Psychoactive constituents of cannabis and their clinical implications: a systematic review

Constituyentes psicoactivos del cannabis y sus implicaciones clínicas: una revisión sistemática

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Abstract

Objective This systematic review aims to summarize current evidence on which naturally present cannabinoids contribute to cannabis psychoactivity, considering their reported concentrations and pharmacodynamics in humans.

Design Following PRISMA guidelines, papers published before March 2016 in Medline, Scopus-Elsevier, Scopus, ISI-Web of Knowledge and COCHRANE, and fulfilling established a-priori selection criteria have been included.

Results In 40 original papers, three naturally present cannabinoids (Δ-9-Tetrahydrocannabinol, Δ-8-Tetrahydrocannabinol and Cannabinol) and one human metabolite (11-OH-THC) had clinical relevance. Of these, the metabolite produces the greatest psychoactive effects. Cannabidiol (CBD) is not psychoactive but plays a modulating role on cannabis psychoactive effects. The proportion of 9-THC in plant material is higher (up to 40%) than in other cannabinoids (up to 9%). Pharmacodynamic reports vary due to differences in methodological aspects (doses, administration route and volunteers' previous experience with cannabis).

Conclusions Findings reveal that 9-THC contributes the most to cannabis psychoactivity. Due to lower psychoactive potency and smaller proportions in plant material, other psychoactive cannabinoids have a weak influence on cannabis final effects. Current lack of standard methodology hinders homogenized research on cannabis health effects. Working on a standard cannabis unit considering 9-THC is recommended.

Keywords: Delta(9)-Tetrahydrocannabinol; Cannabinol; Cannabis; Cannabinoids; Psychotropic drugs.

Resumen

Objetivo Esta revisión sistemática pretende resumir la actual evidencia sobre qué cannabinoides naturalmente presentes contribuyen a la psicoactividad final del cannabis, considerando sus concentraciones registradas y su farmacodinamia en humanos.

Metodología Siguiendo las guías PRISMA, se revisaron artículos científicos publicados antes de marzo 2016 en Medline, Scopus-Elsevier, Scopus, ISI-Web of Knowledge y COCHRANE, que cumplieran unos criterios establecidos a-priori.

Resultados En 40 artículos científicos, se identificaron tres cannabinoides naturalmente presentes (Δ-9-Tetrahydrocannabinol, Δ-8-Tetrahydrocannabinol y cannabinol) y un metabolito humano (11-OH-THC) con relevancia clínica. De éstos, el metabolito produce los efectos psicoactivos más potentes. El cannabidiol (CBD) no es psicoactivo, pero sí ejerce un efecto modulador sobre los efectos psicoactivos del cannabis. La concentración 9-THC en derivados cannábicos (hasta 40%) supera en gran medida la de otros cannabinoides (hasta 9%). La farmacodinamia descrita varía, dada la heterogeneidad en aspectos clave de la metodología (dosis, rutas de administración y experiencia previa con cannabis de los participantes).

Conclusiones Los resultados evidencian que el 9-THC es el cannabinoide que más contribuye al efecto psicoactivo del cannabis. Otros cannabinoides psicoactivos contribuirían mínimamente, dada su menor potencia psicoactiva y su baja concentración en los derivados cannábicos. La falta de estándares metodológicos dificulta el avance en los conocimientos sobre los efectos del cannabis en la salud. Establecer una unidad estándar de cannabis basada en 9-THC ayudaría a superar estas limitaciones.

Palabras clave: Delta(9)-Tetrahidrocannabinol; Cannabinol; Cannabis; Cannabinoides; Drogas psicoactivas.

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Introduction

Cannabis is the third most widely used drug worldwide (United Nations Office on Drugs and Crime, 2015), being its lifetime prevalence of use about 80.5 million Europeans (European Monitoring Centre for Drugs and Drug Addiction, 2012). Many European countries reported an increase in cannabis use during the last two decades (WHO, 2016). Considered the most widely abused illicit drug, Cannabis sativa *(Cannabis Sativa L.)* is one of the oldest plants harvested by man (Appendino, Chianese, and Taglialatela-Scafati, 2011) and has been always accompanied by controversy due to its psychotropic effects- defined by the WHO as the "ability to change an individual's consciousness, mood or thinking processes" (WHO, 2004).

Cannabis use has been associated with psychiatric, physical, and social impairment (Hall and Degenhardt, 2009; Hall, 2009; Volkow, Baler, Compton, and Weiss, 2014). Otherwise, several potential therapeutic effects of cannabis have been found (Mechoulam and Hanuš, 2000). While knowledge on and its therapeutic potentials has grown considerably in the last decades, its use is still polemic due to its potential harmful effects and its marked recreational use (Adams and Martin, 1996). Moreover, difficulties in separating psychotropic effects from the therapeutic effects have been reported (Borgelt, Franson, Nussbaum, and Wang, 2013; Greenwald and Stitzer, 2000).

One reason is cannabis' complex composition, containing more than 500 compounds from almost all the chemical classes, as for example mono- and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids, simply fatty acids, among others (Appendino et al., 2011; ElSohly and Slade, 2005). Exclusive of cannabis are the phytocannabinoids, being Δ-9-Tetrahydrocannabinol (9-THC) the most studied cannabinoid due to its known psycho activity (Dewey, 1987; Gaoni and Mechoulam, 1964; Hollister, 1987). The rest of cannabinoids, around 100, have commonly been neglected (Mechoulam, 2005). This is especially worrisome as consumers mostly smoke or ingest whole plant material, which presents variable proportions of cannabinoids.

This knowledge gap has also complicated cannabis health assessment. As no reliable and homogeneous registration systems exist, cannabis assessment remains focused on the frequency of consumption. One example is the definition for risky cannabis users given by the EMCDDA, which bases only on the frequency of cannabis use in the last month (European Monitoring Centre for Drugs and Drug Addiction, 2012). Meanwhile the consumed quantity of cannabis, and more concretely the quantity of cannabinoids, remains unexplored.

One option already defined for other drugs as alcohol are standard units (Gual et al., 1999; Stockwell, Blaze-Temple, and Walker, 1991), which consider the main constituent with implication on health. However for cannabis, consensus on which cannabinoids, other than 9-THC, may have implications on the sought psychoactive effects on humans, is still needed. Information on the influence of other cannabinoids on cannabis effects, considering their concentrations and effects on cannabis pharmacodynamics is still required.

In order to analyze the contribution of other cannabinoids to cannabis final health effects, we conducted a systematic literature review, which is intended to conclude which naturally present cannabinoids have shown psychoactive effects, considering their concentrations and their pharmacodynamics in humans.

Methods and materials

The information for this systematic review was gathered with an advanced document protocol in accordance with the PRISMA guidelines (Liberati et al., 2009; Urrútia and Bonfill, 2010). Electronic research was performed consulting the following four scientific data bases: Medline (1950-March 2016), Scopus- Elsevier (2004- March 2016), Web of Science (1900- March 2016) and COCHRANE (1991-March 2016). A combination of the following truncated terms were used as keywords to conduct the search: "Cannab*", "marijuana", "hash", "chemical", "structure" "constituent", "psycho" and "effect".

Selection criteria

All studies published before October 2015 were taken into account following the next parameters: (1) Studies on psychoactivity in humans with cannabinoids which are naturally present in cannabis or their pure synthetic alternative, (2) Pharmacodynamical properties of cannabinoids contributing to cannabis final psychoactive effects, (3) Reports of cannabis potency. Exclusion criteria: (1) Studies focusing mainly on pharmacokinetic properties of cannabinoids (2) Reviews or monographs. No language or publication date restrictions were applied.

Data extraction

Data was extracted by two reviewers (CC and HL) and two senior researchers (AG and MB) were asked in case of doubts. From the selected articles, the following data was extracted: authorship, year of publication, identified psychoactive substances, doses, administration forms, psychoactive effects, plant material used for the study and volunteers previous experience with cannabis.

Results

A total of 1484 unique entries were found, beyond those 87 fulfilled our inclusion criteria. After full-text-revision, 54 were rejected due to meet exclusion criteria, mostly because of being previous reviews (N=41). Finally, as shown

in Figure 1, 40 articles were included in the literature review. The results are divided in three parts: 1) Naturally present cannabinoids affecting cannabis psycho activity; 2) Pharmacodynamical effects; and 3) Reported potencies of naturally present psychoactive constituents.

1) Naturally present cannabinoids affecting cannabis psycho activity

- *Direct effects*

Delta-9-trans-Tetrahydrocannabinol (9-THC) dose-dependent psychoactive effects were observed on subjects after using the intravenous, oral and inhaled routes of administration (Table 2). Also other administration routes like vaporization (Zuurman et al., 2008) and drinking cannabis tea (Hazekamp, Bastola, Rashidi, Bender, and Verpoorte, 2007) have been reported.

Delta-8-Tetrahydrocannabinol (8-THC) and Cannabinol (CBN) produce psychoactive effects in humans but with less intensity than 9-THC (Table 1) (De Souza, Karniol, and Ventura, 1974; Hollister and Gillespie, 1973; Karniol and Carlini, 1973; Pérez-Reyes, 1973). Potency ratio for 8-THC was estimated to be between 1:2 and 2:3 (8-THC: 9-THC) (Hollister and Gillespie, 1973; Karniol and Carlini, 1973). Psychoactive effects of 8-THC were observed after intravenous and oral administration. CBN has a potency ratio of 1:10 (CBN: 9-THC), but psychoactive effects were not present after oral administration (Hollister, 1973).

One metabolite of 9-THC -11-OH-THC- has psychoactive effects by its own if injected pure intravenously, observing faster and stronger psychoactive effects than after the administration of 9-THC (Lemberger, Martz, Rodda, Forney, and Rowe, 1973).

- *Indirect effects*

Cannabidiol (CBD) administration was not followed by psychoactive effects neither after oral nor intravenous administration. CBD presents a modulating effect on 9-THC psychoactive activity, which has shown to depend on several factors. One example is the ratio CBD:9-THC or the order of administration of the cannabinoids, which affects the intensity of the modulating effect (Dalton, Martz, Lemberger, Rodda, and Forney, 1976; Ilan, Gevins, Coleman, ElSohly, and de Wit, 2005; Zuardi, Shirakawa, Finkelfarb, and Karniol, 1982).

Another cannabinoid influencing 9-THC psychoactive effects is Δ-9-tetrahydrocannabivarin (THCV), which potency was estimated to be 25% of 9-THC psychoactive potency (Hollister, 1974). However, evidence on THCV effects on 9-THC is still limited and contested, and suggest that THCV may have a mixed effect on 9-THC. A recent study showed that pre-treatment with THCV resulted in potentiating some of the effects produced by 9-THC, while minimizing others (Englund et al., 2016).

2) Pharmacodynamical effects

Pharmacodynamical effects of naturally present psychoactive cannabinoids have shown to include psychological and systemically effects (Table 2).

- *Psychological measures*

Pure 9-THC and whole plant material produced dose-dependent effects and feelings of intoxication and stimulation were the most often described. Other effects frequently observed were anxiety, sedation, deviations of psychomotor performance, memory impairment, worse-

Table 1. *Psychoactivity of naturally present cannabinoids and related metabolites in humans, identified in the selected articles.*

Molecule	Author	Administration route	Psychoactive potency
Naturally present psycho active cannabinoids			
9-THC	All authors	Smoked Intravenous Oral	Naturally present cannabinoid with the highest psychoactive potency
8-THC	Hollister (1973)	Oral Intravenous	Potency ratio: 2:3 (8-THC : 9-THC)
	Karniol and Carlini (1973) De Souza (1974)	Smoked	Potency rate: 1:2 (8-THC : 9-THC) Less potent than 9-THC
CBN	Pérez Reyes (1973)	Intravenous	1:10 (CBN : 9-THC)
		Oral	No psychoactive effects
THCV	Hollister (1974)	Intravenous	Potency ratio: 1:4 (THCV: 9-THC)
Directly related psychoactive metabolites of cannabis			
11-OH- 9-THC	Lehmberger (1973)	Intravenous	Greater psychological effects than 9-THC with earlier onset.

Note. 9-THC: 9-Delta-Tetrahydrocannabinol; 8-THC: 8-Delta-Tetrahydrocannabinol; CBN: Cannabinol; THCV: Δ-9-Tetrahydrocannabivarin, 11-OH-9-THC: 11-Hydroxy-Delta-9-Tetrahydrocannabinol.

Table 2. *Human pharmacodynamical properties of cannabinoids described in the selected articles.*

Author	Volunteer characteristics	Administration route	Doses	Observed effects after the consumption
Administration of pure 9-THC				
Curran (2002)	Experienced cannabis users with no current consumption	Oral	9-THC: 7.5, 15 mg	Dose-dependent effects on Impairment of episodic memory and learning, perceptual priming and working memory.
D'Souza (2008)	Current frequent users	Intravenous	9-THC: 2.5, 5 mg	Dose-related perceptual alterations, impaired memory and attention, amnesia, increased subjective effects of "high" and tachycardia.
Martín-Santos (2012)	Cannabis use less than 15 times in lifetime	Oral	9-THC: 10 mg	Positive and negative symptoms like anxiety, dysphoria, sedation and subjective intoxication. 5% of the patients became paranoid and anxious. Increased heart rate and differences in diastolic blood pressure at 2 hours post-administration
Zuurman (2008)	Cannabis use not more than once a week during the previous 6 months	Intrapulmonary (vaporization)	9-THC: 2 mg, 4 mg, 6 mg and 8 mg	Alertness, "feeling high", external perception, tachycardia, changes in body sway and pupil size.
Studies with administration of whole plant material or combinations of cannabinoids				
Bhattacharyya (2010)	Mean lifetime cannabis use	Intravenously	CBD: 5 mg 9-THC: 1.25 mg	Pre-treatment with CBD resulted in reduced psychological/psychotic effects of 9-THC versus pre-treatment with placebo.
Dalton (1976)	Previous cannabis users	Smoking	25 µg/kg of 9-THC together with either placebo or 150 µg/kg of CBD	Combined administration of CBD and 9-THC resulted in significantly attenuated subjective response and intoxication feelings than following the administration of 9-THC. Pretreatment with CBD failed to block 9-THC-induced euphoria.
Greenwald (2000)	Regular marijuana users	Smoking (Marihuana)	9-THC: 3.55 %	Antinociception and behavioral symptoms. Subjective effects showed high variability between participants.
Englund (2013)	Volunteer having consumed at least once in their lifetime	Oral (CBD) Intravenous (9-THC) 1.5mg	CBD 600 mg 9-THC 1.5 mg	Pretreatment with CBD resulted in less psychotic symptoms, paranoia and better episodic memory. Positive psychotic symptoms were lower if pre-treatment with CBD had been present, however in comparison to placebo, differences did not reach not statistical significance
Englund (2016)	Males who have not consumed cannabis more than 25 times in their lifetime	Oral (THCV) Intravenous (THC)	THCV 10mg capsules 1 mg of 9-THC	Pre-treatment with THCV inhibited some effects of THC (for example less subjective intense effects of 9-THC), while potentiating others (anxiogenic effects of 9-THC).
Haney (2015)	Cannabis users of at least half a cannabis cigarette 4 or more times per week in the last month	Oral (CBD) Smoking (THC)	Pretreatment with oral CBD (200 mg, 400 mg or 800 mg) Smoking half of an inactive or active (5.30–5.80% 9-THC) cannabis cigarette was smoked 90 min later	Oral CBD pretreatment does not alter the subjective, reinforcing, or cardiovascular effects of smoked cannabis relative to placebo in cannabis smokers
Hunault (2008)	Cannabis users (2-9 joints/month)	Smoking (Marihuana and tobacco)	9-THC: 9.8%, 16.4%, 23.1%	Increased doses raised heart rate and drowsiness, produced vomiting, changes in blood pressure and tachycardia.
Hunault (2009)	Cannabis users (2-9 joints/month)	Smoking (Marihuana and tobacco)	9-THC: 9.8%, 16.4%, 23.1%	Increased doses slowed down response time and worsened both linearly motor control. Some participants showed no impairment in motor control even at serum concentrations higher than 40 ng/mL. Subjective effects (high feeling and drowsiness) differed significantly between treatments.
Ilan (2005)	Previous cannabis experience (more than 10 times in lifetime)	Smoking (Marihuana)	9-THC: 1.8-3.6% CBC: 0.1-0.5% CBD: 0.2-1%	Varying concentrations of CBD and CDC do not affect significantly the effect of 9-THC. CBD tended to antagonize only if 9-THC was present in high concentration.
Morgan (2010)	Cannabis used at least once a month during the previous year	Smoking	Participants own cannabis	Acute deficits in prose recall and memory impairment, being more evident if CBD concentrations were low.

Author	Volunteer characteristics	Administration route	Doses	Observed effects after the consumption
Morgan (2012)	Current cannabis smokers	Smoking	Participants own cannabis.	High THC concentrations increased rates of depression and anxiety and resulted in worse prose recalls and source memory. In recreational users, presence of CBD decreased presence of psychosis-like symptoms. In daily users, CDB presence resulted in better recognition memory.
Ramesh (2013)	Current daily marijuana consumers	Smoking	1 to 6 puffs: 9-THC: 5.5%, 6.2%	Feeling "high", impaired psychomotor performance and decreased accuracy of immediate recall. Participants also presented decreased Carbon Monoxide levels.
Schaefer (1977)	Occasional and habitual smokers	Smoking	9- THC: 1.5%, 2.2%	Increased heart rate and slower reaction time. Subjective effects were dose-dependent.
Schwope (2012)	Heavy and chronic cannabis smokers	Smoking	9- THC: 6.8%	Feelings of "high", stimulation, sedation, slurring speech, shakiness. Increased food intake and dry mouth.
Zuardi (1982)	Cannabis use at least on 15 days prior to the study	Oral	9-THC: 0.5 mg/kg CBD: 1 mg/kg Combination of 9-THC (0.5 mg/kg) and CBD (1 mg/kg)	THC anxiogenic, CBD antagonized subjective psychotropic effects of THC, pulse rate was not affected.
Studies comparing administration of pure 9-THC and whole plant material				
Wachtel (2002)	Cannabis use at least once in the last two months and at least 10 times in their lifetime.	Oral and smoking	9-THC: 8.4 mg, 16.9 mg CBN: 0.30% CBD:0.05%	*Oral group:* Volunteer report higher drug effect after pure 9-THC than after taking marijuana. *Smoking group:* Pure 9-THC induces less drug effects than smoking marijuana, especially at the lower dose.
Chait (1992)	Experienced cannabis users	Oral vs smoking	Oral: 10mg, 15mg Smoked: 2.6%, 3.6%	Smoking and oral ingestion resulted in similar subjective effects. Smoking marihuana was rated in overall greater drug effects, greater heart rate and lower food intake.
Hart (2002)	Current cannabis smokers, with average of 6 joints/day	Oral vs smoking	Oral: 20 mg of 9-THC Smoking: 3.1 % of 9-THC	Smoking and oral ingestion resulted in similar subjective effects. Slightly more pronounced subjective effects with slower decrease over time were observed after smoking marijuana. Negative subjective effects and abstinence were identified only in the smoking group and not in the oral administration group.

Note. 9-THC: 9-Delta-Tetrahydrocannabinol; 8-THC: 8-Delta-Tetrahydrocannabinol ; CBN: Cannabinol; CBD: Cannabidiol; CBC: Cannabichromene.

ned prose recall, mood changes and decreased perceptual accuracy (Curran, Brignell, Fletcher, Middleton, and Henry, 2002; D'Souza et al., 2008; Hunault et al., 2009; Martin-Santos et al., 2012; Ramesh, Haney, and Cooper, 2013; Schaefer, Gunn, and Dubowski, 1977).

Articles comparing the effects of cannabis in different administration routes (oral vs smoked) conclude that oral administration of pure 9-THC produces lower subjective ratings than smoking whole plant material (Chait and Zacny, 1992; Hart et al., 2002) and does not result in craving and abstinence symptoms (Hart et al., 2002).

When comparing the effects of pure 9-THC and whole plant material within same administration routes, minor differences in subjective effects were observed (Wachtel, ElSohly, Ross, Ambre, and Wit, 2002). Basing on visual analog scales (Folstein and Luria, 1973), orally ingested marihuana produces less subjective effects than pure oral 9-THC. In contrast, when smoked, marihuana resulted in greater subjective effects than smoking pure 9-THC. These results are consistent with other study results which have shown that cannabinoids as CBN lose their psychoactive effects if taken orally (Pérez-Reyes, 1973).

Studies analyzing the influence of specific cannabinoids on 9-THC effects mostly focused on CBD. Although devoid of psycho activity (Pérez-Reyes, 1973), several studies included in our review suggest that CBD has an potential influence on cannabis final effects. CBD has shown to antagonize and to modulate 9-THC effects, as for example memory impairment and prose recall (Morgan, Schafer, Freeman, and Curran, 2010). Also anxiety and psychotic-like symptoms induced by 9-THC seem to be affected if CBD is present (Morgan et al., 2012; Zuardi et al., 1982). However, CBD role seems complex as its effects not to depend only on its own concentration but also on the concentration of 9-THC as well the administration order (Bhattacharyya et al., 2010; Ilan et al., 2005).

- *Systemic effects*

Dose-dependent cardiovascular effects, characterized by marked increases in heart rate were found in most of the volunteers participating in the cannabis studies. Smoking pure 9-THC induced less tachycardia than smoking whole plant material (Wachtel et al., 2002). Other systemic symptoms were feeling hungry (Schwope, Bosker, Ramaekers, Gorelick, and Huestis, 2012), increased body sway as well as pupil size (Zuurman et al., 2008).

Effects on the respiratory system were not described in the selected articles. Because cannabis is commonly smoked along with tobacco, some studies analyzed the potential interaction between the two drugs. Although little, available information indicates that tobacco increases the proportion of released cannabinoids (Van der Kooy, Pomahacova, and Verpoorte, 2009).

3) Reported potencies of naturally present psychoactive constituents

- *9-THC*

With only a few exceptions, 9-THC is the cannabinoid present in the highest proportion. The highest concentrations of 9-THC identified in the review were in English cannabis powder (40.63%) and Dutch hashish (39.85%). Lower concentrations of 9-THC were reported in herbal cannabis, with a maximum of 25.5% of 9-THC found in New Zealand. Studies analyzing changes in 9-THC concentrations over time, describe high increases in the proportion of the main psychoactive cannabinoid (Bruci et al., 2012; Burgdorf, Kilmer, and Pacula, 2011; ElSohly et al., 2000, 2016; Mehmedic et al., 2010) (Table 3).

- *Other cannabinoids contributing to cannabis psychoactivity*

Concentrations of psychoactive cannabinoids other than 9-THC, were not always registered (Table 3). When present, concentrations were generally low in comparison to 9-THC. One example is CBN, which maximum registered was of 7.7% present in confiscated hashish oil in the USA (Mehmedic et al., 2010).

In contrast, although not psychoactive, concentrations of CBD were frequently registered. Over time, percentages of CBD in cannabis show a negative tendency, which is especially visible in herbal cannabis (ElSohly et al., 2016; Mehmedic et al., 2010; Niesink, Rigter, Koeter, and Brunt, 2015; Potter, Clark, and Brown, 2008). In resin cannabis variable potencies were found depending on the origin of the derivate (Niesink et al., 2015; Pijlman, Rigter, Hoek, Goldschmidt, and Niesink, 2005; Tsumura et al., 2012).

Discussion

Our review summarizes the current evidence on which naturally present cannabinoids contribute to cannabis final psychoactive effects. We have identified three cannabinoids (9-THC, 8-THC and CBD) and one human metabolite of 9-THC (11-OH-THC) which have shown psycho active effects. Beyond naturally present psychoactive constituents, 9-THC has the strongest psychoactive effects and is present in the highest concentration. Its metabolite 11-OH-THC produces more intense effects with an earlier onset. Cannabis psychological and systemically effects are primarily induced by 9-THC, while the contribution of other psychoactive cannabinoids is estimated to be very low.

Burdens in cannabis pharmacodynamical reports

Included studies present huge differences in crucial aspects of methodology, hindering direct comparison and more exhaustive analysis, as for example a meta-analysis. One of these aspects is volunteer's previous experience, which varied largely (going from cannabis use more than 10 times in lifetime to heavy and chronic cannabis users). When studying cannabis pharmacodynamia, previous experience is determinant to estimate acute and long-term effects, due to the presence of depot levels and tolerance (Abood and Martin, 1992; De Souza et al., 1974; Sharma, Murthy, and Bharath, 2012). Methodological differences also affect how outcomes have been measured, going from self-ratings of subjective marihuana-like effects in the older studies (Pérez-Reyes, 1973) to much more complex descriptions using validated scales in the most recent retrieved articles (Englund et al., 2016).

Another important aspect to be considered is the administration route. With direct impact on cannabinoids pharmacokinetic, differences play a key role in cannabis effects. One example is CBN which produces psychoactive effects if injected intravenously but not after oral administration (Pérez-Reyes, 1973). Another example are abstinence symptoms which appeared after smoking marihuana but not after oral ingestion of pure 9-THC (Hart et al., 2002). As cannabis extract is commonly smoked, these studies have important implications for the evaluation of cannabis health effects.

Moreover, 9-THC doses in the selected articles differed widely. In consequence, as cannabis has dose-dependent effects (D'Souza et al., 2008; Wachtel et al., 2002), variable symptoms were described. We cannot reject that due to cannabis complex composition even whole plant material containing similar 9-THC levels may have been different in regard to other cannabinoids. Characteristics as the origin of the plant material, part analyzed or cannabis derivate product should always be considered. Meanwhile, in order to permit comparisons between studies, also data on other cannabinoids but 9-THC should be registered.

Evaluating the role of other cannabinoids but 9-THC

Our review highlights that, by now, 9-THC is considered the main cannabinoid responsible for cannabis psychoactive effects. Research has focused on 9-THC although canna-

Table 3. *Registers of cannabinoids concentrations given in the selected articles.*

Author	Origin and year	Derivate type	Registered concentrations of analyzed cannabinoids					
Bruci et al (2012)	Albania, 2011	Herbal	9-THC: 1.07%- 12.13 % CBD: 0.65% -2.02% CBN: 0.02% - 1.12%					
Burgdorf et al (2011)	USA; 1996-2008	Not indicated	9-THC: 11.75 % CBD: 0.08 %					
ElSohly (2000)	USA, 1980-1997	cannabis, hashish, or hash oil	Marijuana samples had less than 1.5% 9-THC in 1980 and rose to 4.2% 9-THC in 1997. Hashish and hash oil showed no specific potency trends. Other cannabinoids CBD, CBN and CBC showed no significant change in their concentration over the years.					
ElSohly (2016)	USA, 1995-2014	marihuana, hashish, or hash oil	9-THC potency in herbal cannabis has risen over time from approximately 4% 9-THC in 1995 to approximately 12% in 2014. Other cannabinoids with significant content are CBD and CBN (in hashish oil approximately 2-5%). CBD content in plant material has fallen on average from approximately 0.28% in 2001 to ‹0.15% in 2014. In resin derivate CBD maintains on average below 5%.					
Knight (2010)	New Zealand	Hydroponic grown cannabis plants	9-THC: 4.3% -25.2%					
Mehmedic (2010)	USA, 1993-2008	Marijuana Sinsemilla Ditch weed Hashish Hash oil	%	Marijuana	Sinsemilla	Ditch weed	Hashish	Hash oil
			9-THC	3.4-6.1	5.8-13.4	0.3-0.5	2.5-29.3	6.5-31.5
			CBD	0.2-0.5	0.2-0.5	1.5-2.4	0.8-4.9	0.1-1.3
			CBN	0.2-0.4	0-0.2	0-0.2	1.3-2.3	0.6-7.7
			CBC	0.2-0.3	0.2-0.3	0.1-0.2	0.5-0.9	0.3-1.6
			CBG	0.1-0.3	0.1-0.5	‹0.1	0.3-1	0.2-1.2
			THCV	‹0.1	‹0.1	‹0.1	0.1-0.4	0.1-0.7
Niesink (2015)	The Netherlands, 2005-2015	Herbal cannabis (Nederwiet and imported herbal cannabis), cannabis resin (Nederhasj and imported cannabis resin)	Herbal Cannabis: Nederwiet showed high doses of THC but hardly any CBD; fewer than 1% of these samples contained more than 1% CBD. Mean potencies of the most popular and the strongest Nederwiet were 16.0±4.0%, 17.0±3,9%. Imported herbal cannabis had lower 9-THC potencies (6.5±3.5%). Imported cannabis resin had 16.5±6.3% and Nederhasj presented higher 9-THC levels (30.2±16.4%).					
van der Pol (2013)	Netherlands, year not indicated	Herbal cannabis and resin cannabis joints	Herbal: 9-THC: 12.4% (range 1.1–19.5, SD= 3.0); CBD: 0.2% (range: 0.0–0.5, SD= 0.1)					
Pijlman (2005)	Netherlands, 2000-2004	Imported marijuana, home-grown marijuana, imported hashish and home-grown hashish	%	Imported Marihuana	Home-grown Marihuana	Imported Hashish	Home-grown Hashish	
			9-THC	7.2	21.5	18.5	39.8	
			CBN	0.7	0	1.5	0.6	
			CBD	0.20	0.25	8.10	0.60	
Potter (2008)	England, 2005	Resin	%	Herbal	Resin	Sinsemilla	Powder	
			9-THC	2.14	3.54	13.98	40.63	
			CBD	‹0.1	4.17	‹0.10	0.18	
			CBC	0.22	0.34	0.2	0.41	
			THCV	0.17	0.10	‹0.03	0.29	
			CBG	0.21	0.29	0.41	1.59	
			CBN	0.55	1.55	0.16	0.57	
Tsumura (2012)	Japan, 2010-2011	Leaves	%	Leaves	Seeded buds	Seedless buds	Powder	
			9-THC	1.8	3.8	8.3	8.9	
			CBN	0.5	1.1	1.3	1.2	
			CBD	0.2	0.2	0.1	0.1	
Turner (1974)	Different origins, 1970s	Cannabis plants	Nepal: 2.81% THC, 0.21% CBD Mexico: 1.68% THC, 0.27% CBD Pakistan: 1.30% THC, 1.14% CBD USA: 0.35% THC, 1.42% CBD Other cannabinoids found were: CBC, THCV and CBL.					

Note. 9-THC: 9-Delta-Tetrahydrocannabinol; CBN: Cannabinol; CBD: Cannabidiol; CBC: cannabichromene; CBG: cannabigerol; THCV: Tetrahydrocannabivarin; CBL: Cannabicyclol.

bis is mostly consumed as whole plant material. In order to avoid conflicting pharmacological reports, several authors have indicated that other plant cannabinoids need to be considered when evaluating cannabis effects (Eichler et al., 2012; Mechoulam, 2005; Turner, 1974). Our review shows that in most occasions other psychoactive cannabinoids are not even analyzed.

A common profile of cannabis effects could be found, including subjective effects (feeling 'high', stimulated) and systemic effects (changes in heart rate). Studies testing if 9-THC is the only responsible for cannabis psychoactivity conclude that administration of pure 9-THC and whole plant material produce similar effects, which do not significantly differ (Ilan et al., 2005; Wachtel et al., 2002). Clinical implications due to 9-THC interaction with CBD is still being contested, and included articles evidence that CBD's acute modulating effects depends on several factors, as for example the concentration ratio, the administration form or the order of administration (Englund et al., 2013; Haney et al., 2016; Ilan et al., 2005; Zuardi et al., 1982). Described effects reflect laboratory conditions, which may differ from real life conditions. In fact, reported data on concentrations of CBD indicate that especially in herbal cannabis, CBD is only present in minor concentrations. Therefore and as stated in previous reviews on the interaction of CBD and 9-THC, evidence suggests that CBD clinical implications on cannabis health outcomes need further research, that includes larger sample sizes and analyses of long-term effects (Haney et al., 2016; Hollister and Gillespie, 1975; Leweke, Mueller, Lange, and Rohleder, 2016; Zhornitsky and Potvin, 2012).

Cannabis potencies and implications for health

In our article selection, the highest concentration used to analyze pharmacodynamical effects was 69 mg of 9-THC (23%) (Hunault et al., 2008, 2009). Even though high concentrations used in research may be lower than some of the registered potencies, as samples containing between 30% and 40% of 9-THC were reported by several authors. However, due to the fact that some registries correspond to policy seizures, data on potency may not be representative of common street cannabis.

Some authors affirm that when growing for recreational use, getting stronger cannabis has become a common target (Knight et al., 2010; Mehmedic et al., 2010; Pijlman et al., 2005). Concentration changes have focused on 9-THC, while other cannabinoids maintain or decrease (Mehmedic et al., 2010). Concentrations of 9-THC were mostly higher than the concentrations of other cannabinoids, which did mostly not exceed 8%.

Information about which harmful effects of cannabis are expected to get worsened by higher doses, especially in cases of chronic heavy use, need further research. Nonetheless, our review shows that in research there is a tendency to simulate real conditions of cannabis consumption. One example is analyzing cannabis extracts mixed with tobacco (Hunault et al., 2008, 2009; Van der Kooy, Pomahacova, and Verpoorte, 2008; Van der Kooy et al., 2009) or volunteers' own preparations (Morgan et al., 2012; van der Pol et al., 2013).

Another issue of growing concern is the use of highly potent synthetic cannabinoids, which can result in serious harmful effects on health. Our review did not consider these compounds due to the fact that their prevalence of use in our context is much lower than the use of whole plant (Observatorio Español de la Droga y las Toxicomanías, 2015; Plan Nacional sobre Drogas, 2016).

Limitations and strengths of the systematic review

Our review has several potential study limitations. On the one hand, differences in study characteristics hindered equivalent data extraction for its comparison in a meta-analysis. On the other hand, publication bias and limitation of the data bases may have implicated some loss of information. However, our review was designed in order to find and assess relevant or high quality studies addressing the question of the review.

Our review has several positive aspects. To our knowledge it is the first systematic literature review focusing on psychoactivity, considering pharmacodynamical properties and potencies of several cannabinoids. Our study also points out that several aspects of cannabis psychoactivity are still unclear, mostly because research has not focused on how cannabinoids may influence individually on cannabis final effects.

Conclusions

Current evidence indicates that of cannabis naturally present constituents, 9-THC is the most potent psychoactive cannabinoid. Moreover, in comparison to other cannabinoids, its concentration in plant material is greatly higher. Therefore, when evaluating cannabis effects, 9-THC should be considered the main contributor to cannabis psycho activity.

Cannabis is the most abused illicit drug worldwide and constitutes an important public health problem. Standardized methodology is needed to overcome current burdens in cannabis research. Working on a standard cannabis unit which quantifies cannabis main cannabinoid with implication on psychoactivity is needed. This unit is expected to facilitate homogenization of cannabis registers, which is essential to improve epidemiological research and public health interventions.

Contributions

Cristina Casajuana Kögel, Hugo López-Pelayo, María Mercedes Balcells and Antoni Gual designed the study. Cris-

tina Casajuana wrote the first draft of the manuscript. All other authors contributed to the editing and final review of the manuscript. All authors approved the final paper.

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