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Current Pharmaceutical Biotechnology, XXXX, *XX*, 1-17

SYSTEMATIC REVIEW

Cannabinoids and Brain Damage: A Systematic Review on a Frequently Overlooked Issue

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Abstract: ***Background*:** Although cannabinoid consumption represents a current social and health problem, especially in a historical context characterized by an open orientation for recreational and therapeutic purposes, risks regarding the neurotoxicity of such substances are frequently overlooked.

***Objective*:** The present systematic review aims to summarize the available evidence regarding the mechanism of cannabinoids-induced brain damage as a substrate of neurological, psychiatric, and behavioral effects. Another objective is to provide support for future investigations and legislative choices.

***Methods*:** The systematic literature search through PubMed and Scopus and a critical appraisal of the collected studies were conducted. Search terms were "(("Cannabinoids" OR "THC" OR "CBD") AND "Brain" AND ("Damage" OR "Toxicity"))" in the title and abstracts. Studies were included examining toxic effects on the brain potentially induced by cannabinoids on human subjects.

***Results*:** At the end of the literature selection process, 30 papers were considered for the present review. The consumption of cannabinoids is associated with the development of psychiatric, neurocognitive, neurological disorders and, in some cases of acute consumption, even death. In this sense, the greatest risks have been related to the consumption of high-potency synthetic cannabinoids, although the consumption of phytocannabinoids is not devoid of risks.

***Conclusion*:** The research carried out has allowed to highlight some critical points to focus on, such as the need to reinforce the toxic-epidemiologic monitor of new substances market and the importance of information for both medical personnel and general population, with particular attention to the mostly involved age groups.

ARTICLE HISTORY

Received: February 27, 2022
Revised: March 30, 2022
Accepted: April 27, 2022

DOI:
10.2174/1389201023666220614145535

Keywords: Toxicology, cannabinoids, cannabis, brain damage, toxicity, THC, CBD.

1. INTRODUCTION

Cannabis, derived from a female plant Cannabis sativa, has been used for centuries in many cultures under different names [1, 2]. Two of the most common preparations, Marijuana and Hashish, respectively refer to a mixture of the leaves and flowering tops, and dried resin and compressed flowers. Cannabis contains more than 100 chemical compounds known as "phytocannabinoids", or commonly cannabinoids, to distinguish them from pharmacologically analogous endocannabinoids and artificially produced compounds (synthetic cannabinoids or SCs) [3-5]. The principal cannabinoids are Δ9-tetrahydrocannabinol (Δ9-THC or THC), cannabidiol (CBD) and cannabinol (CBN). THC and CBD are lipophilic metabolites of resorcinol [3].

Despite its millenary usage, the isolation and characterization of its components has been delayed until recent years. Firstly, in 1940, CBD was identified in an extract of Minnesota wild hemp by the Nobel laureate Lord Alan Todd [6] and Roger Adams [7], while Δ9-THC was characterized the as the primary psychoactive compound in Cannabis plant preparation in 1964 by Gaoni and Mechoulam [8]. At the same time, the discovery of cannabinoid receptors CB1 and CB2 and their basic mechanisms only took place between the end of the 80s and the beginning of the 90s of the last century [9].

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1389-2010/XX $65.00+.00

The consumption of cannabinoids is a current social and health issue related to their progressive use in the medical field, the introduction of new synthetic products and the policies adopted by individual states [10]. As regards the medical field, for example, cannabinoids find main application in the treatment of adult chronic pain, spastic symptoms of multiple sclerosis, as an antiemetic during chemotherapy and in the control of some types of seizures; there is also partial evidence for their use in the treatment of diseases such as glaucoma, dementia, Parkinson and sleep disorders [11]. Depending on the indication, compounds with different ratio of THC and CBD, or other synthetic derivatives, can be used for medical purposes. For example, currently FDA-approved cannabis-derived medications are dronabinol and nabilone (two synthetic forms of delta-9-tetrahydrocannabinol), as well as cannabidiol [12]. Nabiximol (at 1:1 THC/CBD compound) has instead been approved in some states including Canada and the United Kingdom; however, some studies are focusing on experimenting further synthetic derivatives for use in the medical field.

1.1. Endocannabinoids

Endocannabinoids are eicosanoid neurotransmitters able to modulate many physiological and cognitive processes. Anandamide [N-arachidonoylethanolamine, AEA] (from the Sanskrit word "*ananda*" for "*bliss*") was identified in 1992 as the first endogenous cannabinoid ligand [12]. Other endocannabinoids include Palmitoylethanolamide (PEA) and 2-arachido-noylglycerol (2-AG).

Endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the proteins that transport, produce, and degrade these lipidic compounds are parts of the endocannabinoid system (ECS). It plays a central role in the developing nervous system and in modulating neuronal activity and network function [13] other than being involved in many aspects of mammalian physiology and pathology [14], as well as participating in the regulation of the levels of other endogenous signals and influencing the activity of noncannabinoid receptors [15].

1.2. THC

THC, a high-affinity partial agonist of CB1 and CB2 receptors, is responsible for almost all the psychomimetic activity of the plant. It has a concentration lower than 5% for traditional plants, while in newer genetically modified plants such as the popular "skunk" or "sinsemilla" may arrive to raise to much larger percentage such as 12-16% or higher. The concentration of THC can also reach about 80% in butane hash oil [16].

THC is involved in many neurotransmission pathways [3] thus determining several therapeutical, recreational, and collateral effects.

1.3. Cannabidiol

CBD is a non-psychoactive compound with numerous molecular targets. It has a lower affinity for CB1 but may antagonize the receptor function by negative allosteric modulation of the orthosteric receptor site [17-20] and consequently modulate psychotropic and other effects of THC.

CBD also shows an indirect agonism by increasing the constitutional activity of CB1 receptors ("endocannabinoid tone") and has been studied for its sedating, antiepileptic, antiemetic, anti-inflammatory, anxiolytic and neuroprotective properties [18].

1.4. Synthetic Cannabinoids

SCs represent a heterogeneous group of substances originally designed and developed for scientific purposes under the impulse of the description of cannabinoid receptors and enzymatic machinery [21], to study both the endogenous cannabinoid receptors system and the potential therapeutic relevance [22].

Three main families of synthetic compounds have been developed: new agonists and antagonists of CB1/CB2 receptors, inhibitors of the hydrolase enzymes or of endocannabinoid metabolism, and allosteric modulators of CB1/CB2 receptors [21].

Since 2008, SCs started to spread, sold as incense products or 'legal highs', often labeled not for human consumption and usually designated with the name of "spice" or "fake cannabis" [2, 23]. Although they have been developed for experimental purposes, SCs are currently widespread in the illigal drugs market, especially for their high potency, easy access, difficulty of detection, and the rapid development of ever new substances that can escape legal restrictions [22, 23].

The SCs most frequently reported are the "JWH" series [24] (encompassing JWH-018, JWH-019, JWH-073, JWH-250), HU-210, cyclohexylphenol (CP) cannabinoids, WIN55212, RCS-4, MAB-CHMINACA, MDMB-CHMICA, among many others. Properties of SCs are a generally very high agonism at CB1 receptors (2-100 times more potent than THC) [25] and the absence of cross-reaction with cannabinoid immunoassays, necessitating the use of LC-MS(-MS) or other high-sensitivity mass-spectrometric techniques for their identification [2].

1.5. Cannabinoid Receptors

Cannabinoid receptors CB1 and CB2, G protein-coupled receptors (GPCRs), were the first to be discovered and still are the best characterized.

CB1 receptors are largely ubiquitous on different types of neurons (*i.e.*, glutamatergic, cholinergic, glycinergic, dopaminergic, serotonergic, and opioid neurons) [26], but particularly abundant on certain GABAergic interneurons [27]. CB1 receptors are practically present in whole neuronal structure, especially on synaptic terminals [28], but also on somata, dendrites [29-31] and mitochondria [32]. In glial cells, CB1 receptors are expressed by some astrocytes [33] and, in a lower amount, on oligodendrocytes.

CB1 receptors are particularly expressed in CNS areas involved in cognition, reward, anxiety, pain perception and movement, such as the cortex, hippocampus, olfactory area, basal ganglia (substantia nigra, pars reticulata and globus pallidus), cerebellum and spinal cord, [34,35]. Conversely, their poor concentration in the brainstem has been associated with the low recurrence of respiratory depression in cannabinoid abuse.

While CB1 receptors are mainly expressed into the brain and central nervous system (CNS), CB2 receptors are predominantly localized in the peripheral nervous system and the immune system [11, 36] including microglia, [37, 38] and in a lower proportion by CNS neurons [39].

These receptors are only two of the many that constitute the ECS. In recent years, scientific interest in ECS has grown contextually to the discovery of its central role both in the developing nervous system and in the modulation of neuronal activity and network function [40].

1.6. Purposes

The use of cannabinoids, despite the therapeutic possibilities, is not free from side effects and possible damage for health, which are currently still little known. Although neurocognitive and psychiatric alterations are extensively reported in literature, there is less evidence about the organic effects of cannabinoids on the central nervous system and the subsequent functional impairment [21, 23]. The present systematic review aims to summarize the available evidence regarding the mechanism of cannabinoid-induced brain tissue damage as a substrate of neurological, psychiatric, and behavioral effects. The data obtained from our study, other than being helpful for future investigations, could hopefully be support legislative choices that should be led by an accurate and scientifically based analysis of the benefits and risks of cannabinoid use.

2. MATERIALS AND METHODS

2.1. Search Criteria and Critical Appraisal

A systematic literature search through PubMed and Scopus and a critical appraisal of the collected studies were conducted. Boolean operators, MeSH terms, and free-text terms were used to expand results and not to exclude potentially relevant articles. “Human”, “English”, “Full Text” were applied as filters. The last research was carried out on November 10th, 2021.

The “*Similar articles*” sections and the references of the selected articles were consulted to expand the research.

Search terms were “(("Cannabinoids" OR "THC" OR "CBD") AND "Brain” AND ("Damage" OR "Toxicity"))” in title and abstracts.

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement’s criteria were used in the inclusion of articles in the present systematic review [41,42].

Evaluation of bias was included in the methodological appraisal of each study. Two researchers independently examined the papers resulting from the research and selected those that analyzed brain damage or toxicity due to the assumption of cannabinoids. Disagreements between the two researchers during the articles’ selection phase were resolved through a consensus process. Unpublished and gray literature was not considered. Data were extracted by a single investigator and subsequently verified by another one.

2.2. Eligibility Criteria

Studies examining toxic effects potentially induced by cannabinoids on human subjects were included. Study designs comprised case reports, case series, retrospective and prospective studies, book chapters, institutional reports, as well as simple or mini- or systematic reviews.

3. RESULTS

The application of the search strategies above allowed us to find a total of 68 studies in PubMed and 69 studies in Scopus database, resulting in a total of 137 papers. Initially, 32 duplicate results were removed. Of the 105 remaining articles, 15 were removed during a title/abstract screening because irrelevant. Full text review conducted on 90 studies allowed to select of 16 eligible contributions. Further 14 studies were added during the analysis of similar articles and references. At the end of the process, 30 papers were considered for the present review in the PRISMA flow diagram (Fig. **1**, Tables **1**-**3**).

3.1. Psychiatric Aspects

Cannabis is mostly used for its recreational effects, inducing sociability, happiness, and calmness. Anyway, unpleasant mood, as well as irritability, anxiety, anger, depression, agitation, and suspiciousness, can be frequent not only with users but also with drug withdrawal [43-46].

Acute cannabis use can adversely affect cognitive integrity by inducing bizarre thoughts, feelings of depersonalization [47] and schizophrenia-like symptoms [48]. These acute effects are well demonstrated to hesitate in drug-induced psychosis and other psychiatric problems such as depression, mania, and anxiety in protracted consumption [43, 49].

Other than acute intoxication, also chronic, frequent, and high-potency cannabis assumptions are related to an increased risk of psychosis [50]. As abnormal dopamine neurotransmission is considered the core of the genesis of psychotic symptoms, studies have highlighted a possible relationship between cannabis and dopamine signaling alterations [51]. Despite some preclinical research suggesting the influence of THC on dopamine transmission in animals [51], such results in humans are still partial, with more evidence for those genetically predisposed or chronic users. As shown by some animal models, dopamine transmission is also called into question for the rewarding effects of THC, with its own probable mediation in the mesolimbic system [52].

Also, glutamatergic transmission could be involved [53], as animal studies have indicated how THC can depress glutamate transmission in different brain regions (cerebellar striatal, midbrain, hippocampal), while its chronic administration can affect glutamatergic signalling and disrupt glutamate synaptic plasticity.

Cannabis can also adversely affect the hypothalamic-pituitary-adrenal axis with an increase in cortisol secretion in acute THC administration and lower hormonal reactivity to social stress in regular users [43].

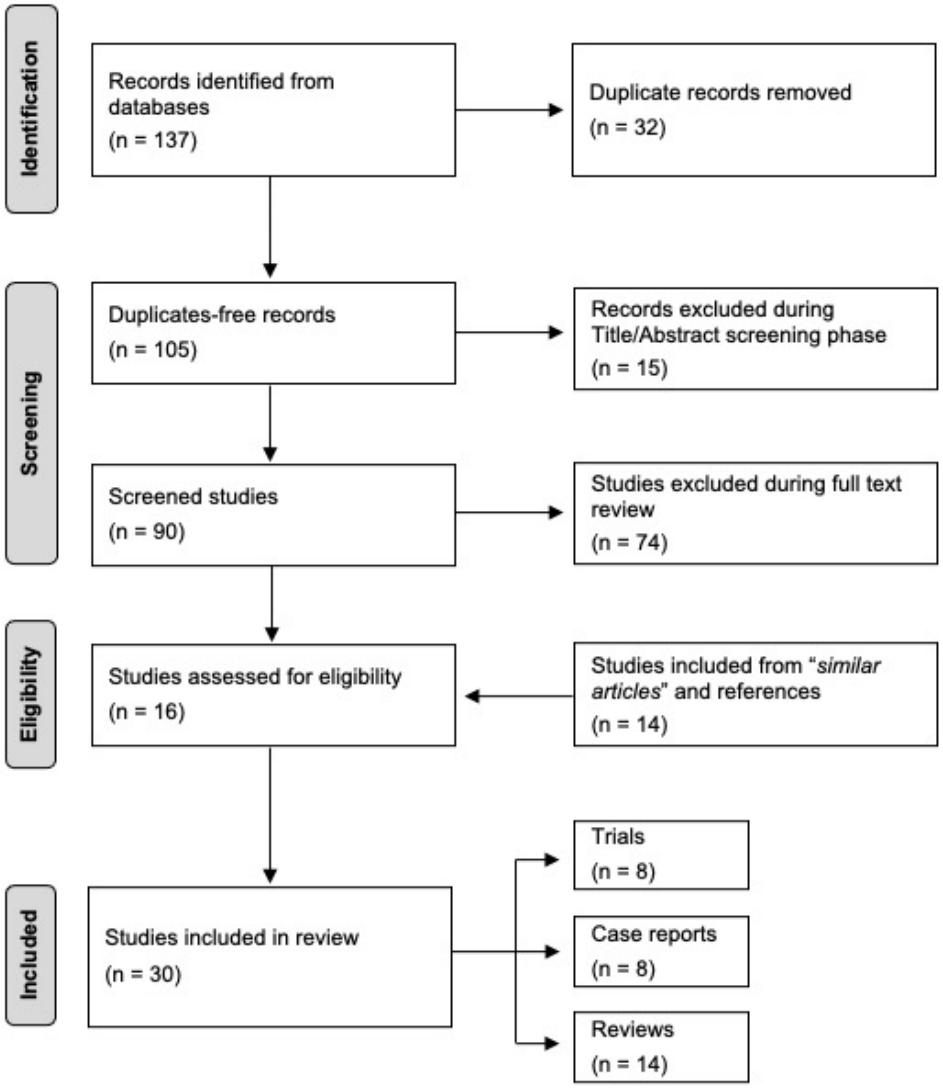

Fig. (1). PRISMA flow diagram.

3.2. Neurocognitive Effects

Many cognitive skills are impaired by acute cannabis use, including memory learning new information, sustained attention, higher cognitive abilities such as executive functions, and more basic abilities such as psychomotor integrity [43, 54].

As concerns chronic effects, Fried *et al.* [55] conducted a longitudinal study including young adults using neurocognitive tests that had been administered prior to the first experience with marijuana smoke. Urination samples and self-reports stratified individuals as “light” (fewer than five times a week) or “heavy” (greater than five times a week) and “current" or “former” (abstinent for at least three months) users. Worse performances in overall Intelligence Quotient (IQ), processing speed, and immediate and delayed memory tests were recorded only in current heavy users, while former heavy marijuana smokers did not show any cognitive impairment. It has been assumed that the effects of cannabis on prospective memory are attenuated in long-term abstinence (at least three months) [56].

Anyway, results in this field are conflicting. For example, Meier *et al.* showed that long-term users who commence usage during adolescence undergo a slow decline in intelligence test scores over time [57]. Adolescence is a critical period of neurodevelopment during which synaptic modelling and myelination are in constant evolution and so particularly sensitive to drugs and toxins [58, 59]. In addition, in this period, cannabinoid receptors are highly abundant in white matter and its connections and integrity can be damaged by cannabis use [60].

Similar reports came from animal studies [52]. The impairment of working memory by THC in adult rats is enhanced in chronic exposure and attenuated by abstinence from the drug [61], but those treated with very high escalating doses of THC when adolescents remained impaired in spatial working memory during their adulthood even if abstinent. Moreover, working memory deficits were accompanied by a decrease in hippocampal dendritic spine density and length [62].

Furthermore, the use of cannabis as a medical drug has been shown to determine decline in working memory

Table 1. Trials.

Study	Model	Results
Bladen *et al.* (2021) [106]	*In vitro.* Activity of Synthetic Cannabinoid Receptor agonists (SCRAs) on T-type calcium channels and involvement in a possible mechanism of toxicity.	SCRAs were potent agonists of CB1 receptors and could be extremely toxic. Many SCRAs tested were potent modulators of Cav3.2, raising the possibility that toxicity may be partly due to this mechanism.
Coccini *et al.* (2021) [107]	*In vitro.* Cell culture applying human-derived CNS cells (neurons and astrocytes) exposed to synthetic cannabinoid MAM-2201.	Cytotoxic effects of synthetic cannabinoid MAM-2201 on human primary neurons (hNLCs) and astrocytes cell line (D384) were concentration- and time-dependent.
Schloss *et al.* (2021) [136]	Tolerability study on two different ratios of medicinal cannabis in adult patients diagnosed with a high-grade glioma.	No serious adverse events occurred. Neurological side effects included: tiredness at night (11%), dizziness at night (10%), drowsiness (7%). Psychiatric side effects reported by 6% of participants (mild hallucinations, paranoia, or euphoria at night).
Tzadok *et al.* (2016) [131]	A retrospective study describing the effect of cannabidiol (CBD)-enriched medical cannabis on children with drug-resistant epilepsy.	CBD reduced the frequency of seizures but almost a half of patients experienced secondary effects such seizure aggravation (18%), somnolence/fatigue (22%) and irritability (7%).
Battistella *et al.* (2014) [65]	Neuroimaging investigation on gray matter changes in a group of regular cannabis smokers.	Regular cannabis use was associated with gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex. Age of onset of drug use, frequency of cannabis use and heavy consumption represented significant variables.
Solowij *et al.* (2011) [80]	Neuroimaging investigation on cerebellar gray and white matter in cannabis users with and without schizophrenia.	Cerebellar white-matter volume was reduced in cannabis users with and without schizophrenia by 29.7% and 23.9% respectively, and by 17.7% in patients not exposed to cannabis.
Yücel *et al.* (2008) [58]	Neuroimaging investigation on brain changes in a group of long-term heavy cannabis users.	Cannabis users had bilaterally reduced hippocampal and amygdala volumes. Cumulative exposure to cannabis mediated left hippocampal volume reduction and subthreshold positive psychotic symptoms.
Klegeris *et al.* (2003) [105]	*In vitro.* Study on neurotoxic and neuroprotective effect of CB1 and CB2 receptors ligands.	Δ9 and Δ8-tetrahydrocannabinol (THC) were toxic when added directly to SH-SY5Y neuroblastoma cells. Specific CB2 receptor ligands could be useful anti-inflammatory agents, while avoiding the neurotoxic and psychoactive effects of CB1 receptor ligands such as THC.

Table 2. Case reports.

Study	Model	Results
Černe (2020) [130]	Review of studies on cannabis effects on humans and animals, *in vivo* and *in vitro*.	A summary of acute and chronic toxicological effects of THC and CBD was reported.
Claudet *et al.* (2017) [127]	Retrospective cohort study of children (29) admitted to a pediatric emergency department due to unintentional cannabis exposure over a 10-year period from 2004 to 2014.	More severe presentations occurred from 2012 to 2014; they were possibly explained by (1) the increased THC concentration in cannabis and (2) the widespread use in young adults.
Katz *et al.* (2016) [121]	Case series describing 11 patients exposed to the synthetic cannabinoid MAB-CHMINACA.	Report of life-threatening toxicity including obtundation, severe agitation, seizures, and death.
Hill *et al.* (2016) [117]	A case series of seven men with toxicity induced by synthetic cannabinoid MDMB-CHMICA.	Clinical features included respiratory, metabolic, or mixed acidosis, reduced level of consciousness, mydriasis, tachycardia, bradycardia, tonic–clonic convulsions and agitation.

(Table 2) Contd….

Study	Model	Results
Dines *et al.* (2015) [124]	Case series of cannabis-related presentations to the emergency departments, reported in the first 6 months of data collection from the Euro-DEN project.	1 fatal and 35 non-fatal lone cannabis cases, with neurobehavioral features reported as the most common clinical presentation.
Lapoint *et al.* (2011) [122]	A case of severe toxicity following synthetic cannabinoid JWH-018 ingestion.	Report of agitation and generalized seizure.
Trecki *et al.* (2015) [120]	Clusters of cases of adverse health effects or severe toxic effects and deaths associated with Synthetic Cannabinoids (SC) product use from 2012 to 2014.	Increase in the incidence of clusters of synthetic cannabinoids intoxication resulting in severe ill-ness and death.
Pélissier *et al.* (2014) [125]	A case series of children under the age of 6 years admitted to emergency department with cannabis poisoning reported as accidental.	Symptoms were mainly neurological: drowsiness, hypotonia, dilated pupils, ataxia.
Appelboam & Oades (2006) [126]	A case report of coma due to cannabis ingestion in an 11-month-old toddler.	Serious decrease of the level of consciousness (GCS=9) with normal CT and lumbar puncture. At EEG performed after admission: no epileptiform orencephalitic activity, but occipital medium voltage irregular slowing suggesting intoxication.

Table 3. Reviews.

Study	Model	Results
Kaczor *et al.* (2021) [129]	Description of temporal, demographic, and clinical characteristics of accidental and intentional exposures of children/adolescents to cannabis.	High frequency of neurological side effects, including lethargy/somnolence (59%), ataxia/dizziness (50%), and confusion (34%), while seizures were found to occur only in few cases (3% in all population and 8% in 0–9 years patients).
Parrott *et al.* (2017) [43]	Review of the empirical literature on recreational cannabinoids.	Mood changes as unpleasant mood, irritability, anxiety, anger, depression, agitation, and suspiciousness were found not only with use but also with drug withdrawal. Potential addictive power for high-potency products such as "skunk" and SCs.
Mandelbaum & La Monte (2017) [60]	Focus on benefits and harmful effects of cannabis exposure. An illustration of the neuropathologic findings in a fatal case of cannabis-induced psychosis is also provided.	White matter was a demonstrated target of cannabis-mediated neurodegeneration, with prominent demyelination and axonal damage within fornix, corpus callosum, and central cerebral white matter.
Wolff & Jouanjus (2017) [83]	Review on the role of cannabinoids in the occurrence of neurovascular complications among young consumers.	Ninety-eight patients were described in the literature as having a cannabinoids-related stroke, mainly ischemic (85 after cannabis use and 13 after synthetic cannabinoids). Vascular role and cellular effect of cannabis on brain mitochondria (as oxidative stress) were suggested as potential causes.
Colizzi *et al.* (2016) [53]	Systematic review on human and animal model, both *in vivo* and *in vitro*.	Probable involvement of glutamatergic transmission in cannabinoids neurotoxicity. Animal studies indicated how THC can depress glutamate transmission in different brain regions (cerebellar striatal, midbrain, hippocampal), while its chronic administration can affect glutamatergic signalling and disrupt glutamate synaptic plasticity.
European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2016) [116]	Report on the risk assessment of a new synthetic cannabinoid MDMB-CHMICA conducted by EMCDDA (data collected from 7 Member States during 2014 and 2015).	42 acute intoxications were associated with MDMB-CHMICA, mainly presenting with neurological features (coma, unconsciousness, syncope, mydriasis, seizures, and convulsions). In 29 fatalities MDMB-CHMICA was reported either as the cause of death or as contributing to death.
Mechoulam & Parker (2013) [52]	Focus on the actions of the endocannabinoid system on anxiety, depression, neurogenesis, reward, cognition, learning, and memory.	Dopamine transmission, probably mediated by the mesolimbic system, was called into question for the rewarding effects of THC.

(Table 3) Contd….

Study	Model	Results
Sarne *et al*. (2011) [108]	Review focused on the dual neuroprotective/neurotoxic effects of cannabinoids. Study on animals (mice) of effects of low *versus* high doses of cannabinoids.	Low dose of THC, which induces minor damage to the brain, showed to probably activate preconditioning and/or postconditioning mechanisms and thus protect the brain from more severe insults.
Pellegrini-Giampietro *et al*. (2009) [87]	*In vitro.* Focus on role for the endocannabinoid system in post-ischemic neuronal death.	Endocannabinoids may act as protective agents only in a time- and space-specific manner, whereas they might contribute to neurodegeneration if their action loses specificity.
Galve-Roperh *et al.* (2008) [98]	*In vitro.* Focus on role for the endocannabinoid in the control of neuron survival.	A role of ionotropic TRPV1 receptors hypothesized in determining the balance of protective versus toxic actions of cannabinoids, among others (prostanoids, free radicals by cyclooxygenase, pro-apoptotic c-Jun N-terminal kinase, p38 mitogen-activated protein kinase cascades, calpains, p53-dependent lysosomal permeability, cyclooxygenase-2).
Wang *et al.* (2008) [128]	Systematic review of safety studies of medical cannabinoids.	Medical cannabis side effects were in relation with THC dosage. Adverse events were mostly (96.6%) not serious. Nervous system disorders were the most frequent reported category, both for serious (9; 23.1%) and nonserious (1412; 39.7%) side effects. Psychiatric disorders were recorded in 4 serious adverse events (10.3%) and in 1265 nonserious adverse events (35.6%).
Gouzoulis-Mayfrank & Daumann (2006) [64]	Combined cross-sectional and longitudinal study with ecstasy and cannabis co-users. Baseline and re-examination 18 months later of 60 currently abstinent polydrug ecstasy users and 30 matched controls.	Self-reported psychopathology such as obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, phobic anxiety, and paranoid ideation, mainly associated with the extent of cannabis rather than MDMA use.
Sarne & Keren (2004) [54]	Considerations, based on prior authors' *in vitro* findings and *in vivo* pharmacokinetic data, on neuroprotective and neurotoxic activity of cannabinoids.	Probable neurotoxicity of low and long-term concentrations of cannabinoids associated with a likely protective effect of acute high dose administration.

performance and increase activity in its anatomical substrates, such as parietal and anterior cingulate regions [63].

3.3. Neuroimaging

Based on well-documented cannabis-induced neuropsychological deficits, several studies on brain neuroimaging have been conducted to identify anatomical alterations determined by cannabis use (alone or in combination with other drugs); on the other hand, heterogeneous results are reported [64].

MRI results of a recent study on long-term effects of cannabis on brain structure [65] show lower gray matter volume in regular cannabis users, compared with occasional ones, in temporal pole and *para*-hippocampal gyrus bilaterally left insula and the left orbitofrontal cortex, regions particularly rich in cannabinoid CB1 receptors and functionally associated with emotional, motivational, and affective dimensions. These changes were highly correlated with the monthly frequency of cannabis use in the 3 months before inclusion in the study and with the age of onset of drug use. Moreover, atrophy in the gray matter of cerebral hemispheres was related either to heavy cannabis consumption independent of the age of first use or with recreational consumption started in adolescence.

The hippocampus and amygdala, two other regions with a high density of cannabinoid receptors, were also found to be affected by cannabis consumption [58], with a large effect size dose-related volume reduction.

These results seem to mirror cannabis-neurotoxic effects in the hippocampus highlighted by animal studies [66]. In such studies, morphological changes in the hippocampus, including neuronal death and reduced synaptic density and dendritic length of pyramidal neurons, were demonstrated as caused by chronic treatment with cannabinoids [67-70]. Such findings of neuronal death were confirmed by in vitro studies using neuronal cell-lines, cultured hippocampal neurons or hippocampal slices treated with THC [71, 72].

Morphometric abnormalities suggesting disruption of the normal neural organization in the left nucleus accumbens and right amygdala have also been associated with cannabis use [73, 74]. These findings were particularly relevant, as cannabis consumption may affect different aspects of brain morphology besides the volume, especially in the early stages.

FMRI studies revealed altered brain activity in ventromedial prefrontal (VMPFC) and orbitofrontal cortices and insula (core regions linked to the motivational and affective aspects of decision making) [75, 76].

Two fMRI studies reported greater activation in typical working-memory brain regions, such as the prefrontal cortex and anterior cingulate, during a spatial working memory

task, with a deficient deactivation of the hippocampus [77] and recruitment of additional regions such as in the basal ganglia, leading to hypothesize a compensation of subtle deficits by 'working harder' [78].

In addition, white matter is a demonstrated target of cannabis-mediated neurodegeneration as shown by neuroimaging studies [60]. Brain regions most affected include the white matter in the frontal lobes, fornix, fimbria of the hippocampus, frontal-limbic connections, corpus callosum, commissural fibers and cerebellar structure [79, 80].

Neuropathologic studies confirmed these data, revealing prominent demyelination and axonal damage within fornix, corpus callosum, and central cerebral white matter [60].

Microstructural white matter, as studied with diffusion tensor imaging (DTI), has revealed morphological alterations in chronic marijuana users [60], in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum and commissural fibers [79, 81] besides reductions in left frontal fractional anisotropy (a measure of the degree of directionality and coherence of white matter fiber) and increased apparent diffusion coefficients in the right genu of the corpus callosum [82].

3.4. Cannabis and Stroke

A recent review of Wolff and Jouanjus [83] found ninety-eight patients having a cannabinoids-related cerebral ischemic event (proper ischemic stroke and/or a transient ischemic attack) described in the international scientific literature. In 85 of them, the attack occurred after cannabis use, and in 13 cases after synthetic cannabinoids. Patients were predominantly young adults, 81% of them were chronic users, and for 18% of them, an increase in the amount of cannabis consumption occurred during the previous days. The prevalent macroscopic abnormality discovered was the presence of multifocal intracranial arterial stenosis; on the other hand, besides this vascular role, a cellular effect of cannabis on brain mitochondria has been suggested by animal studies [84]. It has been hypothesized that THC could have a toxic effect on brain mitochondria, interfering with its respiration chain and inducing an increased production of reactive oxygen species, which is a known mechanism involved in stroke in humans [85]. Oxidative stress and endothelial dysfunctions due to the imbalance of the vasodilator and vasoconstrictor substances are pathogenic alterations suggested [86].

3.5. Neurotoxic *Versus* Neuroprotective Effects

Abnormal levels of the amino acid glutamate, causing 'axon-sparing' neurotoxicity, are also called into question as mechanisms underlying post-ischemic neuronal death in the mammalian brain [87]. From this perspective, observations indicating that CBs could attenuate glutamate-induced injury by inhibiting glutamate release *via* presynaptic CB1 receptors coupled to G-proteins and N-type voltage-gated calcium channels [88, 89] addressed investigations on the potential neuroprotective role of cannabinoids in this field. A review of the data available in the international literature [87] summarized these results, supporting either a beneficial or a detrimental role for the endocannabinoid system in post-ischemic neuronal death. CB receptor agonists and antagonists result in having both protective or toxic effects in ischemia, depending on several factors: among these, the most important appear to be the dose of the cannabinoids and the specific endocannabinoid that accumulates in the specific model. Regarding this latter point, attention the neurotoxicity mediated by CB receptors has been given to the increase of AEA rather than 2-AG [90-92], whereas the opposite result, when activated CB receptors are involved in neuroprotection [93, 94].

In this view, the transient receptor potential vanilloid 1 (TRPV1) channel, a non-CB1⁄CB2 receptor activated by AEA but not by 2-AG, may have a role [95, 96].

This would explain how synthetic, plant-derived, and endogenous cannabinoid agonists could have a different action through the activation of metabotropic CB1 receptors (neuroprotective) rather than ionotropic TRPV1 receptors (neurotoxic) [95, 97, 98]. However, this is only one of many mechanisms suggested for cannabinoid-induced toxicity [98], alongside the production of free radicals by cyclooxygenase activation or prostanoid synthesis [72], involvement of kinase proteins, [99, 100] proteases, [96, 101] and alteration in lysosomal permeability [102]. Also, a different modulation of cyclooxygenase-2 expression [103, 104] and an agonism on CB2 receptor [105] may contribute to the final balance between neuroprotection and neurotoxicity.

Studies on the toxicity of synthetic Cannabinoid Receptor agonists (SCRAs) like MDMB-CHMICA and AMB-CHMINACA resulted in a possible role of Cav 3.2 modulation, a low-voltage-activated calcium channel (T-type I Ca) [106].

The use of novel *in vitro* models for neurotoxicology, as human-derived CNS cells, has recently allowed demonstrating the cytotoxicity of MAM-2201 ([1-(5-fluoropentyl)-1H-indol-3-yl] (4-methyl-1-naphthalenyl)-methanone), a naphthoyl indole derivative with potent cannabinoid CB1 receptor full agonism, on human primary neurons and astrocytes [107].

The contrasting findings between neuroprotective or neurotoxic effects of cannabinoids were also the focus of interest of many "*in vivo*" studies. Here, acute administration of cannabinoids was found to be protective in various models, while chronic and heavy assumptions were found to result in neurotoxic consequences [108]. As mentioned, another diriment factor on the balance of neuroprotective/neurotoxic effects of cannabinoids, is represented by the dose. In this regard, synthetic CB agonists appear to exert protective effects only at low doses [93, 109], while extremely low doses of THC exert neuroprotective effects through activation of preconditioning (where a minor noxious stimulus protects various organs, including the brain, from a subsequent more severe insult) and/or postconditioning (where the protective intervention is applied following the insult) mechanisms that protect the brain from more severe insults [108].

Differences in pharmacokinetics are considered as involved, too [54]. Based on evidence that elevation in intracellular calcium levels can cause neuronal cell death and that cannabinoids modulate these levels in different manners depending on their concentration [110, 111], it has been suggested that low doses could be neurotoxic while high doses

are neuroprotective. This could not be contrast with evidence that *in vivo* neurotoxic effects are observed in chronic, [112, 113] while they show neuroprotective effects when administered acutely after the induction of the insult [114, 115]. Acute administration results in a high concentration of the drug immediately after injury and so protects the brain from damage, while chronic exposure to low concentrations of cannabinoids (due to the lipophilic nature of cannabinoids and to their low clearance) causes repeated minor neuronal deficits.

3.6. Acute Intoxication

In recent years, several studies have reported cases of acute intoxication determined by cannabinoids, an increasing phenomenon in view of the widespread and rapidly expanding consumption of synthetic compounds. A report of European Monitoring Centre for Drugs and Drug Addiction (2016) [116] resumed data of forty-two subjects acutely intoxicated by MDMB-CHMICA [IUPAC name: methyl (2S)-2-[[1-(cyclohexylmethyl)indazole-3-carbonyl]amino]-3,3-dimethylbutanoate], a synthetic cannabinoid with potent and full agonism at the CB1 receptor, occurred during 2014 and 2015. In absolute, coma and unconsciousness were the most frequent side effects; other neurological side effects were syncope, mydriasis, seizures and convulsions, somnolence, serotonin toxicity, urinary and fecal incontinence, confusion, agitation, aggressiveness, changes in mood and hallucinations. Also, a total of twenty-nine deaths were reported as associated with MDMB-CHMICA by five Member States.

Similar clinical features were reported in further studies regarding intoxication due to MDMB-CHMICA or other synthetic cannabinoid receptor agonists [117-119]; a trend of a rapidly increasing number of emergency visits and deaths was also observed [120].

The use of MAB-CHMINACA [IUPAC name: (2S)-2-[[1-(cyclohexylmethyl)indazole-3-carbonyl]amino]-3,3-dimethylbutanoic acid], a novel carboxamide indazole synthetic cannabinoid, was associated, in eleven patients, to the following neurological effects: unconsciousness, hallucinations, delirium, sluggish pupils responsiveness, agitation and combativeness, seizures and also anoxic brain injury (together with rhabdomyolysis and acute renal failure) confirmed at magnetic resonance imaging (MRI) scan, followed by death [121].

Agitation and generalized seizure also occurred after ingestion of JWH-018 [IUPAC name: naphthalen-1-yl-(1-pentylindol-3-yl)methanone] [122], a popular synthetic compound of products labeled as "K2", with approximately a fourfold higher affinity to the cannabinoid CB1 receptor and 10-fold higher affinity to CB2 receptor compared with THC [123].

Similar data were collected by the European Drug Emergencies Network (Euro-DEN), in a six-month observation of acute recreational drug toxicities of cannabis compounds, not including synthetic cannabinoids (*i.e*., marijuana, hashish, weed, skunk or THC) [124]. The study focused on the clinical features of the 36 patients that involved lone use of cannabis (1.6 % of all Emergency Department admissions for acute drug toxicity), one of which was a fatality. Amongst the non-fatal, toxicity was typically associated with neurobehavioral symptoms and vomiting: agitation/aggression in 8 cases (22.9 %), psychosis in 7 (20.0 %), anxiety in 7 (20.0 %) and vomiting in 6 (17.1 %). The only case of death concerned an 18-year-old male with an asystolic cardiac arrest during cannabis consumption and with hypoxic brain injury related to prolonged cardiac arrest.

A particular kind of poisoning is the case of rare and mostly accidental intoxication reported in toddlers. Ingestion of pieces of hashish (resin) by children with a mean age of 16.6 months has been found to cause mainly neurological symptoms: drowsiness, hypotonia, dilated pupils, ataxia (with no pathological results at non-contrast brain computed tomography) [125].

CT scan or MRI are usually negative, while EEG can show signs of intoxication like occipital medium voltage irregular slowing [126].

An increase in THC concentration in cannabis has been hypothesized as connected to the recent increase in severity of child poisonings, including a very low level of consciousness (Glasgow Coma Scale (GCS) <8), agitation and seizures [127]. Further, some evidence has been found between cannabis overdose (*i.e*., high dose Δ-9-THC) and seizures. [52, 128].

A recent review on accidental and intentional exposures of children/adolescents to cannabis, conducted by Kaczor *et al*. [129], has shown a high frequency of neurological side effects, including lethargy/somnolence (59%), ataxia/ dizziness (50%), and confusion (34%), while seizures have been found to occur only in few cases (3% in all population and 8% in 0–9 years patients). Anyway, the small size of cases doesn't allow us to draw conclusions on frequency.

3.7. Medical Cannabinoids

A systematic review of safety studies of medical cannabinoids published over the past 40 years [128] resulted in a collection of 31 studies in which these substances were used for a median duration of 2 weeks (range 8 hours to 12 months). A total of 4779 adverse events (of which 96.6% were not serious) were reported. In the subgroup analysis, Δ-9-tetrahydrocannabinol preparations were identified as the main cause of side effects.

Also, 8 observational studies were collected, with 3592 side effects recorded, including 39 serious. Nervous system disorders were the most frequently reported category, both for serious (9; 23.1%) and nonserious (1412; 39.7%) side effects. Secondly, psychiatric disorders were recorded in 4 serious adverse events (10.3%) and in 1265 nonserious adverse events (35.6%).

Cannabidiol has been approved for years for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in children two years of age or older [130] and for refractory epilepsy, resulting in a widely tested cannabinoid.

Although CBD has been reported to reduce the frequency of seizures in pediatric patients with drug-resistant epilepsy, almost a half of them experienced secondary effects such as seizure aggravation (18%), somnolence/fatigue (22%), gas-

trointestinal problems and irritability (7%) [131]. Same effects, such as somnolence, sedation, and lethargy, were also reported in other studies, at therapeutic dosage (maximum recommended dose is 10 mg/kg twice a day), in a dose-related manner [130].

Higher doses of CBD and concomitant use of valproate, other than an increased risk of transaminase elevation, resulted in hepatocellular injury, metabolic acidosis, and encephalopathy too.

The combination of THC and CBD in a 1:1 ratio has been approved in several countries for the treatment of multiple sclerosis-associated spasticity in adult patients after failure of all other treatments. Data from clinical trials showed dizziness, fatigue, and gastrointestinal disorders (*e.g*., nausea, vomiting, diarrhea) as the most common adverse effects, as well as the main reasons for some patients, to discontinue therapy [132-135].

In a tolerability study involving adult patients diagnosed with high-grade glioma, a treatment with oil-based organic whole plant extracts of cannabis-based on a 1:1 and 4:1 ratio of THC:CBD was conducted for 12 weeks in add-on to the standard treatment. MRI scan was performed at baseline and 12-week. Results showed no serious adverse events; neurological side effects were tiredness at night (11%), dizziness (mainly at night, 10%), and drowsiness (7%). Psychiatric events were reported in terms of mild hallucinations, paranoia, or euphoria at night for the 6% of participants. No further effects than those specifics for the tumor were found [136].

In clinical trials in which Dronabinol was prescribed as an appetite stimulant (5 mg/day), or as antiemetic (2.5–40 mg/day), the most frequently reported adverse events were euphoria, dizziness, somnolence, and thinking abnormalities (5 mg/day). Other undesirable effects were drowsiness and transient impairment of sensory-perceptual functions (ad doses between 2.5–40 mg/day). The same occurred for Nabilone when prescribed at a dosage of 3–5 mg/day [130].

4. DISCUSSION

Main phytocannabinoids (namely Δ-9-tetrahydrocannabinol and cannabidiol) and synthetic cannabinomimetic drugs (SCs) are reported to exert either neurotoxic or neuroprotective effects. The present review summarizes the main neurological, psychiatric, and behavioral side effects of cannabis use, both in acute and chronic use (Table **4**). Long-cannabis heavy use was correlated with an impairment in many cognitive skills, such as overall IQ, processing speed, immediate and delayed memory tests, and psychomotor integrity [56, 58], especially if consumption started in adolescence [57] and/or is still ongoing. Cognitive impairment is paired with brain damage associated with cannabis long-term use. The regions most affected are those particularly rich in cannabinoid CB1 receptors, such as the temporal pole and para-hippocampal gyrus bilaterally, left insula, left orbitofrontal cortex [65], nucleus accumbens [73, 74], hippocampus and amygdala [58].

A significant association between cumulative exposure to the drug, left hippocampus volume decrease, and the emergence of psychotic symptoms [137] shows a relationship between these three dimensions. Moreover, it suggests a particular risk for cannabis long and heavy consumption, both for the induction of psychotic symptoms after cannabis exposure [58] and for their exacerbation in psychiatric disorders such as schizophrenia, where left hippocampal abnormalities are already present since early stages [138].

Psychotic positive and negative symptoms have been found to increase both in cannabis-using participants screened for current and history of mental disorder [58], as well as in patients diagnosed with psychosis who continue to use cannabis. Specifically, the last ones have a worse prognosis in symptoms or functional outcomes than those who cease their consumption [139], with a specific influence on age of onset [140], risk of relapse psychosis (partly but not fully mediated by its association with antipsychotic medication non-adherence), length of relapse and medication adherence [141]. Chronic, frequent, and high-potency cannabis assumption is particularly dangerous for these outcomes [50] as well as for mania and suicide risk [142]. Moreover, continuous use of cannabinoids along with antipsychotic treatment could exacerbate the oxidative stress pathways in a life-threatening manner [143].

White matter is yet affected, and that is particularly dangerous during the neurodevelopment phases of adolescence, a critical period of neural maturation and reorganization of cortical and sub-cortical architecture, particularly through mechanisms of myelination [144]. White matter is functional for the cerebral interconnection, and its activity is critical for cognition and executive functioning [145], while its primary disorders are associated with schizophrenia-like psychosis [146].

As regards acute cannabis use, transient psychotic symptoms, as part of Cannabis Intoxication or Cannabis-Induced Psychotic Disorder (CIPD), can occur shortly after consumption in healthy subjects [48] with a degree depending on THC dose [147,148].

The spread of synthetic cannabinoids seems to be particularly deleterious in determining psychiatric symptoms and other neuro-behavioral effects such as unconsciousness, coma, syncope, mydriasis, seizures and convulsions, somnolence, serotonin toxicity, urinary and fecal incontinence, confusion, agitation, aggressiveness, changes in mood, hallucinations [116]. Several deaths during adult intoxication are reported, too and possibly caused by stroke. These are also possible in young adults with chronic cannabis use, especially when an increase in the amount of cannabis consumption recently occurred [83].

A warning should be triggered by the increase of accidental and intentional exposures of children/adolescents to cannabis [149], giving a high frequency of neurological side effects, such as lowered levels of consciousness, hypotonia, drowsiness, ataxia, dizziness, agitation, seizures, and respiratory depression.

Several adverse events, mostly not serious and attributable to higher degrees in Δ-9-tetrahydrocannabinol doses, were also reported in studies on cannabis medical use [128]. Neurological and psychiatric were still the most frequent side effects. Although better tolerated, cannabidiol is not free from neurological side effects [130, 131]; interactions with

Table 4. Main results on cannabinoids-related brain damage.*

Psychiatric	Neurological and Neurocognitive	Structural
Acute symptoms include agitation, aggressiveness, changes in mood, bizarre thoughts, feelings of depersonalization and schizophrenia-like symptoms. Chronic cannabinoids assumption, especially if frequent and with high-potency compounds, are related to an increased risk of psychosis or mood diseases. Cannabinoids use in psychiatric patients is also associated with a worse prognosis in symptoms, functional outcome, and suicidal risk.	Acute cannabis use is associated with the impairment of anterograde memory, sustained attention, higher cognitive abilities (such as executive functions), and psychomotor integrity. Neurological manifestations of acute toxicity due to synthetic cannabinoids are coma, unconsciousness, syncope, mydriasis, seizures and convulsions, somnolence, serotonin toxicity, urinary and fecal incontinence and delirium; some fatalities are also reported. No clear evidence about neurocognitive impairment arises from studies on chronic consumption. Partial evidence suggests poorer Intelligence Quotient (IQ), processing speed, as well as immediate and delayed memory performance in current heavy users. Consumption of CBD for medical purposes is not free from risks: seizure aggravation, somnolence/fatigue, gastrointestinal symptoms, irritability, sedation, and lethargy are reported as side effects.	Lower gray matter volume in temporal pole and para-hippocampal gyrus bilaterally, left insula and left orbitofrontal cortex is observed in regular cannabis users, especially in case of early onset. Volume reductions are also observed, in various degrees, in hippocampus, amygdala and left nucleus accumbens. White matter is affected in frontal lobes, fornix, fimbria of the hippocampus, frontal-limbic connections, corpus callosum, commissural fibers and cerebellum. Multifocal intracranial arterial stenosis, oxidative stress and endothelial dysfunctions seem to be involved in an increased risk of cerebral ischemic events. There are contrasting findings about neuroprotective or neurotoxic effects of cannabinoids; acute administration was found to be protective in various models, while chronic and heavy assumptions were usually associated with neurotoxic consequences.

Note: *when not explicitly reported, adverse events are referred to THC-predominant compounds or synthetic cannabinoids.

other medications may play a role and should be carefully monitored [150].

Finally, although cannabis has been generally considered a safe drug regarding addiction (risk of dependence users was estimated at 9% in the early 1990s), it is now constantly increasing [151]. Several studies show a specific increase in the potential addictive power of high-potency products such as "skunk" and SCs [43].

Regarding brain damage, structural modification of accumbens and amygdala found in cannabis users has been hypothesized as involved in reward reinforcement [73], mirroring similar data reported for other drugs [152]. Further, risks of long-term exposure to cannabinoids toward the development of an addiction disorder could be dangerously increased in association with altered brain activity in ventromedial prefrontal (VMPFC) and orbitofrontal cortices and insula, core regions related to motivational and affective aspects of decision-making [65, 75, 76]. This latter function is often associated with a progression of long-term drug exposure toward the development of substance use disorders and addictive behaviors [153, 154].

CONCLUSION

The present analysis made it possible to point out some of the risks for health associated with the consumption of cannabinoids. In fact, the use of such substances represents a public health problem due to the development of organ damage - with psychiatric, neurocognitive, neurological disorders - and even fatalities. Given that many substances and compounds are currently available for recreational and medical purposes, it's necessary to underline the differences in consumption behaviors and type of products, focusing on those associated with greater risks in order to efficiently address health and safety policies. Current evidence highlights that the greatest risks have been related to the consumption of high-potency synthetic cannabinoids and, secondly, to THC-predominant compounds with a high THC/CBD ratio. Although the current evidence regarding CBD-predominant compounds does not show significant risks relating to the central nervous system (making exception for some mild side effects), no observations on long-term consumption, able to suggest conclusive considerations, are currently available.

The evidence obtained contributes to broadening the knowledge of such a debated and critical issue, especially in a context of possible opening towards the assumption for both recreational and therapeutic purposes. On the other hand, the study carried out highlighted the need to deepen the research on some aspects of cannabinoid toxicity and organ damage, not only at the brain level. In fact, following the review of the available literature, and in line with previously reported considerations [155], it appears difficult to depict a complete summary on this subject due to the wide variety of compounds currently available, differences in consumers groups, and the methodological heterogeneity in the identification the damage, which elicit conflicting results or difficulties to compare different studies.

Therefore, research in this context must necessarily be based on technological development in the biomedical field and be centered on the dynamism of the new substances' market.

Finally, stated the difficulties in facing the complex issue of cannabinoids use, a combined effort must be made by monitoring and prevention agencies, health associations and scientific societies, both for the timely identification of risks and the minimization of damage. Fundamental for such purpose is undoubtedly the transparent information of health professionals and the general population focusing on the most active age groups.

LIST OF ABBREVIATIONS

CBD	=	Cannabidiol
CBN	=	Cannabinol
CNS	=	Central nervous system
ECS	=	Endocannabinoid system
GPCRs	=	G protein-coupled receptors
MRI	=	Magnetic resonance imaging
PRISMA	=	Preferred Reporting Items for Systematic Review and Meta-Analyses

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines have been followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

All authors equally contributed to this paper with conception and design, literature review and analysis, drafting, critical revision, and approval of the final version.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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