing in Australia, underlying consumer behaviours and patterns of use, particularly around sleep disorders, are poorly understood (208-225).

Medical Cannabis is becoming an increasingly popular alternative to common sleep aids (208-225). In Australia, consumer surveys showed that sleep disorders were the third most common indication treated with medical cannabis (either illicit or prescribed), after pain and mental health disorders (208-225). In the US, a recent survey showed that 74% of people accessing Cannabis through adult-use markets in Colorado reported effective treatment for sleep, with a concomitant reduction in the use of prescription sleep aids (208-225). In Canada, 92.6% of patients using prescribed medical Cannabis reported a significant improvement in their sleep after six weeks of treatment (208-225).

One of the study provides a snapshot of medical cannabis use for self-reported sleep disorders among a sample of individuals in Australia at a timepoint four years after the regulatory changes that permitted patient access to legal medical Cannabis (208-225). These results suggested that self-reported sleep disorders, in particular insomnia disorder, are often being treated secondary to, or in addition to, a comorbid health condition such as a chronic pain, or a mental health disorder (208-225).

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The use of inhaled routes of administration, THC-dominant products, and illicit sources of medical Cannabis are common among people with self-reported sleep disorders in Australia (208-225).

Another study suggested that chronic use of a low dose of CBD is safe and could improve sleep quality, though these effects do not exceed that of 5 mg melatonin (208-226). Moreover, the addition of low doses of CBN and CBC may not improved the effect of formulations containing CBD or melatonin isolate (226). Cannabis preparations have also begun to gain attention for their potential therapeutic effects for the treatment of insomnia and other sleep disorders (208-226). To date, the preponderance of clinical research on Cannabis and sleep has focused on Δ9-tetrahydrocannabinol (Δ9-THC), the major active constituent of Cannabis sativa (208-226). Yet use of the non-psychoactive cannabinoid Cannabidiol (CBD) has proliferated in the US, with many new users seeking relief for sleep difficulties (208-226). Preclinical research has demonstrated that CBD possesses anxiolytic, anti-inflammatory, and analgesic properties, which could aid in the improvement of sleep (208-226). Evidence from retrospective and prospective observational studies also suggest that the clinical administration of cannabinoids could improve sleep and other related health issues such as pain and anxiety (208-226).

Clinical research assessing the use of CBD for insomnia and other sleep disorders remains limited, though some small clinical studies have found support for the hypothesis that CBD may improved sleep (226). In a study of 15 individuals with insomnia, those who received 160 mg CBD reported sleeping longer than those who received placebo (226). Another study of 33 individuals with Parkinson's Disease revealed that 300 mg of CBD per day led to a transient improvement in sleep quality relative to placebo (226). Importantly, clinical evidence of CBD also indicated that the cannabinoid has a favorable safety profile, even when taken at doses as high as 1200 mg daily for up to 4 weeks, supporting the exploration of CBD as a potentially safer therapeutic option for the improvement of sleep (226).

Despite the limited clinical evidence, marketing claims regarding the effectiveness of CBD for sleep abound (226). Many manufacturers have also touted the superiority of their CBD products relative to melatonin, though, to date, no clinical study has directly compared the effects of these compounds on sleep (226). Manufacturers have also combined CBD with melatonin and other minor cannabinoids, claiming that these additions could enhance the effect of CBD or melatonin alone (226-227). Melatonin has been called the Hormone of darkness (227). These claims, too, are unfounded (226-227). No large scale randomized clinical trial has evaluated whether CBD could impact the effects of melatonin on sleep (or vice versa) (226). No clinical trials have also evaluated whether the addition of minor cannabinoids, such as Cannabichrome (CBC) and Cannabinol (CBN), could contribute to the therapeutic effectiveness of CBD for sleep improvement (226). CBN, in particular, has gained prominence as a sleep aid additive, though the literature is almost entirely devoid of clinical research supporting its effect on sleep quality (226). Most clinical trials of CBD evaluated doses ranging from 300 to 1500 mg CBD per day, while commercial products' dosage generally range from 5 to 100 mg CBD per day (226). Therefore, more clinical studies are needed to evaluate the therapeutic benefits of chronic CBD use for sleep at dose ranges reflecting that of commercial products (226).

18) Traumatic brain injury (TBI)/ Intracranial hemorrhage (ICH)

Traumatic brain injury (TBI) is an acquired brain injury that can result from a sudden or violent hit to the head (228-231). Traumatic brain injury (TBI) is a common event associated with motor vehicle accidents, sports, assaults, and intimate partner violence (228-231). TBI occurs on a severity spectrum of mild to severe injury. Intracranial hemorrhage (ICH), bleeding that occurs inside the skull, is a common complication of TBI which is associated with a worse prognosis of the injury (228-231). Despite great clinical need there are currently no approved pharmaceutical interventions that improved outcomes after traumatic brain injury (228-231). Traumatic Brain Injury (TBI) is a global public health epidemic that causes death or hospitalization in an estimated 27–69 million people annually (228-231).

There is a small body of literature reporting the neuroprotective effects of cannabinoid analogues in preclinical studies of head injuries as well as in observational studies in humans (228-231). Increased understanding of the endocannabinoid system in health and disease has accompanied growing evidence for therapeutic benefts of *Cannabis sativa* (228-231). Cannabinoids interact with neurons, microglia, and astrocytes, and exert anti-infammatory and neuroprotective effects which are highly desirable for the management of traumatic brain injury (228-231).

The endocannabinoid system is increasingly recognized for its physiological role in regulating cellular activity in the brain and endogenous response to adverse events, such as TBI (228-231). The ability to modulate this system with endogenous, plant-derived, or synthetic cannabinoids is promising for the development of therapeutic strategies for TBI (228-231). Presently, the strongest evidence for neuroprotective properties is seen for compounds containing CBD, or those targeting CB2R, and the efects of THC treatment are less consistent (228-231). CBG (and its derivatives) is the most studied minor phytocannabinoid in neurological disease models, while the most evidence for therapeutic beneft from terpenes relates to BCP, although studies are limited overall (228-231).

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While the number of studies in preclinical models of TBI has increased with generally positive results, data from clinical populations remain limited. The only cannabinoid-based synthetic pharmaceutical to undergo randomized controlled trials in TBI was Dexanabinol, and it was found not effective (228-231). However, the growing literature of cannabinoids in TBI remains promising and further research is warranted (228-231). Diseases with complex, multifaceted pathology, such as TBI, may require treatment that is multi-mechanistic, such as whole plant Cannabis extracts (228-231). Dexanabinol is a synthetic cannabinoid that has been tested in phase II and phase III clinical trials in TBI patients (228-231). Dexanabinol is non-psychoactive and is an antagonist at NMDA receptors with anti-oxidant and anti-infammatory properties (228-231). Cannabidiol (CBD) has numerous pharmacological targets that initiate antiinflammatory, antioxidative, and antiepileptic properties (228-231). These neuroprotective benefits have generated interest in CBD's therapeutic potential against the secondary injury cascade from traumatic brain injury (TBI) (228-231).

Research into Cannabidiol (CBD), a non-intoxicating phytocannabinoid abundantly produced by some chemovars of *Cannabis sativa* L or synthetically produced from several biological systems, has revealed promising protective properties to counter the damaging effects of TBI that warrant concentrated investigation (228-231). Cannabidiol (CBD), unique pharmacodynamic profile and high tolerability in adults affords unique capabilities not shared by currently available treatment strategies (228-231). Cannabidiol (CBD)'s, proposed protective mechanisms against TBI-induced neuroinflammation and degeneration, which may be a plausible intervention for treating and reducing physiological damage and the associated symptoms that arise from TBI (228-231). There is strong mechanistic support that CBD could be an effective pharmacological intervention for TBIs (228-231). However, the current state of the research field is mostly derived from rodent studies (228-231). The mechanistic evidence provided by pre-clinical research showed great potential for CBD as a much-needed improvement in the clinical treatment of TBI (228-231).

19) Posttraumatic stress disorder (PTSD)

Post-traumatic stress disorder (PTSD) is a mental disorder that can develop after a person is exposed to a traumatic event, such as threatened or actual death, serious injury, or sexual violence (232-235). Exposure can be direct, as a witness, as learning a traumatic event happened to a close person, or as repeated or extreme exposure to details of a traumatic event, such as during a line of work (232-235). The clinical presentation varies, and symptoms may include: Fear-based re-experiencing (such as in intrusive recollections, nightmares, or dissociative states), intense physiological or psychological distress when exposed to triggering cues that remind of the traumatic events and persistent avoidance of such cues (internally or externally), negative alterations in cognition or mood including difficulty in remembering important parts of the event, negative expectations about oneself, others or the future (232-235). Persistent negative mood states with decreased ability to feel positive feelings (232-235).

Given the known psychoactive effects of Cannabis, the committee decided to explore the association between PTSD and Cannabis use (232-235). Targeting the endocannabinoid system may have a role in the treatment of post-traumatic stress disorder (PTSD) (232-235). However, few studies have examined the effectiveness of Cannabis on symptoms of PTSD, and more research is needed to ascertain Cannabis effectiveness (232-235). One of the study showed that total sleep score, subjective sleep quality, and sleep duration significantly improved ($p < 0.01$). Total PTSD symptom score and its subdomains (intrusiveness, avoidance, and alertness) showed improvement ($p < 0.05$) (232-235). However, there was no improvement in the frequency of nightmares ($p = 0.27$) (232-235). This study reported consistent with existing literature which indicated a decrease in PTSD symptoms under medical Cannabis treatment (232-235). There are still very few studies examining the effectiveness of medical Cannabis for PTSD patients. This study results suggested the importance of the selection process in terms of patients receiving medical Cannabis (232-235). Future research should clarify the long-term effects of Cannabis on different groups of patients suffering from PTSD (232-235).

Another study reported that strong prospective associations capturing within-person changes suggested that Cannabis use is linked with greater severity of trauma-related intrusion symptoms over time (235). Findings have significant clinical implications for the long-term effects of Cannabis use among individuals with PTSD (235). Posttraumatic stress disorder (PTSD) is the most highly co-occurring psychiatric disorder among veterans with Cannabis use disorder (CUD) (235). Despite some evidence that Cannabis use prospectively exacerbates the course of PTSD, which in turn increases the risk for CUD, the causal nature of the relationship between Cannabis and psychiatric comorbidity is debated (235). In the absence of well-controlled evidence on the long-term efficacy of cannabinoids in improving the symptoms of PTSD, findings based on the statistically rigorous models utilized and other prospective studies do not support the widespread state-sanctioned medical use of Cannabis for the treatment of PTSD (235).

20) Marijuana Drug Addiction

Cannabis drug addiction has been defined as a chronically relapsing disorder that is characterized by the compulsive desire to seek and use drugs with impaired control over substance use despite negative consequence (236-240). Cannabis

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dependence is a substantial public health problem. Behavioural treatments have shown promise, but there are no effective medications for Cannabis dependence (236-240). Cannabis use peaks during adolescence and emerging adulthood, and Cannabis use disorder (CUD) is associated with a wide range of adverse outcomes (236-240). This is particularly pertinent in youth, because the developing brain may be more vulnerable to adverse effects of frequent Cannabis use (236-240).

Medical *Cannabis sativa* L.(drug type or Marijuana) has surpassed heroin and cocaine as the most common illicit drug listed as the primary problem among patients seeking substance abuse treatment, with nearly 300,000 marijuana-related treatment admissions per year (236-240). Several medications have shown potential benefit in reducing some withdrawal symptoms (e.g. mitrazapine, nefazadone) whereas other medications have not shown any clear benefit in mitigating withdrawal symptoms (e.g., bupropion, divalproex) or in reducing the likelihood of relapse (e.g., baclofen) in the laboratory setting (236-240). Dronabinol has been shown to reduce Cannabis withdrawal symptoms in laboratory settings among non-treatment seeking Cannabis users (236-240). Although dronabinol produced modest positive subjective effects among cannabis users in the laboratory, there is little evidence of abuse or diversion of dronabinol in community settings (236-240).

Furthermore, in laboratory settings orally administered Dronabinol has been found to reduce Cannabis withdrawal symptoms in cannabis users who were not seeking treatment to reduce Cannabis, and therefore may be expected to be useful as a substitute to assist to achieve and maintain abstinence of cannabis (236-240). This is the first trial using an agonist substitution strategy for treatment of cannabis dependence (236-240). Dronabinol showed promise, it was well-tolerated, and improved treatment retention and withdrawal symptoms (236-240).

One of the study reported that agonist substitution pharmacotherapy with dronabinol, a synthetic form of THC, showed promise for treatment of cannabis dependence, reducing withdrawal symptoms and improving retention in treatment, although it failed to improve abstinence (236-240). The trial showed that among adult Cannabis-dependent patients, dronabinol was well accepted, with good adherence and few adverse events (236-240). Future studies should consider testing higher doses of Dronabinol, with longer trial lengths, combining dronabinol with other medications acting through complementary mechanisms or more potent behavioural interventions (236-240). Dronabinol is an oral form of Λ-9-tetrahydrocannabinol indicated for treatment of anorexia associated with weight loss in individuals with AIDS, and nausea and vomiting associated with cancer chemotherapy (236-240).Cannabis dependence is a substantial but underappreciated clinical problem (236-240). Based on recent laboratory studies, dronabinol (delta-9-tetrahydrocannabinol) has been shown to reduce cannabis withdrawal symptoms and the subjective effects of marijuana (236-240). Given that agonist agents have been found to be effective for opiate and nicotine dependence, the clinical utility of dronabinol for cannabis dependence is a reasonable approach (236-240).

Evidence from placebo-controlled RCTs suggests that synthetic delta-9-tetrahydrocannabinol (THC) decreases withdrawal symptoms, but not cannabis use, in adults with daily cannabis use/CUD, while findings regarding formulations containing THC combined with cannabidiol (CBD) are mixed (236-240). Preliminary evidence from two placebo-controlled RCTs in adults with CUD suggests that both Fatty Acid Amide Hydrolase inhibitors and CBD can reduce cannabis use (236-240). However, larger trials are needed to strengthen the evidence. In the longer run, once tolerability and safety of cannabinoid treatment strategies have been established in youth, more specific target groups and treatment strategies could be further explored (236-240). However, due to the discussed risks and concerns associated with THC administration, this approach required careful ethical and clinical considerations (236-240).

21) AIDS Wasting Syndrome

Wasting syndrome refers to unwanted weight loss of more than 10 percent of a person's body weight, with either diarrhea or weakness and fever that have lasted at least 30 days (241-243). For a 150-pound man, this means a weight loss of 15 pounds or more. Weight loss can result in loss of both fat and muscle. Once lost, the weight is difficult to regain (241-243). The condition may occur in people with advanced HIV disease, and can be caused by many things: HIV, inflammation, or opportunistic infections (241-243). The person may get full easily or have no appetite at all (241-243). The most important treatment for wasting syndrome is effective treatment of HIV with antiretroviral medications (241-243). In addition, the condition may be controlled, to some degree, by eating a good diet. A "good diet" for a person with HIV may not be the low-fat, low-calorie diet recommended for healthy people (241-243).

Wasting syndrome is a common complication of HIV infection and is marked by progressive weight loss and weakness, often associated with fever and diarrhea (241-243). Considerations include inadequate diet, malabsorptive phenomena, metabolic derangements, and cytokine activity (241-243). Potential cytokines that may promote weight loss in AIDS patients include tumour necrosis factor, interleukin-1, interleukin-6, and alpha-interferon and at present there is no effective treatment (243).

One of the study concluded that there was some evidence suggesting that cannabinoids were effective in weight gain in HIV (241-243). The trials compared dronabinol or inhaled cannabis with a placebo or with each other. In one of the study the

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individuals' weights increased significantly more ($p < 0.01$) on higher doses of cannabis (3.9 percent THC) and dronabinol (10 mg) than on lower doses. In a second trial, median weight was increased with inhaled Cannabis (3.5 percent) by 3.0 kg ($p = 0.021$) and dronabinol (2.5 mg) by 3.2 kg ($p = 0.004$) when compared with a placebo (a 1.1-kg increase over a 21-day exposure) (241-243). In a study with 88 evaluable patients, the dronabinol group gained an average of 0.1 kg, while the placebo recipients lost a mean of 0.4 kg ($p = 0.14$). These investigators concluded that the evidence for the efficacy and safety of Cannabis and cannabinoids is lacking to support utility in treating AIDS-associated anorexia (241-243).

Marijuana and cannabinoids reduced the nausea and vomiting brought on by AIDS medications remains to be determined in the clinic (241-242). Another factor also may contribute to the popularity of medicinal marijuana among people with AIDS: the drug's purported ability to soothe a variety of debilitating symptoms (241-242). Many such patients echo the comments of the HIV-positive man cited in one of the chapter who claimed that marijuana calmed his stomach after taking medication, stimulated his appetite, eased his pain, and lifted his mood (241-242). Because HIV attacks the immune system, it wreaks havoc throughout the body. Finally, in addition to the physical discomforts inflicted by HIV, many people with AIDS also struggled with depression and anxiety (241-242). Marijuana, some patients confirmed, eases all of these problems and more. In the meantime, some people with AIDS who take THC in the form of dronabinol (Marinol) to combat weight loss may also find that it reduces their feelings of nausea (241-242). AIDS patients who took the drug in a four-week clinical study showed a trend toward decreased nausea compared with those who took a placebo, as well as a significant increase in appetite (241-242). In addition to appetite stimulation, marijuana-based medicines may proved helpful in treating a variety of painful symptoms associated with AIDS (241-242). In particular, many AIDS patients suffered from neuropathic pain, a burning sensation of the skin that occurs spontaneously or is triggered by even the most gentle touch (241-242).

22) Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal neurodegenerative disorder that is characterized by the selective loss of motor neurons in the spinal cord, brain stem, and motor cortex (244-249). The average life expectancy of ALS patients is three to five years post diagnosis. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons in the spinal cord, brain stem, and motor cortex, ultimately leading to complete paralysis (244-249). The pathogenesis of ALS remains unclear, but the disease is thought to result from the interplay of a number of mechanisms, including neurofilament accumulation, excitotoxicity, oxidative stress, and neuro-inflammation all of which may be amenable to manipulation of the endocannabinoid system and cannabinoid receptors (244-249). Cannabis may have therapeutic benefits to relieve symptoms of amyotrophic lateral sclerosis (ALS) (244-249).

One of the study is the first to present a large questionnaire-based survey about the "real-life" situation regarding Cannabis use in the medical context in ALS patients in France (244-245). There were 129 respondents and 28 reported the use of cannabis (21.7%) to relieve symptoms of ALS. Participants mostly reported the use of Cannabidiol (CBD) oil and Cannabis weed and declared benefits both on motor (rigidity, cramps, fasciculations) and non-motor (sleep quality, pain, emotional state, quality of life, depression) symptoms and only eight reported minor adverse reactions (drowsiness, euphoria and dry mouth) (245). Even if Cannabis is mostly used outside medical pathways and could expose patients to complications (street and uncontrolled drugs, drug-drug interactions, adverse effects…), most of the participants reported "rational" consumption (legal cannabinoids, with only few combustion and adverse reactions) (244,245-249). Despite some limitations, this study highlights the need for further research on the potential benefits of Cannabis use for the management of ALS motor and non-motor symptoms (245).

23) Depression and Anxiety

Anxiety and depression disorders share features of excessive fear and anxiety which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (250-253). annabis is a drug that has had a somewhat troubled relationship with psychiatry (250-253). Frequency of Cannabis use was not associated with improved pain, anxiety, or depression symptoms but was associated with new-onset Cannabis use disorder in a significant minority of participants (250-253). Daily or near-daily Cannabis use appears to have little benefit for these symptoms after 12 months of use (250-253). The most common conditions for which individuals obtain medical cannabis cards in USA are pain, insomnia, anxiety and depressed mood, but evidence for the efficacy of cannabis to treat these symptoms has been mixed (250-253).

One of the study reported 9-month follow-up study of a 12-week randomized clinical trial of medical cannabis card ownership in USA and found an association between more frequent cannabis use and increased CUD risk, with no significant improvement in pain, anxiety, insomnia, or depression symptom severity as a function of Cannabis use (250-253). The current findings call into question the long-term utility of cannabis as an effective tool in relieving clinical symptoms (250-253). The lack of benefit from Cannabis indicated that individuals with these chronic conditions should consider evidence-based treatments.

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There is an increase in the medical use of cannabis. However, the safety of medical Cannabis, particularly for mental health conditions, has not yet been clearly established (250-253). Another study also confirmed that medical Cannabis authorization was associated with an increased risk of depressive disorders (250-253). This finding highlights the need for a careful risk-benefit assessment when authorizing Cannabis, particularly for patients who seek Cannabis to treat a depressive condition (250-253).

Two recent systematic reviews and meta-analyses concluded there may be some evidence supporting efficacy for cannabinoids in treating anxiety, but that evidence was of very low quality, with a third analysis showing no effect when studies were corrected for publication bias (250-253). The high prevalence of THC-containing products being prescribed is of possible concern given the psychiatric problems associated with this drug (250-253). Evidence-based clinical guidance around the use of medical Cannabis products in psychiatry is lacking and would clearly be of benefit to prescribers (250-253). Not only is there a paucity of evidence to support the use of medical Cannabis to treat conditions such as anxiety and depression, the available data are conflicting, with some data that support its use, and other data to suggest that it may deteriorate or worsen an individual's anxiety or depression, which has led to circumstances that are challenging for patients, physicians and policymakers to navigate (250-253).

Another clinical study in Canada provides some evidence to support the effectiveness of medical Cannabis as a treatment for anxiety and depression (253). However, despite the lack of clinical evidence, when surveyed, the majority of patients using medical Cannabis for anxiety or depression report an improvement in their symptoms and a positive impact on their quality of life (253).

24) Diabetes mellitus

Diabetes mellitus (DM) is a chronic endocrine disorder which is characterized by high blood glucose levels that can interfere with carbohydrate, protein, and fat metabolism (271-279). Diabetic patients defects in insulin secretion or insulin action or both (271-279). Effective treatment of diabetes is still a major challenge in spite of approved drugs such as biguanides, metformin, Januvia (Sitagliptin phosphate tablets), thiazolidinediones, sulfonylureas, a-glucoside inhibitors, thiazolidinediones, and insulin for the diabetes (271-279). However, all these pharmaceutical drugs have serious harmful side effects. Traditional plants are reported to have significant anti-diabetic properties with no harmful side effects (271-279). Ayurveda offers comprehensive safe and effective approaches to manage diabetic disorder (275-279). Ayurvedic treatment is effective to reduce the side effects and to improve general well-being of the diabetic patient (275-279).

Cannabis consumption exerts multiple effects on metabolism via various pathways, including glucose regulation and insulin secretion (271-272). Studies concerning the association between cannabis use and diabetes mellitus type 2 are discrepant. A protective effect of cannabis consumption on the odds of diabetes mellitus type 2 development has been suggested (271-272). Recent surveys of Canadian Cannabis users reflect increasing consumption rates, some of whom may have diabetes. However, healthcare providers have limited information resources on the effects of recreational Cannabis in people with diabetes. According to the review commissioned by Diabetes Canada to synthesize available evidence to guide recommendations for care of people 13 years of age and older who lived with diabetes (274). Recreational Cannabis use may negatively impact diabetes metabolic factors and self-management behaviours in people with Type- 1-diabetes (274). In people with Type-2-diabetes, recreational Cannabis may increase risks for peripheral arterial occlusion, myocardial infarction and renal disease (274). However, the evidence base of this rapid review was limited to six observational studies of poor to fair methodological quality, and thus, further robust, higher quality research is required to confirm the potential impact of cannabis on diabetes (274).

One of the study in Iran evaluated the safety profile and efficacy of a Cannabis-based sublingual spray, CBDEX10® (containing 100 μg cannabidiol and 10 μg Δ9 -tetrahydrocannabinol per puff; CBD/Δ9 -THC 10:1), in improving lipid profile and glycemic state of the diabetic patients (273). Fifty diabetic patients were randomly allocated to the treatment (n = 25; receiving two puffs of CBDEX10® twice daily) or the control groups (n = 25; receiving two puffs of placebo) (273). Regarding safety, the mentioned adjunctive regimen was well, and there were no serious or severe adverse effects. Overall, CBDEX1® sublingual spray could be a new therapeutic agent for lipid and glycemic control in diabetic patients (273). Diabetic patients administered a sublingual spray containing CBD and THC showed improvements in their blood sugar and cholesterol levels (273).

25) Migraine (Headache disorder)

Migraine is a primary headache disorder and a clinical syndrome that is characterized by nausea, vomiting, photophobia, and phonophobia (280-298). Globally, migraine is a common disorder and the second leading cause of disability in both males and females younger than 50 years (280-298). It is estimated that migraine affects 1 billion people worldwide and 37 million people in the United States, with a prevalence of 20.7 and 9.7% in females and males, respectively (280-298). Migraine is either episodic or chronic. Episodic migraines occur fewer than 15 days in a month, while chronic migraine is present ≥15 days per month (280-298). Chronic headaches have adverse effects on social relationships, job and may cause family distress. The usual

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treatment modalities for migraine include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) (280-298). Although 47% of patients who had surgery reported complete elimination of migraine, some people with chronic migraine did not have any benefits, despite the risks of surgical exposure (280-298). This has led both physicians and patients to try dietary and herbal remedies, including the use of medical cannabis (MC) for migraine treatment (280-298).

Globally, disability due to migraine headaches is enormous, yet the commonly used medical treatments for episodic or chronic migraines have disturbing short- and long-term adverse (280-298). There is promising evidence that medical *Cannabis sativa* (drug or Marijuana) may have a beneficial effect on the onset and duration of migraine headaches in adults. However, well-designed experimental studies that assess medical Cannabis's effectiveness and safety for treating migraine in adults are needed to support this hypothesis (280-298).

Patient-reported relief of migraine symptoms has fuelled recent interest in the use of medical Cannabis for migraines. In a survey of medical use of Cannabis products in Germany, Austria, and Switzerland, 10.2% of patients with migraine reported self-use of Cannabis (280-298). Also, 35% of respondents reported using medical Cannabis for headaches/ migraine in another study (280-298). However, there is limited compelling evidence of its effectiveness in treating migraines (280-298). In addition to a lack of empirical evidence to support medical Cannabis's safe use for migraine, there is some evidence that long-term or high-dose marijuana may pose health risks and exacerbate headaches (280-299). In the State of Arizona, United States, medical Cannabis use is predominantly (94%) for chronic pain, including migraines, by medical Cannabis cardholders (280-299).

Medical Cannabis was effective in decreasing daily analgesic intake, dependence, and level of pain intensity (280-299). Some patients experienced a prolonged and persistent improvement in their health and well-being (both physically and mentally) after long-term use of medicinal Cannabis (280-299). Overall, patients reported more positive effects rather than adverse effects with medical cannabis use (280-299). Chronic pain and mental health are the two reasons where medical cannabis is used often. Further research should be performed to determine a favorable delivery method, dose, and strain for migraine and chronic headache management and possible long-term effects of medical Cannabis use (280-299).

26) Covid-19 (SARS-CoV-2)

The SARS-CoV-2 pandemic has swept the world and poses a significant global threat to lives and livelihoods (300-319). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV- 2) is a novel coronavirus responsible for human pandemic (COVID-19). Coronaviruses are the large family of enveloped single- stranded positive -sense RNA viruses (300-319). Coronavirus disease-19 caused by the novel RNA betacoronavirus SARS-CoV2 has first emerged in Wuhan, China in December 2019, and since then developed into a worldwide pandemic with >99 million people afflicted and >2.1 million fatal outcomes as of 24th January 2021 (300-319). SARS-CoV-2 targets the lower respiratory tract system leading to pneumonia with fever, cough, and dyspnea (300-319). Most patients developed only mild symptoms (300-319). Most of the COVID-19 symptoms are related to hyperinflammation as seen in cytokine release syndrome and it is believed that fatalities are due to a COVID-19 related cytokine storm (300-319).

Herbal medicine is the use of medicinal plants for the prevention and treatment of diseases (300-319). Cannabis is a plant notorious for its psychoactive effect, but when used correctly, it provides a plethora of medicinal benefits (300-303). With more than 400 active compounds that have therapeutic properties, Cannabis has been accepted widely as a medical treatment and for recreational purposes in several countries (300-306). The compounds exhibit various clinical benefits, which include, but are not limited to, anticancer, antimicrobial, and antioxidant properties (300-303). Among the vast range of compounds, multiple research papers have shown that cannabinoids, such as cannabidiol and delta-9-tetrahydrocannabinol, have antiviral effects (300-303). The role of cannabis compounds in combating viral infections and the potential of both cannabinoids and terpenes as novel antiviral therapeutics has been reviewed (300-306).

One of the study reported that Cannabidiol (CBD) inhibits infection of SARS-CoV-2 in cells and mice (300-301). CBD and its metabolite 7-OH-CBD, but not THC or other congeneric cannabinoids tested, potently block SARS-CoV-2 replication in lung epithelial cells (300-306). Cannabidiol (CBD) acts after viral entry, inhibiting viral gene expression and reversing many effects of SARS-CoV-2 on host gene transcription (300-301). Cannabidiol (CBD) inhibits ribonuclease endoplasmic reticulum (ER) stressα SARS-CoV-2 replication in part by up-regulating the host IRE1 response and interferon signaling pathways (300-301). In matched groups of human patients from the National COVID Cohort Collaborative, Cannabidiol (CBD) (100 mg/ml oral solution per medical records) had a significant negative association with positive SARS-CoV-2 tests (300-301). This study highlights Cannabidiol (CBD) as a potential preventative agent for early-stage SARS-CoV-2 infection and merits future clinical trials (300-301). Cannabidiol (CBD) induces interferon expression and up-regulates its antiviral signaling pathway (300-301). A cohort of human patients previously taking CBD had significantly lower SARSCoV- 2 infection incidence of up to an order of magnitude relative to matched pairs or the 10 general population (300-301). This study highlights CBD, and its active metabolite,

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7-OH-CBD, as potential preventative agents and therapeutic treatments for SARS-CoV-2 at early stages of infection. Therefore, this study cautioned against current use of non-medical formulations as a preventative or treatment therapy (300-306).

Inhibition of viral entry and thereby spread constitute plausible therapeutic avenues. Similar to other respiratory pathogens, SARS-CoV2 is transmitted through respiratory droplets, with potential for aerosol and contact spread (302). It uses receptor-mediated entry into the human host via angiotensin-converting enzyme II (ACE2) that is expressed in lung tissue, as well as oral and nasal mucosa, kidney, testes, and the gastrointestinal tract (302). Modulation of ACE2 levels in these gateway tissues may prove a plausible strategy for decreasing disease susceptibility (302). Cannabis sativa, especially one high in the antiinflammatory cannabinoid Cannabidiol (CBD), has been proposed to modulate gene expression and inflammation and harbour anti-cancer and anti-inflammatory properties (302). Working under the Health Canada research license, Canada, one of the research study developed over 800 new *Cannabis sativa* lines and extracts and hypothesized that high-CBD *Cannabis sativa* extracts may be used to modulate ACE2 expression in COVID-19 target tissues (302). Screening of *Cannabis sativa* extracts using artificial human 3D models of oral, airway, and intestinal tissues, this study identified 13 high CBD C. sativa extracts that modulate ACE2 gene expression and ACE2 protein levels (302). Experimental initial data suggested that some C. sativa extract down-regulate serine protease TMPRSS2, another critical protein required for SARS-CoV2 entry into host cells (302). While the most effective extracts required further large-scale validation, and this study is crucial for the future analysis of the effects of medical cannabis on COVID-19 (302). The extracts of the most successful and novel high CBD C. sativa lines, pending further investigation, may become a useful and safe addition to the treatment of COVID-19 as an adjunct therapy (302). They can be used to develop easy-to-use preventative treatments in the form of mouthwash and throat gargle products for both clinical and at-home use (302). Such products ought to be tested for their potential to decrease viral entry via the oral mucosa (302). Based on our preliminary data, extracts of novel efficacious C. sativa lines, pending further investigations, may become a useful addition to the treatment of COVID-19, and an excellent GRAS adjunct therapy (302).

Recently, another study found that both compounds can reduce severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral infection by downregulating ACE2 transcript levels and by exerting anti-inflammatory properties (300-303). These compounds also act as the SARS-CoV-2 main protease inhibitors that block viral replication. Apart from cannabinoids, terpenes in cannabis plants have also been widely explored for their antiviral properties (300-303).

Hemp compounds identified by Oregon State University, USA research via a chemical screening technique invented at OSU showed the ability to prevent the virus that causes COVID-19 from entering human cells (304). As a complement to vaccines, small-molecule therapeutic agents are needed to treat or prevent infections by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its variants, which cause COVID-19 (300-304). Affinity selection−mass spectrometry was used for the discovery of botanical ligands to the SARS-CoV-2 spike protein (304). Cannabinoid acids from hemp (*Cannabis sativa* L.) were found to be allosteric as well as orthosteric ligands with micromolar affinity for the spike protein (304). In follow-up virus neutralization assays, cannabigerolic acid (CBG) and cannabidiolic acid prevented infection of human epithelial cells by a pseudovirus expressing the SARS-CoV-2 spike protein and prevented entry of live SARS-CoV-2 into cells (304). Importantly, cannabigerolic acid and cannabidiolic acid were equally effective against the SARS-CoV-2 alpha variant B.1.1.7 and the beta variant B.1.351 (300-304). Orally bioavailable and with a long history of safe human use, these cannabinoids, isolated or in hemp extracts, have the potential to prevent as well as treat infection by SARS-CoV-2 (300-304).

Recently, the therapeutic potential of phytocannabinoids, the unique active compounds of the cannabis plant, has been discovered in the area of immunology (305). Phytocannabinoids are a group of terpenophenolic compounds which biological functions are conveyed by their interactions with the endocannabinoid system in humans (305). Another study explored the anti-inflammatory function of cannabinoids in relation to inflammatory events that happen during severe COVID-19 disease, and how cannabinoids might help to prevent the progression from mild to severe disease (305).

Cannabis sativa L. is widely used for medical purposes and has anti-infammatory activity. Another study intended to examine the anti-infammatory activity of cannabis on immune response markers associated with coronavirus disease 2019 (COVID-19) infammation (300-306). An extract fraction from C. sativa Arbel strain (FCBD) substantially reduced (dose dependently) interleukin (IL)-6 and -8 levels in an alveolar epithelial (A549) cell line (306). FCBD contained cannabidiol (CBD), cannabigerol (CBG) and tetrahydrocannabivarin (THCV), and multiple terpenes (306). Treatments with FCBD and a FCBD formulation using phytocannabinoid standards (FCBD:std) reduced IL-6, IL-8, C–C Motif Chemokine Ligands (CCLs) 2 and 7, and angiotensin I converting enzyme 2 (ACE2) expression in the A549 cell line (300-306). Treatment with FCBD induced macrophage (diferentiated KG1 cell line) polarization and phagocytosis in vitro, and increased CD36 and type II receptor for the Fc region of IgG (FcγRII) expression (306). FCBD treatment also substantially increased IL-6 and IL-8 expression in macrophages. FCBD while maintaining antiinfammatory activity in alveolar epithelial cells, led to reduced phagocytosis and pro-infammatory IL secretion in macrophages in comparison to FCBD (300-306). The phytocannabinoid formulation may show

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superior activity versus the cannabis-derived fraction for reduction of lung infammation, yet there is a need of caution proposing Cannabis as treatment for COVID-19 (306).

Cannabis strains produce more than 500 compounds, including phytocannabinoids, terpenes and flavonoids (306). Cannabinoids have been suggested to be immune modulators and to change the balance between pro- and anti-infammatory cytokines (306). Cannabinoids can also infuence macrophage activity. For example, Δ9-tetrahydrocannabivarin (THCV) inhibits nitrite production and IL-1β protein levels in lipopolysaccharide activated macrophages (306). Further, Δ9-tetrahydrocannabinol (THC) can inhibit macrophage phagocytosis by 90% (306). Cannabidiol (CBD) is also suggested to have anti-infammatory efects in various conditions (300-306). For example, CBD increases intracellular calcium levels in rheumatoid arthritis synovial fbroblasts and reduces the production of IL-6 and IL-812 (306). Because Cannabidiol (CBD) showed anti-infammatory activity, and is approved by the Food and Drug Administration (FDA) for the treatment of children with intractable epilepsy for seizure reduction, it has been suggested that CBD might alleviate COVID-19 related infammation (300-306).

27) Leishmaniasis (Kala Azar)

Leishmaniasis (Kala-Azar) is one of the infectious neglected tropical diseases caused by a protozoan parasite vector of genus *Leishmania* which is transmitted to humans through an infected blood-sucking sandfly (320-322). Leishmaniasis (Kala-Azar) is prevalent in tropical and temperate regions of world which is fatal and life threatening if ignored and untreated (320-322). Leishmaniasis is transmitted through the bite of female sand flies infected with the protozoan (321). Kala Azar is a hyper endemic tropical disease for which no vaccine has been approved yet. However, many drugs that are available for the treatment of Leishmaniasis diseases possess serious side effects and drugs are active only in the acute phase of the disease Kala Azar (321). Another major limitation of existing drugs are severe toxicity with side effects and drug resistance (320-322). The emergence of drug resistance has created the main hindrance for Kala Azar control with one critical target in the state of Bihar in India (321). Therefore, there is an urgent need to search for cheaper, more effective, easily available and less toxic chemotherapeutic agents for combating Leishmaniasis (320-322). Therefore, herbal medicines without any side effects play an important role in controlling human health disorders and infectious diseases, Leishmaniasis (Kala Azar) (320-322).

There are three different clinical syndromes of leishmaniases, 1) Visceral leishmaniasis (VL) (also known as Kala-Azar), 2) Cutaneous leishmaniasis (CL), 3) Mucocutaneous leishmaniasis (ML) (321). Thus, the development of effective, risk-free alternative therapeutics based on natural compounds against leishmaniasis is urgent (320-322). Arginase, the key enzyme in the polyamine biosynthetic pathway, plays a critical role in leishmaniasis outcome and has emerged as a potential therapeutic target (320-322). Cutaneous leishmaniasis (CL) is characterized by localized skin lesions in which arginase is upregulated and involved in Leishmania proliferation (320-322).

One of the study reported that *Cannabis sativa's* phytochemical components (cannabinoids and terpenoids) through molecular docking against Leishmania and human arginase enzymes has been evaluated (320). These results showed that Λ-9-tetrahydrocannabinol (THC) possessed the best binding energies of −6.02 and −6.35 kcal/mol with active sites of Leishmania and human arginases, respectively (320). Λ-9-THC interacted with Leishmania arginase through various amino acids including His139 and His 154 and linked to human arginase via His 126 (320). In addition to Λ -9-THC, caryophyllene oxide and Cannabidiol (CBD) also showed a good inhibition of Leishmania and human arginases, respectively (320). Overall, the studied components were found to inhibit both arginases active sites via hydrogen bonds and hydrophobic interactions. These components may served as therapeutic agents or in co-administrated therapy for leishmaniasis (320). Since Cutaneous leishmaniasis (CL), is still a public health problem in low-income and developing countries, the discovery of an efficient, less toxic, and accessible therapy is a necessity (320-322). This study in silico was the first to investigate *Cannabis sativa's* selected constituents as selective inhibitory agents for parasitic as well as host arginases, which play an important role in this parasitic infection pathology (320). Interestingly, THC showed a great inhibitory potential for both species enzymes and will allow a better control of leishmaniasis (320-322). Although these docking results were interesting and promising, they required in vitro as well as in vivo experiments to corroborate and develop new approaches to leishmaniasis treatment and control (320). Interestingly, the application of a *Cannabis sativa*-based cream on Cutaneous leishmaniasis (CL) associated skin lesions promoted the healing process (320-322).

28) Monkeypox

Monkeypox is an emerging zoonotic viral disease infecting both animal and human (323-327). Monkeypox is a large double stranded DNA virus, and always infection has been considered as rare and self-limiting (323-327). However, recent sporadic reports of monkeypox outbreak in non-endemic region in 2022 is very disturbing. Therefore, monkeypox virus is considered as a high threat pathogen causing a disease of public health importance. WHO has considered monkeypox outbreak represents a public health emergency of international concern. This is the highest level of warning issued by the UN agency, which currently applies only to the COVID-19 pandemic and polio (323-327). The outbreak of monkeypox viral disease in non-

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endemic region (31 countries) in 2022 outside of Africa could be disastrous (323-325). The clinical features of monkeypox are very similar to those of smallpox. Routine smallpox vaccination ended decades ago, there is growing concern that monkeypox may become the next emerging poxvirus to plague humankind (323-327). Therefore, there is an urgent need to focus on building surveillance capacities which will provide valuable information for designing appropriate prevention, preparedness and response activities (323-327).

Monkeypox produces smallpox-like skin lesions, but symptoms are usually milder than those of smallpox (323-327). Flu-like symptoms are common initially, ranging from fever and headache to shortness of breath (323-327). One to 10 days later, a rash can appear on the extremities, head or torso that eventually turns into blisters filled with pus (323-327). Overall, symptoms usually last for two to four weeks, while skin lesions usually scab over in 14 to 21 days (323-327). Monkeypox, like smallpox, begins with a brief (2–3 day) febrile prodrome period prior to the appearance of enanthem and then exanthema, the latter with centrifugal distribution (323-327). The total lesion burden at the apex of rash can be quite high (>500 lesions) or relatively slight (<25) (323-327). Patients suffering from monkeypox viral disease has a range of complications that can include secondary infection of the integument, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision (323-327). The hallmark feature of monkeypox is disseminated vesiculo-pustular rash (323-327).

In India during the recent outbreak of Monkeypox, Cannabis oil was used for the external body applications as a preventive measures to control the monkeypox viral disease. But the no of monkeypox cases in India were very low and preventive measures were adopted by the local traditional healers. Himalayan hemp was also used for controlling the monkeypox disease. Howercr, there are no clinical trials and systematic studies were not reported. On the basis of lieterature survey it was reported that licensed medical Marijuana (*Cannabis sativa* L.) can be used to treat monkeypox (325-327). The potential role in symptomatic and supportive care, particularly for pain management, is suggested (323-327). The role of Cannabidiol in virus suppression is also mentioned (325-327). However, there has been no concrete research on Marijuana potential to treat monkeypox. Several behavioral factors could be associated with high levels of different sexual partners such as Cannabis use and alcohol consumption (325-327). As Vallee (327) points out, cannabis and alcohol consumption may have two negative effects on the monkeypox virus (MPXV) outbreak: increasing the number of sexual partners, which is primarily responsible for the increase in the number of new MPXV-infected cases, and impairing the immune response to a viral infection (325-327). It should be noted, however, that medical Marijuana with a well-controlled therapeutic approach can be useful and is not linked to addiction. Medical Marijuana potential role in the treatment of monkeypox should be investigated further (323-327).

29) Neuropathic pain (NP)

Neuropathic pain (NP) is a chronic disease that affects the normal quality of life of patients (329-331). To date, the therapies available are only symptomatic and they are unable to reduce the progression of the disease. Neuropathic pain (NP) is a chronic pathology of the central nervous system (CNS), due to a lack of balance between the inhibitory and excitatory transmission pathways which leads to a strong alteration of homeostasis at the central level (329-331). The main symptoms associated with NP are spontaneous burning, numbness, hyperalgesia (increased perception of pain from noxious stimuli), and allodynia (hypersensitivity of pain to normally harmless stimuli (329-331). One of the main systems involved in the maintenance of normal transmission function is the endocannabinoid system (ECS) and, among the most studied targets, there are certainly the cannabinoid receptor 1 (CB1) and 2 (CB2) (329-331). Neuropathic pain (NP) is the most difficult type of pain to treat. Indeed, currently available therapies have a symptomatic effect only, but they do not resolve the real cause of the disease, the chronicity of which strongly affecting patient quality of life (329-331). Patients with neuropathies usually do not achieve a complete pain relief, but they can only expect a temporary and partial attenuation in their pain symptoms (329-331). A 30% reduction in pain is generally considered as clinically relevant. Drugs used in this ambit mainly include antidepressants, antiepileptics, local anesthetics, and opioids, accompanied by psychological therapies (329-331). These treatments are effective in less than 50% patients, and they are characterized by many side effects that limit their long-term use (329-331).

In recent years, an alternative treatment for patients, who do not adequately respond to current drug therapies based on opioids or antidepressants, is the use of synthetic cannabinoids, such as Dronabinol (Marinol®) and Nabilone (Cesamet®), both containing Δ9- tetrahydrocannabinol (Δ9-THC) as the active compound (329-331). Many studies reported the efficacy of Cannabis sativa L. (C. sativa) on NP, but no Δ9-tetrahydrocannabinol (Δ9-THC)-free extracts have been investigated in detail for this activity so far (329-331). One of the study reported the use of cannabidiol-rich non-psychotropic C. sativa oils, with a high content of terpenes (K2), compared to the same extract devoid of terpenes (K1) (329-331). Oral administration of K2 (25 mg kg^{-1}) induced a rapid and long-lasting relief of pain hypersensitivity in a mice model of peripheral neuropathy (329-331). In spinal cord samples, K2 reduced mitogenactivated protein kinase (MAPKs) levels and neuroinflammatory factors (329-331). Tthese results demonstrated that K2 oral administration attenuated Neuropathic pain (NP) symptoms by reducing spinal neuroinflammation and underline the important role of the synergism between cannabinoids and terpenes (329-331). Therefore, the oral administration of a non-psychotropic C. sativa oil (K2), containing high concentrations of both CBD and terpenes,

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attenuated SNI-induced NP symptoms with a higher efficacy than an extract with a comparable concentration of CBD, but devoid of terpenes (K1), suggesting the importance of CBD-terpene interaction to control NP (329-331). K2 activity was related to a CB2-mediated reduction of spinal neuroinflammation, and it may represent a novel and interesting candidate for the management of Neuropathic pain (NP) (329-331).

30) Lumpy Skin Viral Disease

Lumpy Skin Disease (LSD) is an infectious disease in cattle and Asian water buffalo caused by Lumpy Skin Disease Virus (LSDV) belongs to the family Poxviridae (332-334). Lumpy Skin Disease (LSD) was first time reported from India in 2019 and second outbreak is recorded in **2022** which has emerged as a challenge for the dairy sector (332). In India, currently epidemiological status of the disease is unknown. A lump like **nodules** in the external skin and mucous membrane with fever and swollen lymph nodes are the preliminary noticeable clinical signs of this devastating disease. Lumpy skin disease (LSDV) is caused by the double - stranded DNA virus belongs to genus Capripoxvirus and family Poxviridae (332-334). Lumpy Skin Disease (LSD) is not zoonotic infecting cattle's but not humans. Lumpy Skin Disease (LSD) is a contagious vector-borne disease spread by the vectors like mosquitoes, some biting flies, and ticks (332-334). The hallmark feature of LSD is the skin lesions with nodules. Vaccination along with strict quarantine measures and vector control could be effective for preventing the spread of the disease (332-334). In India, the Goat Pox Virus Vaccine (GTPV) Uttarkashi strain is being evaluated for the level of protection against Lumpy Skin Disease (LSD) as compared to the LSDV (332). Its name originates from the clinical presentation of the disease generally associated with the appearance of **skin nodules** that may cover the entire body of the animal during severe infection and vaccine is already used for emergency vaccination (332-334). Ethno veterinary practices concern to animal healthcare is as old as the domestication of various livestock species. There is a rich and efficient ethno veterinary traditions exist in the villages of India (332). Therefore, Cannabis oil with turmeric powder has been used as a Cattle skin topical ointment in order to control the viral growth. Cannabis oil contains mainly THC and CBD and other compunds which might inhibit the further sperad of the virus. Many herbal traditional healers have practiced the use of Cannabis oil as a mosquito repellent during the recent outbreak of Lumpy skin viral disease. However, there are no clinical and scientific studies were reported to support the Cannabis oil as the best treatment and remedy fot this viral studies. Therefore, further clinical studies are warranted.

II. Conclusion

Research is currently examining the efficacy of potential therapeutic uses of Cannabinoid products for conditions such as multiple sclerosis, psychiatric disorders, epilepsy, inflammatory diseases, cancer, obesity, glaucoma and neurodegenerative disorders. The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS). Nabilone is a synthetic Cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy. Cannabidiol (CBD) and its metabolite 7-OH-CBD, but not THC or other congeneric Cannabinoids tested, potently block SARS-CoV-2 replication in lung epithelial cells. Cannabis has a bronchodilator effect on the airways and might have an anti-inflammatory effect, yet there are many harmful effects on the lungs of asthmatic patients. *Cannabis sativa*-based cream on Cutaneous leishmaniasis (CL) associated skin lesions promoted the healing process. Cannabis oil was used as a body lotion for controlling monkeypox viral disease. However, there are some adverse reactions and insignificant effect of medical Cannabis and hemp was also noticed in the treatment of diseases. Cannabis and Cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear. Furthermore, the clinical results remained controversial and warranted further investigation.

Although findings from this research are either mixed or insufficient to draw conclusions, there is promising research emerging for the treatment of some of these conditions. Evidence suggests that Cannabis and Cannabinoids are effective for the relief of nausea and vomiting, and certain types of pain, as well as the stimulation of appetite. However, there is insufficient research to promote Cannabis and Cannabinoids as a primary or first line option for these symptoms.

Cannabis and Cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear. There was moderate-quality evidence to support the use of Cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that Cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

Based on the available evidence, the approved therapeutic use of Cannabis is mainly limited to the treatment of nausea, vomiting and certain types of pain, and the stimulation of appetite in AIDS patients. Further research is needed to determine its most appropriate use relative to that of other current treatments for nausea and pain. The possible benefits of combining Cannabinoid therapy with other drugs might well lead to better methods of clinical use. Much of the more recent research has focused on a broad range of other proposed therapeutic uses for Cannabinoids (e.g., multiple sclerosis, cancer, epilepsy,

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inflammatory conditions) and the results from this work are encouraging, but not yet well-enough supported by properly designed clinical trials to permit their recommendation for those clinical uses.

An important distinction needs to be made between the risks associated with smoked Cannabis and Cannabinoid products that are delivered in controlled doses by nontoxic delivery systems. Moreover, patients who smokeed Cannabis for medical purposes are not assured the reliable, standardized and reproducible dose that they would otherwise received from using other Cannabinoid products and could experience chronic respiratory ailments.

It appears unlikely that Cannabis will realize the full therapeutic potential that has been observed when studying the effects of the endocannabinoid system. Preparations containing THC or other drugs acting on the two known Cannabinoid receptors will still suffer from the very broad spectrum of action that gives rise to the side effects. There is promise in further clinical studies of CBD, as well as in designing tailored medications developed from Cannabinoids for specific conditions or symptoms with improved risk–benefit profiles. Research is currently underway to develop a new generation of safe and effective Cannabinoid medications that avoid the adverse effects associated with smoking or ingesting whole Cannabis.

More research is needed to determine the risks associated with the medical use of Cannabis. However, research on chronic Cannabis use has linked to risks and harms such as reduced cognitive functioning and negative respiratory symptoms. Patients who ingest Cannabis for medical purposes are not assured the reliable, standardized and reproducible dose they would otherwise received from using Cannabinoid products delivered in controlled doses (e.g., capsules, oral sprays). Research supports the medical use of Cannabis to relieve nausea, vomiting and chronic pain, and to stimulate appetite, but the research is still emerging in its application to other disease conditions. Future development is likely to be focused on exploiting CBD and possibly other Cannabinoids without psychoactivity, and improving the specificity of synthetic Cannabinoids and their delivery by safer methods than smoking.

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