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Cannabis for medicine and food: A benefit vs risk critical appraisal

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ABSTRACT

The use of cannabis for health purposes continues to gain significant attention due to the presence of important phytochemicals, chiefly, cannabidiol (CBD) and Δ -9-tetrahydrocannabinol (THC). The therapeutic potentials of CBD and THC in the management of cancer-associated chronic pain, anxiety, stress, nausea, vomiting, and weight loss are well-reported. These benefits are triggered by the intricate interactions of the cannabinoids with their receptors in the endocannabinoid system (ECS) leading to pharmacodynamic actions. Conversely, the possible physiological, psychiatric, cognition, addiction, and dependency risks, especially due to chronic intake of THC, are huge limitations in fully harnessing the clinical utility of cannabis. Here, an up-to-date critique of the potential merits and adverse effects of cannabis and cannabis-containing products is provided. A thorough knowledge of the interplay between CBD, THC, and the ECS gives deep insights that can be explored for consumer health without the attendant complications. Future directions in cannabis research must be guided by a nuanced understanding of its molecular mechanisms of action and potential risks, enabling the development of targeted and effective medical interventions. Besides, standardized regulations and comprehensive education that are backed by empirical evidence are crucial to fostering the safe and responsible use of cannabis for food or medicine.

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1. Introduction

Cannabis sativa L. is an annual herbaceous plant belonging to the Cannabaceae family and is commonly characterized by its tall and erect structure of 1–6 m in height. It has palmate leaves composed of serrated leaflets arranged oppositely on the angular, furrowed, branched stem. The roots usually have a branched taproot, 30–60 cm deep in loose soils, and closer to the surface in wet soils, extending up to 2.5 m (Farag and Kayser, 2017). *C. sativa* is a dioecious plant, with separate male and female species, although some monoecious varieties exist, they are mostly unstable. The plant produces glandular trichomes, primarily on female inflorescences, which secrete cannabinoids (Farag and Kayser, 2017; Strzelczyk et al., 2022). Alongside its controversial use in recreation, its potential use in medicine and as a source of fiber, seeds, and bioactive compounds has been documented for centuries, making it a subject of extensive

pharmacological and agricultural research as well as media attention (Coelho et al., 2023). Though first recorded in China, the medical uses of cannabis in the management of various conditions such as malaria, arthritis, nausea, anxiety, muscle problems, and pain relief have been globally reported (Almogi-Hazan and Or, 2020; Crocq, 2020). Cannabis may have been intended for medicinal use traditionally. Still the smoking or vaporizing of dried cannabis flower for recreational purposes as well as the consumption of cannabis-infused food have become widespread following its legalization in many countries (Iftikhar et al., 2021; Karen, 2022; Rasera, Ohara and De Castro, 2021).

The three major sub-species of cannabis commonly utilized in these applications are *C. sativa*, *C. indica*, and *C. ruderalis* in that order (Chayasirisobhon, 2021). Based on strain differences, the drug-type cannabis popularly referred to as marijuana is characterized by high concentrations of Δ -9-tetrahydrocannabinol acid (THCA) and Δ -9-tetrahydrocannabinol (THC), which can induce euphoria or intoxication in humans (Cherney and Small, 2016). Whereas, the fibre-type cannabis, hemp, is rich in cannabigerolic acid (CBGA) and cannabidiolic acid (CBDA), as well as their decarboxylated counterparts, cannabigerol (CBG), and cannabidiol (CBD). Hemp contains significantly lower levels of THC and does not induce psychoactive effects (Cerino

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et al., 2021; Iftikhar et al., 2021). Apart from dried cannabis flowers, products such as high-power extracts, vape cartridges, topicals, and edibles have gained market share, reflecting an increase in cannabis consumption and a growing demand for alternative consumption methods (Iftikhar et al., 2021). Research into the utilization of cannabis as an ingredient in various industries such as bakery, confectionery, beverages, dairy, fruits, vegetables, and meat also continues to increase (Iftikhar et al., 2021). All parts of the cannabis plant, including the stem, seeds, roots, and flowers, are nutritionally rich and are used in food products (Appendino et al., 2011).

Although cannabis contains other active compounds including terpenoids, polyphenols, phenolic acids, tocopherols, and fatty acids (Wishart et al., 2024), the cannabinoids, THC and CBD are the most studied to date. These two primary constituents are attributed to the biological properties of cannabis products with their presence or proportion often used as the distinguishing markers for marketing and quality control purposes (De Petrocellis et al., 2011). The cannabinoid constituents in cannabis vary between species and *C. sativa* the most common, contains the least THC: CBD ratio among the three major strains (Iftikhar et al., 2021). The health benefits attributed to cannabis consumption either as a food component or medicine are primarily due to the CBD whereas the 'high' or toxic effects were mostly credited to the presence of THC. CBD has demonstrated several pharmacological effects including antipsychotic, anxiolytic (Batalla et al., 2021), antibacterial (Iseppi et al., 2019), antioxidant (Cheng et al., 2014), anticancer (Cerino et al., 2021), antiemetic (Mersiades et al., 2018), and anti-inflammatory (Stith et al., 2019). Despite the therapeutic potentials of THC in chronic pain management, antiemetic effects, and appetite stimulation (Coelho et al., 2023; Louis-Gray, Tupal and Premkumar, 2022), its consumption is often associated with side effects, including cognitive impairment, dependency, and exacerbation of psychiatric conditions especially in adolescents (Murray et al., 2022).

A major limitation in the applications of medicinal cannabis globally, stems mostly from the lack of standardization of dosages due to batch-to-batch variations of the plant's raw materials that result from the sensitivity of the secondary metabolism to environmental and cultivation conditions (Gorelick and Bernstein, 2017) and thereby alterations in the medicinal constituents due to a range of exogenous factors. These factors may include the fertilization regime supplied to the plant (Saloner and Bernstein, 2022a; Shiponi and Bernstein, 2021; Song et al., 2023), harvesting season, and geographical location (Massuela et al., 2022), light conditions (Danziger and Bernstein, 2021; Magagnini, Grassi and Kotiranta, 2018), planting density (Danziger and Bernstein, 2022; Massuela et al., 2022) and more. Variability in standardization of the cannabis product sources can also be from the genetic differences in the therapeutic profile between plant parts (Saloner and Bernstein, 2022b) and the spatial position of the inflorescences in the plant (Bernstein, Gorelick and Koch, 2019; Gorelick and Bernstein, 2017).

Over 40 countries including the USA, Uruguay, and Portugal have legalized medical cannabis, with 7 of these allowing recreational usage (Karen, 2022). While hemp seed-derived food products are generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA), the inclusion of CBD in foods or dietary supplements remains prohibited by US law (Britch, Babalonis and Walsh, 2021). Conversely, the European Commission classifies CBD as a novel food, subject to compliance with relevant European Union (EU) regulations, but the European Food Safety Authority (EFSA) is yet to endorse this classification citing safety concerns, a lack of information on potential health hazards, and existing knowledge gaps (Nutrition, Novel Foods and Food Allergens | EFSA, 2022). In South Africa, the South African Health Products Regulatory Authority (SAHPRA) classifies cannabis and cannabis-related products as scheduled substances, closely regulating their cultivation and manufacture for medical or research purposes. Although the sale of cannabis plants is still illegal

in South Africa, CBD and hemp products containing less than 0.001 % THC are permitted.

In this review, a detailed analysis of the recent scientific updates on the health and nutritional importance of cannabis and cannabis-containing products is presented vis-a-vis the potential risks they can pose to consumers. We also discussed the delicate balance between the endocannabinoid system (ECS) and the immune system, as well as the potency of CBD & THC in modulating these systems to propagate their bioactivities. If these complex but interconnected interactions are optimally exploited, they may aid the responsible applications of the plant for food or medicine.

2. Literature search and data collection methods

In this comprehensive literature review, relevant published studies (original articles and reviews) on the therapeutic or nutritional potentials, and adverse effects of cannabis, CBD & THC were searched, identified, selected, and synthesized by following well-established guidelines (Kraus et al., 2022). The search terms on PubMed, Scopus, and Web of Science databases included "cannabis", "cannabinoids", "cannabidiol", "CBD", "delta-9-tetrahydrocannabinol", "THC", "endocannabinoid system", "THC dependence", "cannabis nutrients", "cannabis medicines", "cannabis benefits", and "cannabis safety". Boolean operators ("AND" and "OR") were applied to refine the search results and target studies focused on both therapeutic or nutritional benefits and risks associated with cannabis use. Only studies published between 2010 and 2024 were selected so the most up-to-date information is presented. The search criteria were limited to (1) studies published in the English language, (2) studies on cannabinoids (notably CBD and THC) and nutrient composition in cannabis, (3) studies that investigated the molecular mechanisms of CBD and THC in the endocannabinoid and immune systems, and (4) reports with data on the therapeutic and nutritional effects or risks of cannabis intake. Conference abstracts and other articles not directly related to the aspects listed in the inclusion criteria were excluded. We employed a narrative synthesis approach in this review by organizing the important aspects into key sections starting with a description of the cannabis plant and its important cannabinoids, CBD & THC. The pharmacodynamic interactions of CBD and THC with receptors in the endocannabinoid system were discussed in detail, focusing primarily on CB1, CB2, and other potential receptor targets. The therapeutic and nutritional potentials of cannabis, CBD & THC were then integrated to provide a critical analysis of the plant benefits in humans. Data on the adverse effects were also supplied for a balanced perspective. The major mechanisms of actions, characteristics, and endpoints of cannabis use in these studies were highlighted using figures and tables for clarity.

3. The bioactive compounds in cannabis

The cannabis plant contains hundreds of bioactive compounds, including cannabinoids, terpenoids, polyphenols, phenolic acids, tocopherols, and other volatile compounds (Wishart et al., 2024). Of these, the cannabinoids, mainly cannabidiol (CBD) and Δ -9-tetrahydrocannabinol (THC) are the most studied and are primarily attributed to the therapeutic actions of cannabis. The former was first isolated in 1940 and the latter in 1964 (Crocq, 2020; Marzo, 2018). THC is psychoactive, capable of inducing alterations in neural function that can contribute to the development of psychotic symptoms (Neill et al., 2021). In contrast, CBD is non-psychoactive and exhibits greater affinity for receptors primarily located in the peripheral rather than the central nervous system (Almogi-Hazan and Or, 2020). Recent findings indicated the capacity of CBD to counteract the effects of THC, making it suitable for the treatment of psychosis (Neill et al., 2021). CBD profiling studies also demonstrated its safety for human consumption, particularly in comparison to THC (Aviello et

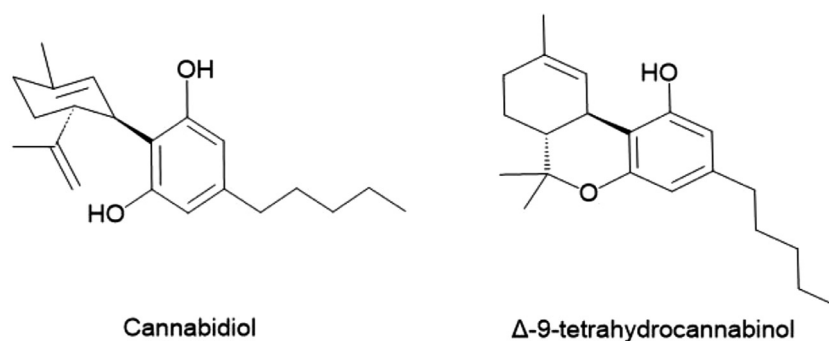


Fig. 1. The chemical structures of the major cannabinoids in cannabis.

al., 2012) hence the preferred cannabinoid constituent of various health supplements (Vlad et al., 2020). The approval of CBD-containing products and the prohibition of those with high THC contents has generated comparatively more significant interest in the former (Vlad et al., 2020).

3.1. Cannabidiol (CBD)

CBD is an alkaloid consisting of a tetrahydrobiphenyl skeleton and 21-carbon terpene phenol that is formed through the decarboxylation of its precursor, cannabidiolic acid (Azad et al., 2021; Nelson et al., 2020). CBD can undergo decarboxylation, transforming from its acidic form to a neutral form (Stollenwerk, Pollock and Hillard, 2021; Sullivan, Stevenson and Laviolette, 2021). The phytocannabinoid exerts its effects on the human body by binding to CB2 receptors of the endocannabinoid system (ECS) and indirectly modulates the action of the CB1 receptor (Sullivan, Stevenson and Laviolette, 2021). CBD, and its analogs, exhibit various structural features, including a phenol ring, a C3-alkyl chain, or the presence of the limonene moiety. The unique structure of CBD has attracted interest in understanding its pharmacological effects. The anti-inflammatory properties of CBD have been associated with the action of specific compounds (H2-CBD and H4-CBD) generated through the hydrogenation of its double bonds (Nelson et al., 2020). The chemical structure of CBD bears a close resemblance to that of THC (Fig. 1), accounting for the similarities in their metabolism (Britch, Babalonis and Walsh, 2021; Nelson et al., 2020). They however differ in their overall molecular configuration with CBD being bicyclic while THC is tricyclic (Vlad et al., 2020).

The affinity of CBD to both CB1 and CB2 is 50-fold less compared to that of THC (Nelson et al., 2020). Additionally, a significant amount of CBD is excreted from the body compared to THC, leading to less bio availability and action of CBD on its target receptors compared to THC (Nelson et al., 2020; Stollenwerk, Pollock and Hillard, 2021). The low solubility of CBD hinders its absorption by the small intestines, resulting in a limited uptake into the bloodstream (Vlad et al., 2020). Consequently, a higher proportion of CBD remains unabsorbed compared to THC. Therefore, increasing the administration of CBD relative to THC may enhance the binding of CBD to its target receptors, compensating for its lower affinity and potentially enhancing its pharmacological effects.

3.2. Delta-9-tetrahydrocannabinol (THC)

THC exerts its effect through an action like the normal physiological action of endocannabinoids such as anandamide and 2-arachidonylglycerol (McKenna and McDougall, 2020). THC is one of the primary psychoactive compounds found in cannabis. It is responsible for the "high" or euphoric sensation often associated with cannabis use. THC interacts with cannabinoid receptors in the brain and central nervous system, particularly the CB1 receptors, to produce its psychoactive effects (Vlad et al., 2020). The mechanism of action of

THC involves its interaction with the endocannabinoid system (ECS) in the body which leads to the metabolism and degradation of these compounds. When consumed, it binds to CB1 receptors primarily located in the brain and central nervous system. This interaction leads to the activation of various signaling pathways, including the modulation of neurotransmitter release. Specifically, THC inhibits the release of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, while enhancing the release of dopamine, serotonin, and other neurotransmitters associated with pleasure and reward (Lu and Mackie, 2016). These neurochemical changes result in the characteristic effects of THC, including euphoria, relaxation, altered perception, and changes in mood and cognition. Additionally, THC's interaction with CB1 receptors in regions of the brain involved in pain perception and appetite regulation contributes to its analgesic and appetite-stimulating effects (Hill, 2020).

THC may also exert its effects through interactions with other receptors and signaling pathways in the body. For example, it has been shown to modulate the activity of transient receptor potential (TRP) channels, which play a role in pain sensation and inflammation (McKenna and McDougall, 2020). Additionally, THC may have indirect effects on other neurotransmitter systems, such as the opioid and glutamate systems, further contributing to its analgesic and psychoactive properties (Ibeas Bih et al., 2015). It is important to note that while THC's activation of CB1 receptors is primarily responsible for its psychoactive effects, it may also contribute to potential side effects and risks associated with cannabis use, such as impaired cognition, memory deficits, and addiction with chronic use (Volkow et al., 2014).

3.3. Metabolism of CBD and THC

THC and CBD are metabolized by cytochrome P450 enzymes located in the liver, intestines, and brain cells (Lucas, Galettis and Schneider, 2018) as illustrated in Fig. 2. The transportation of CBD and THC from the cytoplasm to the nucleus for metabolism is facilitated by the fatty acid-binding protein (FABP1) binding, with both cannabinoids binding to the same binding site (Elmes et al., 2019). During the metabolism of CBD, metabolites such as glucuronides, alkyl hydroxylation, and allylic hydroxylation products are formed (Nelson et al., 2020). These metabolites have been detected in blood and urine after CBD-containing products were ingested. However, the specific effects of these metabolites have not been extensively studied (Nelson et al., 2020). The metabolism of CBD after oral administration results in the formation of 11-hydroxy cannabidiol (11-OH-CBD), 7-hydroxy cannabidiol (7-OH-CBD), or 7-carboxy-CBD (7-COO—CBD) (Beers, Fu and Jackson, 2021). In contrast, inhalation of the same compound leads to the generation of several additional metabolites, including 1'-hydroxycannabidiol (1'-OH—CBD), 2-hydroxycannabidiol (2'-OH-CBD), 3'-hydroxycannabidiol (3'-OH-CBD), 4'-hydroxycannabidiol (4'-OH-CBD), and 5'-hydroxycannabidiol (Vlad et al., 2020). The different metabolic pathways observed

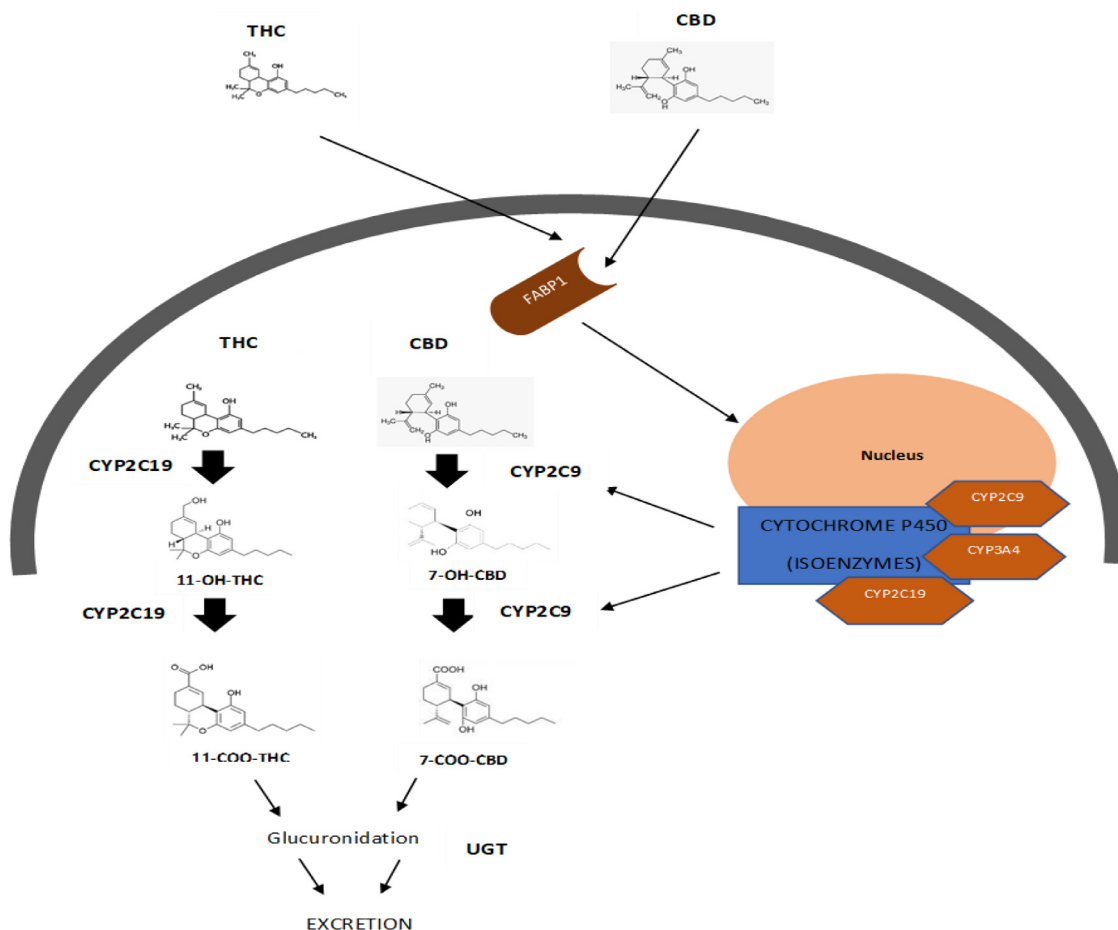


Fig. 2. The CBD and THC metabolism pathway. CBD and THC are transported from the cytoplasm to the nucleus through the binding of fatty acid-binding protein (FABP1) and metabolized through catalysis by different cytochrome P450 (CYP) isoenzymes (CYP2C19, CYP2C9). CBD is metabolized by CYP2C9 to produce 11-hydroxy cannabidiol (11-OH-CBD) and 7-carboxy-cannabidiol (7-COO-CBD). THC is metabolized by CYP2C19 to produce 11-hydroxy-tetrahydrocannabinol (11-OH-THC) and 11-carboxy-tetrahydrocannabinol (7-COO-THC). Glucuronidation occurs at the final stage through catalysis by UDP-glucuronosyltransferase (UGT).

between oral administration and inhalation contribute to variations in the metabolite profiles of CBD. This poses the question of which route of administration is most suitable for the consumption of CBD. The various effects of CBD on several health conditions can be attributed to its interaction with different compounds in the body, such as receptors, transporters, and enzymes (Britch, Babalonis and Walsh, 2021; Sullivan, Stevenson and Lavolette, 2021). Further metabolism of 7-COO-CBD for example, by UDP-glucuronosyltransferase (UGT) leads to the production of 7-COO-CBD-glu as an end-product excreted in urine or fecal matter (Elmes et al., 2019).

For THC, the first stage of metabolism results in the formation of 11-hydroxy-THC (11-OH-THC) in the reaction catalyzed by CYP2C9, CYP3A4, and CYP2C19 isoenzymes (Zhu and Peltekian, 2019). 11-OH-THC is associated with the psychotic effects exerted by THC (Lucas, Galettis and Schneider, 2018). Further metabolism through the process of glucuronidation leads to the formation of 11-carboxy-THC glucuronide (7-COO-THC-glu) which is further eliminated from the body through fecal or urinary excretion (Beers, Fu and Jackson, 2021). Both hydroxylated and carboxylated metabolites or glucuronides of THC are excreted, with the latter majorly detected in feces and the former in urine (Chayasirisobhon, 2020).

4. The endocannabinoid and immune response systems are central to CBD and THC bioactivities

In this section, the interactions of CBD and THC with their receptors in the endocannabinoid and immune systems are briefly

discussed to gain a better understanding of the health utility of cannabis. These systems regulate many physiological processes, including immune modulation and neuroinflammation hence their thorough knowledge may assist in the therapeutic applications of cannabinoids for immune-related, inflammatory, and neurological disorders.

4.1. The endocannabinoid system

The study of the endocannabinoid system (ECS) gained momentum shortly after the identification of the two cannabinoids extracted from cannabis. It was discovered that THC binds to specific receptors to initiate its pharmacological effects (Crocq, 2020). The presence of these receptors in the body led to the discovery of endocannabinoids, which exhibited structural similarities to the phytocannabinoids (Almogi-Hazan and Or, 2020). The presence of the ECS receptors predominantly in the central nervous system (CNS) and the immune system suggests a potential interaction between these two systems, both of which are regulated by the ECS. The ECS is composed of three key components: cannabinoids, cannabinoid receptors, and enzymes (Argenziano et al., 2019). Endogenous and exogenous cannabinoids bind to their respective receptors to propagate signals. Enzymes such as fatty acid amide hydrolase (FAAH), monoacylglycerol and diacylglycerol lipases, and N-acyl phosphatidyl-ethanolamine phospholipase D catalyze the synthesis and breakdown of endocannabinoids, regulating their availability to initiate signaling pathways and influencing the overall balance of the ECS (Acharya et al., 2017; Lu and

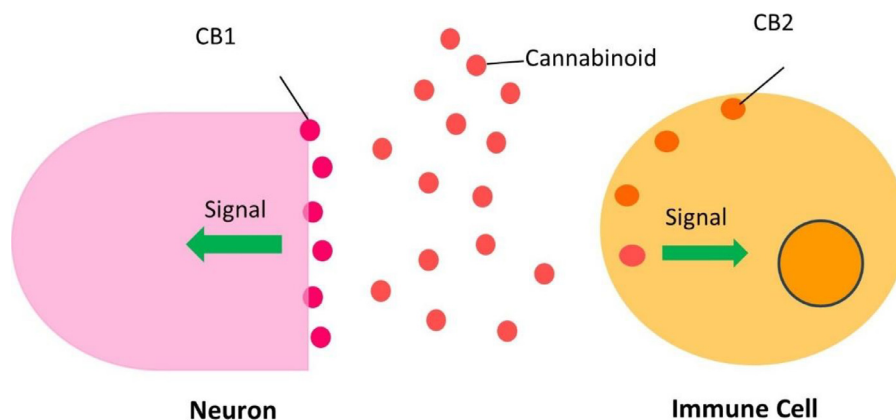


Fig. 3. The endocannabinoid system. The endocannabinoid system comprises the cannabinoids, CB1 and CB2 receptors, and other functional enzymes, which once activated, lead to a wide array of physiological processes including mood regulation, pain perception, immune function, and neuroprotection.

Mackie, 2016). The intricate interplay between these components forms the basis of the complex ECS and its diverse physiological effects.

The two main G protein-coupled receptors (GPCR) associated with the ECS are cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) as illustrated in Fig. 3. CB1 receptors are primarily distributed in the CNS, including the brain and spinal cord, and significantly regulate various functions such as pain perception, mood, appetite, and memory. On the other hand, CB2 receptors are predominantly found outside the CNS, particularly in the immune system, but also in peripheral tissues and organs. CB2 receptors modulate immune response, inflammation, and other immune-related processes. The widespread occurrence of CB1 and CB2 receptors in the human body reflects the broad regulatory potential of the ECS in maintaining homeostasis and influencing various physiological processes (Argenziano et al., 2019; Kienzl, Kargl and Schicho, 2020; Seltzer et al., 2020). Major ligands called endocannabinoids, namely anandamide (AEA) and 2-arachidonoylglycerol (2-AG) were identified following the discovery of the cannabinoid receptors. These endocannabinoids were observed to also bind to CB1 and CB2 receptors to elicit their actions (Almogi-Hazan and Or, 2020). In addition to the CB1 and CB2 receptors, endocannabinoids can bind to other molecules to achieve downstream pharmacodynamic effects. For instance, AEA binds to calcium channels reducing the calcium influx and neurotransmitter release, as probable mechanisms of its neuroprotective roles (Marzo, 2018). Endocannabinoids may also modulate other GPCRs such as GPCR55, GPCR18, and GPCR110 (Marzo, 2018). AEA has demonstrated an affinity for the transient receptor potential cation channel subfamily V member 1 (TRPV1), a protein channel that activates peroxisome proliferator-activated receptor (PPAR γ), ultimately leading to apoptosis (Marzo, 2018). The occurrence of ECS in the brain suggests its role in the modulation of the CNS (Kienzl, Kargl and Schicho, 2020). During the transmission of an electrical impulse, cannabinoids are secreted from the postsynaptic nerve and bind to their receptors in the presynaptic nerve to send a signal that stops the secretion of neurotransmitters, thereby ending the response (Kienzl, Kargl and Schicho, 2020).

4.2. The interconnection between the endocannabinoid system, immune response, inflammation, and adenosine signaling

Cannabinoids and their receptors are also secreted by various immune system cells, including macrophages, mast cells, lymphocytes, and natural killer cells, as well as in the spleen, tonsils, and lymph nodes (Argenziano et al., 2019). These cells and organs play crucial roles in eliminating foreign substances, neutralizing threats,

and producing essential molecules like cytokines and reactive oxidative species (ROS) during infections or injuries (Sender et al., 2023).

Inflammation is a natural immune response to an infection caused by foreign pathogens or tissue damage (Dongiovanni et al., 2023). When the body is injured or invaded by pathogens, the immune system becomes activated and secretes specific biomarkers of inflammation by immune cells for tissue repair and healing (Hildebrandt, Ibrahim and Peltzer, 2023). The immune response during acute inflammation involves the release of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-8 (IL-8), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), interferon-gamma (IFN γ), monocyte chemo-attractant protein-1 (MCP-1), monocyte chemo-attractant protein-2 (MCP-2), and vascular endothelial growth factor (VEGF). However, the inflammatory process is regulated by the production of counteracting anti-inflammatory cytokines such as interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-10 (IL-10), and interleukin-13 (IL-13) (Lowe et al., 2021). These anti-inflammatory cytokines help to balance and control the inflammatory response, ensuring that it does not become excessive or prolonged. Additionally, these cytokines contribute to the attenuation of inflammation once the process of tissue repair is complete (Scheffer and Latini, 2020). Chronic inflammation occurs when there is a deficiency in the production of anti-inflammatory cytokines, resulting in a sustained immune response that can cause tissue damage and contribute to the development of various diseases. The loss of the delicate balance between pro- and anti-inflammatory cytokines leads to the overactivation of the immune system and the continuous release of pro-inflammatory molecules. This persistent inflammation affects tissues and organs, leading to chronic conditions such as cardiovascular disease, autoimmune disorders, and certain types of cancer (Hong et al., 2023; Liu et al., 2023).

The ECS plays a significant role in regulating immune response. The activation of CB1 receptors leads to the release of neurotransmitters, which subsequently results in the suppression of pro-inflammatory cytokines such as IL-1 and cyclooxygenase-2 (COX2) during inflammation. This mechanism helps to attenuate chronic inflammation and maintain a balanced inflammatory response within the nervous system. The modulation of inflammatory processes by CB1 receptors in the nervous system highlights their potential as therapeutic targets for addressing neuroinflammatory conditions (Lowe et al., 2021). CB2 receptors are widely expressed across the immune system and can be found in various immune cells. The interaction between endocannabinoids and CB2 receptors in the immune system plays a role in modulating immune responses. Specifically, the binding of endocannabinoids to CB2 receptors has been shown to inhibit the maturation of B-cells by impeding their migration from the bone marrow to the blood plasma. This effect ultimately leads to a

reduction in the overall immune response. By influencing the development and movement of B-cells, the activation of CB2 receptors helps regulate immune processes and maintain immune homeostasis. These findings highlight the potential of targeting CB2 receptors as a therapeutic approach for immune-related disorders (Almogi-Hazan and Or, 2020). Additionally, AEA initiates anti-inflammatory responses by promoting the production of anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 (Khuja et al., 2019). These cytokines play crucial roles in suppressing inflammation and promoting immune balance. The ability of endocannabinoids to induce the production of anti-inflammatory cytokines highlights their potential as modulators of immune responses and suggests their involvement in regulating inflammatory processes. The attenuation of the proliferation of T and B lymphocytes and macrophages, the reduction of cytokines, as well as the reduction in immune cell migration as a result of endocannabinoids binding to CB2 clearly shows the immunosuppressive effect of the ECS (Argenziano et al., 2019). Fig. 4 below shows the possible attenuation of inflammation by cannabinoids binding to CB2 receptors. Furthermore, the inhibition of the degrading enzymes FAAH and MGL, which are responsible for the breakdown of endocannabinoids, has been shown to increase the levels of endocannabinoids. This increase was associated with a notable elevation in the production of anti-inflammatory cytokines (Acharya et al., 2017). This suggests that modulating the activity of these degrading enzymes may have therapeutic potential in promoting anti-inflammatory effects (Argenziano et al., 2019).

Adenosine, a nucleoside generated through the dephosphorylation of AMP by the enzyme CD73, plays a crucial role in the healing process during acute tissue injury and inflammation. Adenosine is produced from ADP and AMP in response to ATP breakdown, by the enzyme CD39, particularly under hypoxic conditions (DiNicolantonio and Barroso-Aranda, 2020). Adenosine signals cellular pathways that

promote tissue healing and resolution of inflammation in acute injury scenarios (Karmouty-Quintana et al., 2013). Adenosine can bind to ADORA1, ADORA2A, ADORA2B, and ADORA3 receptors in the immune, stromal, endothelial, and epithelial cells to signal downstream effects (DiNicolantonio and Barroso-Aranda, 2020; Karmouty-Quintana et al., 2013). Adenosine levels are regulated by anabolic enzymes, such as CD39 and CD73 (ectonucleotidases), and the catabolic adenosine deaminase enzyme (Karmouty-Quintana et al., 2013). Inhibiting CD39 and CD73 led to a decrease in adenosine levels and an increase in ATP levels (Abouelkhair, 2020). CB1 and the adenosine receptor ADORA2A, have been shown to form heterodimers that signal pathways leading to neuromodulation, behavioral effects, and neuroprotection (Neill et al., 2021). CBD and THC, in addition to the indirect action on CB1 receptors, have also been identified as indirect modulators of ADORA2A (Cajiao-Manrique et al., 2023; Stollenwerk et al., 2021). The interaction between CBD and ADORA2A highlights the complex and diverse ways CBD can exert its pharmacological effects, potentially contributing to its therapeutic properties.

5. Therapeutic potentials of cannabis

The dysregulation of the ECS either due to a deficiency of CB2 receptor ligands or over-activation of the CB2 ligands degrading enzymes, disrupts immune response modulation and contributes to chronic inflammation (Almogi-Hazan and Or, 2020; Marzo, 2018). Chronic inflammation is a primary contributor to the onset of many chronic diseases. For example, chronic inflammation may result in the prolonged elevation of adenosine levels (Karmouty-Quintana et al., 2013). The excessive binding of adenosine to the immune cell receptors, ADORA2A and ADORA2B, leads to the suppression of the immune response (Abouelkhair, 2020). As cellular adenosine

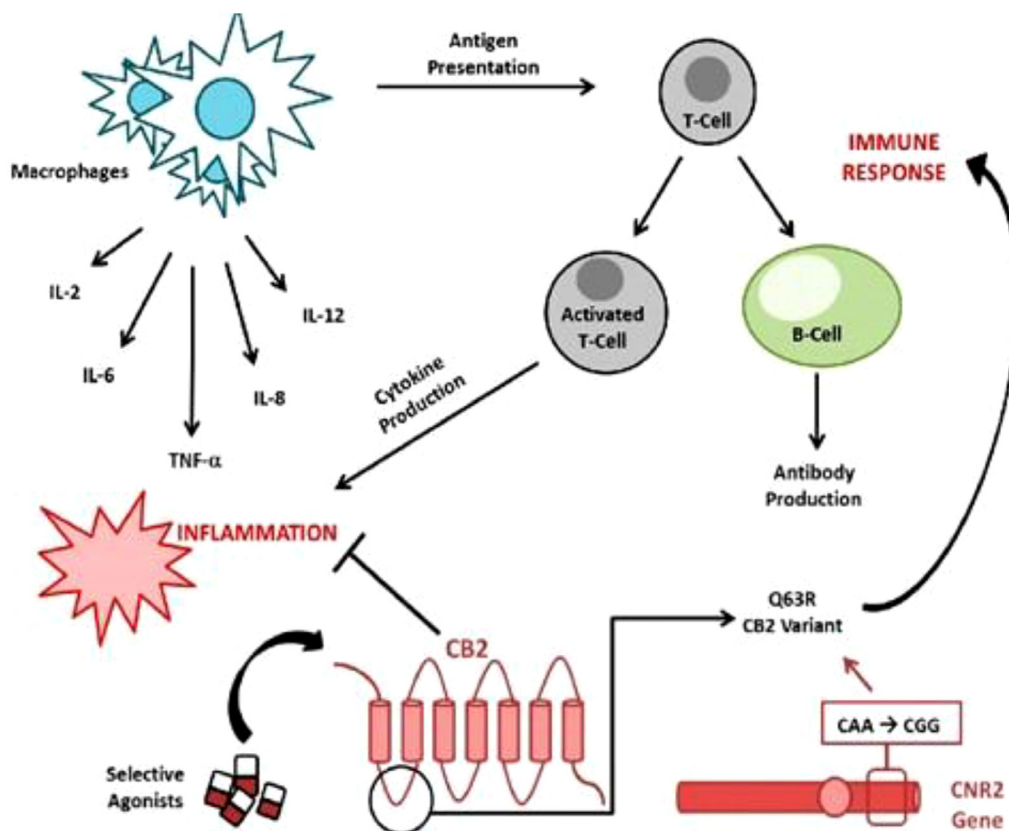


Fig. 4. The activation of the CB2 receptors attenuate pro-inflammation cascades. Activation of macrophages leads to the production and release of pro-inflammatory cytokines, and the activation of B- and T-cells. The binding of CB2 receptors to cannabinoids (selective agonists) inhibits the production of cytokines and the migration of B- and T-cells.

production increases unabatedly, more ATP is broken down leading to its decrease to below the physiological needs, contributing to the establishment of diseased states in cells (Abouelkhair, 2020). However, the polyphenolic structure of CBD makes it a suitable antioxidant and anti-inflammatory compound (Aviello et al., 2012; Malinowska et al., 2021). The immuno-modulatory and neuroprotective effects of CBD against cellular injuries have been well-established in recent scientific reports. Also, the modulation of the TRP channel activity by THC is believed to play a major role in ameliorating chronic inflammation (McKenna and McDougall, 2020). The medicinal attributes of CBD and THC have been exploited in some FDA-approved cannabis-containing drug formulations including Epidiolex® and Sativex® indicated for managing epilepsy, and the alleviation of spasticity and multiple sclerosis-related pain, respectively (Gabarin et al., 2023). These drug formulations contain CBD as the sole active ingredient or both THC and CBD in equimolar concentration, however, the optimal ratio varies depending on the specific condition being targeted. The major protective actions of CBD and THC against the development of some chronic diseases are discussed in detail below. Key therapeutic mechanisms of action of these important phytocannabinoids are further summarised in Table 1.

5.1. Cancer

The levels of endocannabinoids and cannabinoid receptors vary in different cancerous cell types, highlighting the importance of cannabinoids in carcinogenesis (Kienzl et al., 2020). Both CBD and THC are involved in the management of cancer complications, including chronic pain (Valente et al., 2024). A mixture of both THC and CBD was reported to upregulate the BAX gene and Caspase proteins leading to the initiation of apoptosis of cancer cells (Le et al., 2024). In a recent review of the relevant literature, Marzeda and colleagues (Marzeda et al., 2021) posit that CBD and THC may be better candidates for combinational therapy with anticancer drugs in the treatment of melanoma due to the availability of only a limited number of clinical studies on their uses as a single therapy. In an ongoing multi-centre clinical trial (Gurgenci et al., 2024), the use of THC and CBD (1:20) in the management of symptom distress in advanced cancer patients is being explored underscoring their applications in palliative care.

CBD has been investigated for its potential in cancer treatment, as it can modulate the immune response in cancer patients (Wang et al., 2020). Inflammation is a major factor in cancer development as it affects the progression or discontinuation of abnormal cell growth (Yamamoto et al., 2021). Immune cells, regulated by the ECS, migrate to the tumor area during cancer development and determine the fate of the abnormal cell growth (Kienzl et al., 2020). CBD inhibited the degrading enzyme FAAH and attenuated inflammation in colon cancer cells (Aviello et al., 2012). Additionally, the immunosuppressive effect of adenosine has been observed in cancer treatment, further supporting the potential of CBD in modulating the immune response in cancer patients. It also reduces the proliferation of cancerous cells through the process of apoptosis. Apoptosis of colorectal carcinoma cells is induced by the binding of CBD to TRPV1, leading to downstream effects that cause cell death and the reduction of tumor size (Aviello et al., 2012). In the study of gliomas, CBD has demonstrated the ability to reduce tumor size. This effect is attributed to CBD's capacity to induce cancer cell death and inhibit the migration of immune cells to the tumor area (Seltzer et al., 2020). The key activities of CBD against the major hallmarks of tumorigenesis have been comprehensively discussed elsewhere (Yan et al., 2023).

THC has been commonly cited as a beneficial cannabinoid in the treatment of different types of cancers (Valente et al., 2024). Although the dosage and frequency are paramount, the use of THC in the treatment of chemotherapy-related complications in cancer patients has been effective (Hatfield et al., 2024). A study conducted

to investigate the effectiveness of cannabinoids in oral drug therapy concluded that THC is less cytotoxic and highly effective in the treatment of cancer due to its physicochemical content (Gallardo et al., 2024). Upon binding to CB1 and CB2 receptors in glioma cells, THC leads to sphingolipid ceramide production, a group of lipids that induces apoptosis (Velasco et al., 2012). Furthermore, THC was shown to halt the process of tumorigenesis and cancer progression by upregulating protein p8 (Velasco et al., 2012).

5.2. Anxiety and stress

The usefulness of cannabis in relieving anxiety and stress continues to be explored as the number of cannabis consumers increases (Mallick et al., 2024). In a previous study, the use of cannabis through inhalation showed over 50 % anxiolytic effects in participants with post-traumatic stress disorder. However, these effects did not allude to any specific cannabinoids present in the plant (LaFrance et al., 2020). However, in a 2020 report, cannabis inhalation by 670 participants led to a decrease in stress and anxiety levels in over 90 % of the participants with the anxiolytic and stress-relieving effects associated with THC rather than CBD as increasing the THC content resulted in more improved results while CBD increase showed no change in the study (Stith et al., 2020a). A more recent study attributed the observed anti-stress effects to CBD although the addition of THC can cause an increase in efficacy (Faraj et al., 2023). CBD doses of 300–1500 mg/day were found to treat anxiety and related symptoms (Vlad et al., 2020). Similarly, clinical and laboratory-based studies revealed a comparative advantage of CBD as an anxiolytic intervention over slow synthetic drugs (Simei et al., 2024). In a quasi-experimental study involving the use of cannabis flowers containing varying concentrations of CBD and THC, the CBD-rich cannabis forms were linked with decreases in acute tension in participants which may translate to anxiety symptoms relief (Bidwell et al., 2024). Despite these promising positive effects against anxiety and stress, it is advised to take precautions when using cannabis. It should be limited to only when other interventions fail due to the lack of data to conclude its efficacy (LaFrance et al., 2020). The tolerability profile, side effects, and abuse of cannabis, specifically THC, have limited the use against stress and anxiety when compared with other management strategies (Short et al., 2022). A combination strategy involving the controlled use of cannabis with other anxiety sensitivity-reducing methods may limit drug abuse and consequent side effects.

5.3. Nausea and vomiting

Vomiting and nausea, also known as emesis, are indicators of underlying disease or adverse effects, associated with the release of serotonin by enterocytes which is controlled by the binding of ligands to CB1 receptors (Serafimovska et al., 2020). The use of cannabis by patients undergoing chemotherapy has been shown to relieve nausea and vomiting (Abrams, 2022). In a clinical trial conducted recently, the combination of CBD and THC (1:1) was effective in the treatment of nausea and vomiting (Grimison et al., 2020; Rock et al., 2020). The binding of CBD and THC to CB1 receptors inhibits serotonin release and reduces nausea and vomiting (Serafimovska et al., 2020). An optimal proportion of both THC and CBD was shown to be beneficial for patients experiencing nausea and vomiting as side effects of chemotherapy with a synergistic effect observed between THC and CBD (Sukpiriyagul et al., 2023). To this end, the American Society of Clinical Oncology (ASCO) recommends a combinatorial approach (cannabis + standard antiemetic drug) in improving refractory, chemotherapy-induced nausea and vomiting (Braun et al., 2024). The antiemetic effect of CBD is not dose-dependent with higher concentrations (more than 5 mg kg⁻¹) showing reduced effects (Rock et al., 2020). Although the therapeutic effect of the combination

Table 1
Potential therapeutic utility of Cannabis in chronic diseases.

Health benefits	Compound	Mechanisms of actions	References
Anticancer	CBD	Induces pancreatic cancer cell stress and death via ceramide synthase 1 and ER stress upregulation. Causes colorectal cancer cell death by inducing apoptosis, paraptosis, and autophagy through MAPK signaling. Inhibits breast cancer cell metastasis via influences on the FAK/ MAPK/Akt/NF- κ B signaling pathways. Reduces tumor size by apoptosis and suppresses immune cell migration to the tumor area in gliomas. Inhibits transcriptional factor Inhibitor of DNA binding protein 1 in advanced-stage breast cancer metastasis mouse models. Decreases cell proliferation by upregulating apoptotic processes. Inhibits the FAAH enzyme activity, and shields DNA from oxidative damage in a mouse model.	(Mangal et al., 2024) (Kim et al., 2024) (Suttithumsatid, et al., 2023) (Seltzer et al., 2020) (Murase et al., 2014) (Aviello et al., 2012)
	THC	Inhibits the proliferation of HCC1806 breast squamous cells. Suppresses tumor progression by inducing ceramide synthesis, which causes endoplasmic reticulum stress and autophagy-mediated cell death. Induces AMPK-dependent autophagy in hepatocellular cancer cells.	(Li et al., 2022) (Murase et al., 2014; Velasco et al., 2012) (Vara et al., 2011)
	Cannabis oil extract (3 CBD:1 THC)	Induces apoptosis by inhibiting the MAPK/ERK signaling in acute myeloid leukemia cells and increases survival rate in a leukemia mouse model.	(Lteif et al., 2024)
Anxiolytic	CBD	Acts as a 5-HT _{1A} receptor agonist in stress-induced hyperthermia and the phencyclidine-induced negative symptoms of schizophrenia mice models. Increases sedation and heart rate variability. Acts as a 5-HT _{1A} receptor agonist; affects amygdala activation and medial prefrontal amygdala connectivity in GAD, PD, and PTSD individuals.	(Shu et al., 2024) (Arnold et al., 2023; Spinella et al., 2021) (Blessing et al., 2015)
	THC	Interacts with the opioid system and 5-HT _{1A} .	(Lichenstein, 2022)
	CBD: THC (24:1) THC-rich cannabis flower	Reduces the DASS scores in a clinical trial. Provides relief from anxiety symptoms in self-reporting patients using the real-time Cannabis effects recording software, Releaf App	(Bidwell et al., 2024) (Stith et al., 2020b)
Anticonvulsant	CBD	Decreases the incidence of drop seizures in patients with Dravet and Lennox-Gastaut syndromes. Acts as a 5-HT _{1A} receptor agonist in decreasing the serotonin release leading to the amelioration of THC-induced nausea during cannabis overdose.	(Devinsky et al., 2018; Thiele et al., 2018) (DeVuono et al., 2022)
	THC	Inhibits serotonin levels through binding to the CB ₁ receptors.	(Serafimovska et al., 2020)
	CBD: THC (53:1)	Reduces the number of seizures in adults with drug-resistant focal epilepsy.	(Navarro, 2023)
Appetite-stimulating effects	CBD: THC (1:1) + standard antiemetics	Ameliorates refractory chemotherapy-induced nausea and vomiting in a clinical trial.	(Grimison et al., 2020)
	CBD	Binds to CB ₁ in the hypothalamus causing neuroendocrine responses which lead to increased food intake.	(Pinto and Martel, 2022)
	THC Cannabis (7% THC)	Increases appetite hormones such as ghrelin and GLP-1. Affects appetite and metabolism by modulating blood concentrations of insulin, total ghrelin, and GLP-1 in human participants.	(Nielsen et al., 2023) (Farokhnia et al., 2020)
Wound healing potential	CBD: THC (1:16)	Binds to the CB ₁ receptor in mediobasal hypothalamic neurons to stimulate appetite in a pre-clinical rat model.	(Wheeler et al., 2023)
	CBD	Promotes gingival fibroblast wound healing in oral inflammation and ulcers by inhibiting TNF- α and IL-1 β production in murine macrophage and human gingival fibroblast cells. Enhances bone healing by elevating the callus mineral density and bone volume fraction in a mouse model of fracture healing.	(Kongkadee et al., 2022) (Gabet, 2023)
	CBD and THC	Improves adipose- and bone marrow-derived stem cell regeneration through improvement in cell migration and faster wound closure.	(Miller et al., 2020)
Neuroprotective effects	CBD	Inhibits anandamide deactivation leading to antipsychotic effects against schizophrenia in a double-blind, randomized clinical trial. Decreases lipid peroxidation, halts antioxidant depletion, and upregulates HIF-1 α in a mouse model of global hypoxia. Enhances cognitive function by protective actions on the microbiota-gut-brain axis in a mouse model of Alzheimer's disease.	(Leweke et al., 2012) (Kletkiewicz et al., 2024) (Ma et al., 2024)
	THC	Downregulates NF- κ B and reduces inflammatory cytokines and free radicals in the nervous system.	(Yousaf et al., 2022)
Antimicrobial properties	CBD	Reduces the growth of pathogenic <i>L. monocytogenes</i> and <i>Staphylococcus</i> species in minced meat and nutrient agar, respectively. Inhibits the adhesion of methicillin-resistant <i>Staphylococcus aureus</i> to keratinocytes thus preventing biofilm formation.	(Duarte, 2016; Pasquali et al., 2020) (Luz-Veiga et al., 2023)
	Cannabis seed extract	Inhibits <i>Staphylococcus aureus</i> biofilm formation while preserving the healthy lactobacillus species population.	(Frassinetti et al., 2020)

(continued)

Table 1 (Continued)

Health benefits	Compound	Mechanisms of actions	References	
Anti-aging activity	CBD	Increases the health span and lifespan by boosting antioxidant status, and activating the glyoxalase, and autophagy pathways in <i>Caenorhabditis elegans</i> preclinical models.	(Wang and Arnold, 2024)	
	THC	Increases collagen formation and inhibits the synthesis of collagenases, such as matrix metalloproteinase-1.	(Trivedi et al., 2017)	
	Anti-obesity /Antidiabetic	THC	Reduces high-fat diet-induced obesity and obesity-induced hepatic steatosis in mice via adipose tissue adaptability and leptin sensitivity. Inhibits α -glucosidase enzyme activity in type 2 diabetic animals. Exhibits antioxidant effects against type 2 diabetes-induced oxidative damage.	(Eitan et al., 2023) (Suttithumsatid et al., 2022) (Kim et al., 2023)
		Cannabis extract (1 CBD:5 THC)	Restores glucose and lipid homeostasis by influences on peritoneal and intramuscular fat deposits and increasing mitochondrial activity.	(Ramlugon et al., 2023)
	Cannabis root extracts	Reduces blood glucose levels, pancreatic β -cell apoptosis, and pro-inflammatory cytokines in insulin-deficient diabetic mouse model.	(Kim et al., 2023)	
Anti-arthritic	Cannabis	Ameliorates disease activity in rheumatoid arthritis patients.	(Schulze-Schiappacasse et al., 2022)	

Akt: Protein kinase B; CBD: Cannabidiol; DASS: Depression, Anxiety, and Stress Scale; ER: Endoplasmic reticulum; FAK: Focal adhesion kinase; GAD: Generalized anxiety disorder; GLP: Glucagon-like peptide; HT1A: Serotonin 1A receptors; HIF-1 α : inducible factor-1 alpha; MAPK: Mitogen-activated protein kinase; NF- κ B: Nuclear factor κ -light-chain-enhancer of activated B cells; PD: Parkinson's disease; PTSD: Post-traumatic stress disorder; THC: Δ -9-tetrahydrocannabinol.

of CBD and THC is well-known and proven, the implementation is limited due to a lack of sufficient evidence on the long-term safety of cannabis in controlling nausea and vomiting (Grimison et al., 2020). Furthermore, CBD can counteract THC-induced nausea and vomiting in cannabinoid hyperemesis syndrome, an adverse effect of cannabis overdose (DeVuono et al., 2022).

5.4. Weight loss

Body weight control through the regulation of metabolism and the balance between nutrient intake and usage is crucial in managing downstream medical complications (Eitan et al., 2023). Although weight loss is a solution to several complications (e.g. obesity), excessive weight loss is often a problematic side complication of other diseases such as HIV and cancer (Osaghae et al., 2023). Excessive weight loss is associated with the deterioration of life quality and health in sick and old age individuals. A study investigated the nutritional and body composition change in old-aged participants and reported the appetite-stimulating effects of cannabis, which subsequently decreased weight loss (Nielsen et al., 2023). Oral ingestion or inhalation of cannabis has been reported to increase appetite and improve weight loss (Abrams, 2022). Inhaling cannabis (7.8 % THC: 0.5 % CBD) was shown to interact with CB1 receptor medio-basal hypothalamic neurons to stimulate appetite in a pre-clinical rat model (Wheeler et al., 2023). Appetite and metabolism are regulated by ECS activation when THC and CBD bind to the CB1 receptor (Eitan et al., 2023). These recent findings suggest the appropriate proportion of THC and CBD for an effective synergistic action in the improvement of weight loss. Moreover, CBD prevented cisplatin-induced myotube atrophy by restoring protein homeostasis and decreasing oxidative stress in cancer-mediated cachexia patients (Le Bacquer et al., 2024). Cannabinoids were also demonstrated to partially improve appetite and weight gain in cancer patients with anorexia of aging (Ceolin et al., 2024). More clinical studies are however needed to conclude its utility in this regard as contrasting results, mostly on homogeneous population, and the lack of sufficient statistical power, have been observed from the few available reports on cannabis use in anorexia-cachexia syndrome (Ceolin et al., 2024; Davis et al., 2024).

5.5. Neurological disorders

Several studies have shown the potential of CBD in the treatment of psychotic behaviors associated with increased neuro-inflammation, including conditions such as schizophrenia, epilepsy, and depression (Jha et al., 2024; Moreira et al., 2024). The antiseizure activity of CBD leading to the improvement in the quality of life in children with refractory epilepsy, Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex has been well-established (Borowicz-Reutt, Czernia and Krawczyk, 2024; Chico, Diaz and Contreras-Puentes, 2024). The FDA approved the consumption of CBD-containing products for the treatment of seizures in children (Britch, Babalonis and Walsh, 2021). Additionally, the neuroprotective potentials of cannabis constituents, including, CBD and THC, have been well-reviewed previously (Laws and Smid, 2022; Pathak et al., 2024). Both THC and CBD are involved in lessening chronic inflammation in neural cells and inhibiting the development of neurodegeneration caused by neuroinflammation (Al-Khazaleh et al., 2024). Due to their anti-inflammatory and antioxidant properties, THC and CBD were reported to restore memory in patients with Alzheimer's disease and reduce pain and tremors in Parkinson's disease (Gabarin et al., 2023). The neuroprotective effect of cannabis has been associated with the downregulation of the NF- κ B pathway and the reduction of free radicals in the nervous system (Yousaf et al., 2022). While both major cannabinoids are neuroprotective in central nervous system damage, THC is more associated with the reduction of inflammatory cytokines in neural cells, while CBD is involved in the inhibition of gliosis (Cooray, Gupta and Suphioglu, 2020).

6. Nutritional values of cannabis and cannabis-infused food products

Besides the well-established medicinal qualities of cannabis, the versatile plant has also received significant interest in its nutritional and food values. For example, hemp seeds are a rich source of nutrients, containing high levels of protein, lipids, minerals, and total dietary fiber (El-Sohaimy et al., 2022; Teterycz et al., 2021). The proteins found in hemp seeds, such as edestin and albumin, are readily digestible and serve as a valuable source of the sulfur-containing amino acids methionine and cystine. Furthermore, hemp seeds have high quantities of the essential amino acids,

arginine and glutamic acid (Cerino et al., 2021). Hemp protein isolate is a source of all nine essential amino acids (El-Sohaimy et al., 2022). Hemp seed oil is low in saturated fatty acids and high in polyunsaturated fatty acids (PUFA) such as linoleic acid, oleic acid, stearidonic acid, and α -linolenic acid and has an ideal ratio (3:1) of α -linolenic acid (ω -6) to linoleic acid (ω -3) (Iftikhar et al., 2021; Montero et al., 2023). This ratio enables the body's fatty acid metabolic pathways to function optimally (USDA, 2015). The abundance of PUFAs in hemp oil is associated with potential benefits in reducing the risk of cardiovascular disease, cancer, rheumatoid arthritis, hypertension, inflammatory issues, and autoimmune diseases (El-Sohaimy et al., 2022).

Hemp seeds are also a good source of vitamins (e.g., vitamins A, B, C, E, and K), minerals (e.g., sodium, calcium, magnesium, iron, phosphorus, potassium, and zinc), and bioactive compounds (e.g., tocopherol, terpenoids, cannabidiol, caffeine, and polyphenols) (Teterycz et al., 2021). These bioactive compounds help manage conditions such as anxiety and oxidative stress, and reduce the risk of developing chronic illnesses such as cancers, neurological disorders, digestive problems, and skin diseases (Farinon et al., 2020). Hemp seeds have water-soluble and water-insoluble fiber in a ratio of 20:80 (El-Sohaimy et al., 2022). The main fiber fraction is found in the seed hull, with the dominant fraction of the total dietary fiber (TDF) being insoluble fiber (Leonard et al., 2020). Insoluble fiber is an important prebiotic compound in reducing appetite, improving insulin sensitivity, and decreasing obesity and diabetes mellitus incidence (Leonard et al., 2020). The common nutrients found in hemp seed cultivars are presented in Table 2.

Cannabis products or edibles are foods or beverages that contain enough cannabis to induce a physiological effect (McClements, 2020). The cannabis plant can serve as an additive or ingredient in diverse food products and the seed or leaves are the most commonly utilized plant parts (Chandra et al., 2017). Adding hemp seeds enhances the nutritional value of food products and improves their sensory properties (Leonard et al., 2020). Historically, whole hemp seeds were crushed and consumed like peanut butter (Crescente et al., 2018). Dehulling is a relatively recent development that has allowed the incorporation of hemp seeds and their by-products into various foods such as yogurt, hemp milk, hemp flour, baked goods, pasta, rice, protein seed powder, energy bars, sauces, pralines, chocolates, beverages, candies, and gummies (Pasquali et al., 2020). Cannabis flowers and sprouts may also be ingested raw, or commonly made into juices and salads (Chandra et al., 2017). The acute reference dose (ARfD) for THC, set at 1 μ g THC per kg of body weight, is derived from its lowest observed adverse effect level (LOAEL). The LOAEL, established by the

European Food Safety Authority (EFSA), is determined to be 2.5 mg per day (corresponding to 36 μ g/kg of body weight in a 70 kg person) (European Food Safety Authority et al., 2020; Dräger et al., 2022). Hemp has a desirable nutritional and therapeutic profile and imparts these benefits to the products to which it is added. The various food applications of hemp currently available in the market are displayed in Table 3.

7. Standardization of CBD and THC contents in cannabis therapeutics and food products

The beneficial effects of cannabis have been attributed to the presence and proportion of its THC and CBD constituents in recent literature (Gottschling et al., 2020). However, extrapolating the positive results from the vast majority of the pre-clinical experiments and the few available well-designed clinical trials to clinical usage in humans is a major challenge. The lack of a standardized cannabinoid dosage in the cannabis forms mostly employed in these studies has contributed to the observed laboratory-to-laboratory variations in the few available clinical data on cannabis efficacy and safety (Azwell et al., 2022). This may be due to the difference in the content yield of different cannabis plants depending on the environment or method of cultivation (Chasiotis et al., 2022). Understanding the link between the geographical location, environment, or cultivation method and the resulting difference in chemical composition among different cannabis cultivars is important for standardizing dosage regimens (Arsenault et al., 2024; Das et al., 2022). This knowledge can also be used to achieve higher cannabinoid content in otherwise low-yield cannabis plant parts, for instance, a recent report observed uniformity in cannabinoid concentrations in the different plant parts by elevating the amounts in the lower part known to exhibit low concentrations through architecture modulation (Danziger and Bernstein, 2022). Thus, harvesting cannabis plant material from different parts of the plant may result in different cannabinoid content without manipulation. The complex interactions between the cannabis plant's morphological features, mineral or trace element composition, essential macro-nutrients, and cannabinoid concentrations have been well-reviewed elsewhere (Bernstein et al., 2019; Saloner and Bernstein, 2022a,; 2022b). In addition to this, plant density, time, and method of harvest of cannabis plants also play significant roles in the cannabinoid content (Danziger and Bernstein, 2021; Massuela et al., 2022). Furthermore, biotic or abiotic stress and the resultant plant responses that affect the chemical profile of cannabis can be harnessed to enhance therapeutic effects (Gorelick and Bernstein, 2017) e.g., differential and cultivar-specific changes in cannabinoid profile were obtained when cannabis was exposed to light spectra (Danziger and Bernstein, 2021). The post-harvest processing also influences the cannabinoid content in cannabis, for example, the drying of cannabis leaves, led to a decrease in CBD content (Das et al., 2022). Besides, the extraction solvent and method in the characterization of cannabis during production also influence the yield and purity of cannabinoids. Different extraction solvents (e.g. methanol, ethanol) and methods (e.g. Soxhlet, supercritical fluid, ultrasonication, percolation, microwave-assisted, etc.) resulted in varying efficiencies in the extraction of cannabinoids and bioactive compounds in cannabis (Martinez et al., 2023). The lack of proper quality control in sample preparation and analytical testing techniques in laboratories and industries may also introduce errors in data interpretation of cannabis doses used in experiments (Azwell et al., 2022). Therefore, the standardization of cannabis based on its cannabinoid composition, especially CBD and THC, is crucial in fully harnessing the medicinal and nutritional qualities. This will also help in the quest to clarify the tolerability and safety profile of the ever-increasing commercially available cannabis applications.

Table 2
Nutritional composition of hemp seeds.

Nutrient	Per 100 g	Reference
Energy	2313 kJ	(FoodData Central, 2015)
Protein	18–35 g	(Montero et al., 2023; Teterycz et al., 2021)
Carbohydrates	8 g	(FoodData Central, 2015)
Lipids	25–49 g	(Montero et al., 2023; Teterycz et al., 2021)
Saturated fat	4.6 g	(FoodData Central, 2015)
Monounsaturated fat	5.4 g	(FoodData Central, 2015)
Polyunsaturated fat	36–40 g	(FoodData Central, 2015)
Dietary fibre	4–28 g	(Teterycz et al., 2021)
Sodium	5–12 mg	(Farinon et al., 2020)
Calcium	90–955 mg	(Farinon et al., 2020)
Magnesium	237–700 mg	(Farinon et al., 2020)
Iron	4–240 mg	(Farinon et al., 2020)
Phosphorus	890–1170 mg	(Teterycz et al., 2021)
Potassium	252–2821 mg	(Teterycz et al., 2021)
Zinc	4–11 mg	(Farinon et al., 2020)

Table 3
Hemp-infused food products and their characteristics.

Product	Major characteristics	References
Hemp seed oil	CBD oil is blended with a carrier oil (e.g., hemp seed or coconut oil) to enhance absorption in the body. High in phytochemicals.	(Iseppi et al., 2019)
Hemp oil cake	By-product from hemp seed oil production. Rich in protein, dietary fiber, and minerals.	(Tetrycz et al., 2021)
Chocolate	Fat-based cannabis concentrates, such as waxes, budder, shatter, and live resin, containing up to 90 % THC are used in chocolate butter or directly in chocolate.	(Beal, 2019)
Dairy substitutes	Cannabis/Hemp milk and yogurt can be fortified with vitamins and minerals. Lactose-free, soy-free, and gluten-free. High-quality protein, essential fats, and minerals. Low in carbohydrates and calories.	(Dabija et al., 2018; Iftikhar et al., 2021)
Beverages	Alcoholic: Hemp-infused wines, cocktails, beers (3.5–6 % v/v, 10 mg CBD). Non-alcoholic: Seltzers, water, tea, coffee. Enhanced TPC, antioxidant activity, sensory, and therapeutic properties.	(Ramírez and Viveros, 2021)
Gluten-Free Products	Biscuits, bread, brownies, crackers. Gluten-free alternatives for gluten intolerance, celiac disease, and wheat allergies. High in protein, dietary fiber, minerals, essential fatty acids, TPC, and antioxidant activity. Softer texture, smaller volume, and darker color.	(Iftikhar et al., 2021; Korus et al., 2017; Mikulec et al., 2019; Wolf et al., 2016)
Cannabis fortified Pasta	High protein, dietary fiber, minerals, and fat content.	(Tetrycz et al., 2021)
Fruits	Fruit slices coated with 5 % cannabis flour. Increased polyphenol content, improved antioxidant capacity, and reduced weight loss.	(Jančíková and Dordevic, 2020)
Meat	Cannabis extract, with significant CBD concentration, is infused into meat. Possesses antimicrobial and antipathogenic properties.	(Pasquali et al., 2020)
Extruded rice	Whole and fat-free hemp powders are blended with rice flour. High in carbohydrates, protein, fat, moisture, TPC, and minerals.	(Norajit et al., 2011)

CBD: Cannabidiol; THC: Tetrahydrocannabinol; TPC: Total Phenolic Content.

8. Risks and adverse effects of cannabis consumption in humans

The legalization and widespread acceptability of cannabis and cannabis products for medicinal, nutritional, religious, or recreational uses continue to increase in recent times, somewhat, oblivious to the concerns raised about its acute or long-term safety assessment which had led to its initial global ban (Alshaarawy et al., 2024; Volkow et al., 2014). The ban may have been responsible for the decades-long lack of important scientific data on THC, as well as the ‘healthy’ non-psychoactive CBD since researchers had no or limited access (after a comprehensive vetting process) legally to use cannabis plants for scientific studies. However, the psychoactive THC has been named the major culprit in cannabis due to its perceived toxicity, especially in increasing the risk of developing mental health disorders such as schizophrenia and other psychoses, and negative neonatal outcomes in pregnant and predisposed individuals (Duperrouzel et al., 2020; Lo et al., 2024; Solmi, 2023). CBD has been largely well-tolerated with little or no adverse effects even at high doses in several pre-clinical and clinical trials (Gundugurti et al., 2024; Henderson et al., 2023; Stern et al., 2024; Tallon and Child, 2023) even as few studies indicate hepatotoxicity concerns (Chen et al., 2024). The impact of drug-to-drug interactions in patients with pre-existing conditions who consume cannabis may be profound, with potentially serious consequences thus necessitating the call for more safety assessment investigations (Hasanpoor et al., 2024). Secondhand cannabis smokers may also be liable for upward adverse effects notably respiratory issues (Cohn et al., 2024). Clinicians are frequently asked about the safety of cannabis by curious patients prompting the need for safety guidance and guidelines regarding its medical uses (Fischer et al., 2022; MacCallum et al., 2021). Current commercially available cannabis-containing products must adhere to regulations by having clear, easy-to-read health warnings on labels or packaging to inform the public about the possible risks of consumption (Massey et al., 2024).

The vast majority of the safety data on cannabis use are observational studies based on surveys detailing the causal association between cannabis and the onset or progression of toxicological consequences. While these reports raise awareness of the potential risks associated with cannabis consumption, more robust experimental studies with clearly defined clinical safety endpoints are warranted. The cross-sectional association between cannabis use and psychiatric disorders has been consistently documented (Degenhardt et al., 2013; Szoke et al., 2014) but other longitudinal studies have yielded mixed results (Bassalov et al., 2024; Crichton et al., 2024). Some studies reported the association of cannabis use with an increased risk of anxiety, depression (Yana et al., 2023), substance use disorders (Blanco et al., 2016), and respiratory or cardiovascular complications (Khoj et al., 2024), but these findings have not been replicated by others (Goldberg et al., 2023; Manrique-Garcia et al., 2012; Shamabadi et al., 2023; Theerasuwipakorn et al., 2023). Discrepancies may be partly explained by the varying demographics of study participants, inconsistent clinical endpoints, and different proportions of the cannabis active ingredients utilized (Degenhardt et al., 2013; Manrique-Garcia et al., 2012; Shamabadi et al., 2023). Due to the variation of cannabis constituents in plant types used in these studies, and with each possibly having a different mode of action and pathway, it is challenging to identify the specific compounds or combinations responsible for the observed effects. Therefore, more research focusing on elucidating the various mechanisms of action will aid in providing sufficient evidence of the significance of specific cannabis components. Despite these limitations, the recent reports of the potential risks and adverse effects associated with cannabis are summarised below and in Table 4 to give consumers a more balanced viewpoint needed to make informed decisions.

8.1. Cannabis use disorder

The use of CBD and cannabis-based medications for the treatment of neurological disorders such as childhood epilepsy, anxiety, sleep

Table 4
Potential toxicological effects of cannabis consumption.

Risks	Compound	Potential toxicological endpoints	Reference
Coronary heart disease	Cannabis	Increases (90 %) the odds of developing the prevalent coronary heart disease in an observational study.	(Skipina et al., 2022)
Hepatotoxicity	CBD	Increases liver-to-body weight ratios, plasma ALT, AST, and total bilirubin in a male B6C3F1 mouse model. Affects lipid metabolism and mitochondrial function in several models of liver injury. Causes hepatic degeneration in zebrafish embryos by regulating fatty acid binding protein 10A, GCLC, and GSR. Weakens liver metabolism in human induced pluripotent stem cells.	(Ewing et al., 2019) (Beers et al., 2024) (Wei et al., 2024) (Gao et al., 2024)
Teratogenicity	CBD	Induces the development of birth defects by downregulating the SHH signaling system in zebrafish embryos. Causes several reproductive malformations and death of adult zebrafish embryos.	(Son, 2021) (Li et al., 2024)
	THC	Suppresses the Hedgehog (HH) signaling system leading to birth abnormalities in genetically sensitized pregnant mice.	(Lo et al., 2021)
	CBD: THC (1:1)	Affects placental development by interfering with extravillous trophoblasts' (EVTs) migration and invasion in vitro.	(Alves et al., 2023)
	Cannabis	Increases the chances of preterm birth, small-for-gestational-age, and perinatal deaths in pregnant consumers.	(Li et al., 2024)
Pharmaco-toxicity	CBD	Increases N-desmethyloclobazam levels when co-administered with Clobazam in patients with pediatric-resistant epilepsy in an apparent drug-drug interaction.	(Geffrey et al., 2015)
Psychosis and Neuro-psychiatric Pathologies	THC	Pre-adolescent exposure induces long-term neuropsychiatric-like characteristics during electrophysiological investigation in rats. It also reduces GABAergic activity in the prefrontal cortex, which results in an inability to regulate subcortical dopamine neurotransmission appropriately.	(Renard et al., 2018)
	CBD: THC (20:1)	Affects visuospatial working memory and pattern recognition via delays in noticing errors and latency, doing tasks, and visual information recall in healthy adults.	(Manning et al., 2024)
Type 2 Diabetes	THC	Decreases sperm motility and testosterone production in a rat model.	(Van Losenoord et al., 2022)

CBD: Cannabidiol; DNA: Deoxyribonucleic acid; TNF- α : Tumour Necrosis Factor alpha; IL-1 β : Interleukin-1 beta; SHH: Sonic Hedgehog; CB1: Cannabinoid receptor 1; TRPV1: Transient receptor potential vanilloid 1; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: transmembrane serine protease 2; PPAR γ : peroxisome proliferator-activated receptor gamma; THC: Δ -9-tetrahydrocannabinol; GABA: Gamma-aminobutyric acid; GCLC: Glutamate-cysteine ligase catalytic subunit; GSR: Glutathione reductase.

disorders, and even as an adjuvant treatment for psychosis has increased over the last decade (McGuire et al., 2018). However, chronic use of cannabis may increase the risk of side effects - such as cannabinoid hyperemesis syndrome, a cannabis use disorder characterized by the inability to quit using the drug or functional impairment (Sorensen et al., 2017). Approximately 23.8 million people worldwide suffer from cannabis use disorder according to the 2019 Global Burden of Disease Report with an estimated prevalence rate of 22 % and 29 % in recreational and medical users respectively (Dawson et al., 2024). Cannabis usage comes in third place among substances that are abused, behind alcohol and tobacco globally (Connor et al., 2021; Hasin et al., 2016; Peacock et al., 2018; Solmi et al., 2023). In line with this, patients using cannabis for therapeutic purposes may become addicted increasing the risk of adverse effects thus highlighting the importance of a greater awareness (Solmi et al., 2023).

8.2. Substance use disorder

Recreational marijuana use and the associated disorders are on the rise (Reece and Hulse, 2021). A three-year follow-up multi-variant adjusted analysis conducted within the general population has revealed an association between cannabis usage and a higher risk of substance use disorders, such as those related to alcohol, nicotine, and other drugs, as defined by the Diagnostic and Statistical Manual of Mental Disorders (Blanco et al., 2016). For the most part, young adults suffer from cannabis dependence, and it is likely that cannabis and other substances developed a cross-adaptation through similar mechanisms of action or neuroadaptation and could account for drug use disorders (Baker et al., 2011). Medical practitioners and policymakers should carefully assess cannabis usage and health consequences, even if it has not been demonstrated to increase mortality as opioids and other types of illicit drug dependence do (Degenhardt et al., 2013).

8.3. Increased risk for psychosis

Cannabis consumption has been associated with an increased risk of behavioral health conditions, including anxiety disorders, depression, delirium, psychosis, and other drug use disorders and somatic issues, especially pulmonary problems. The processes by which cannabis may induce psychosis (such as schizophrenia and schizotypy) have been the focus of clinical and experimental investigation as well as theoretical speculations (Groening et al., 2024). Among the several psychotropic substances found in *C. sativa*, THC is the most prevalent (Bozman et al., 2022). THC acts by binding to CB1 receptors in the brain regulating the release of many neurotransmitters (Serafimovska et al., 2020). The neurobiological effects of cannabis use, such as altered glutamatergic, GABAergic, and dopaminergic cell activity, are congruent with anomalies seen in patients exhibiting psychotic symptoms (Ferland and Hurd, 2020). The majority of chronic usage symptoms are similar to schizophrenia symptoms. Higher doses of THC have reportedly been shown to enhance psychosis and schizophrenia-like symptoms (Kancherla et al., 2021; Shen, 2020).

Research demonstrating that using cannabis during adolescence is linked to an increased risk of psychosis in later life raises the possibility that cannabis may also contribute to psychosis by interfering with normal brain development (Kiburi et al., 2021). According to the reports, the adolescent brain is more vulnerable to THC, which is known to cause psychosis and has receptors spread throughout the brain, especially the prefrontal cortex. However, the mechanism underlying this increased vulnerability is unknown and requires additional research (Burggren et al., 2019; Shen, 2020).

8.4. Adverse effects in pregnancy and lactation

It has been reported that using marijuana when pregnant or lactating is unsafe. For this reason, it is advised that women who are pregnant or intend to get pregnant avoid ingesting marijuana as it may have detrimental impacts on the long-term health of their

children as well as the development of the mother and fetus (Polcaro and Vettrano, 2020). Using generalized linear models with an inverse probability weighting methodological approach, a population-based retrospective cohort study examined the relationship between cannabis use and outcomes for mothers and newborns. Even after accounting for several confounding variables, this study indicated that cannabis ingestion during pregnancy is linked to decreased fetal growth and early postnatal complications (Koto et al., 2022). Avoiding cannabis during pregnancy, lactation, adolescence, and the early stage of adulthood is supported by a growing body of research. Cannabis-based medicines, however not without adverse effects, are helpful for patients with a variety of medical diseases, such as cancer and epilepsy amongst other medical conditions.

A summary of selected studies reporting the specific harmful consequences following exposure to cannabis, CBD, or THC in cell culture, in vivo models, and clinical trials are further displayed in Table 4.

9. Prospects and conclusions

The increasing interest in cannabis for medicinal and nutritional purposes has been primarily fueled by the therapeutic potential of the cannabinoid constituents notably cannabidiol (CBD) and Δ -9-tetrahydrocannabinol (THC) thus underscoring the need for a comprehensive understanding of their effects on human health. While CBD shows promise in alleviating various health conditions such as chronic pain, anxiety, and inflammation, THC's psychoactive properties and associated risks raise concerns, particularly regarding cognition, addiction, and psychiatric health. The interplay between CBD, THC, the endocannabinoid system (ECS), and downstream effects forms the basis of their pharmacological actions, and sadly, accompanying adverse outcomes. Moving forward, future research efforts must prioritize elucidating the specific molecular mechanisms of actions of these important cannabinoids and their interactions with the ECS to develop targeted and effective medical or nutritional interventions. The studies must also employ standardized dosage regimens for an accurate understanding of dose-response relationships and proper interpretation of data or extrapolation of results. Standardized regulations and comprehensive education that are backed by pertinent scientific data are imperative to ensure the safe and responsible use of cannabis-derived products for both food and medicine. By leveraging the recent advancements in cannabinoid science and regulatory frameworks, we can effectively harness the therapeutic benefits of cannabis while mitigating the associated risks. Furthermore, continued exploration into alternative consumption methods and innovative product formulations will expand the accessibility and versatility of cannabis-based therapies, catering to diverse consumer needs and preferences. A nuanced understanding of the potential merits and demerits of cannabis and cannabis-containing products is essential for optimizing their utility in healthcare and ensuring the well-being of patients and consumers worldwide.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

M Nethengwe: Conceptualization, Formal analysis, Investigation, Writing – original draft. **Y Maphosa:** Formal analysis, Investigation, Writing – original draft. **BO Ahiante:** Formal analysis, Investigation, Writing – original draft. **AB Oyenihi:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Project administration, Supervision.

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