

Is cannabidiol hepatotoxic or hepatoprotective: A review

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Abstract

Questions have been raised regarding the potential hepatotoxicity of cannabidiol (CBD). Conversely, several animal studies have demonstrated the hepatoprotective effects of CBD against bile duct ligation, cocaine, thioacetamide, alcohol, and several other chemicals. This review summarizes the current literature concerning the hepatic effects of CBD in humans and animals. Based on the available data, it may be concluded that there is a low probability of serious hepatotoxicity at the high therapeutic doses that are used and a much lower risk of adverse hepatic effects and a potential for hepatoprotection effects at the lower doses commonly used in dietary supplements and food products. However, a detailed safety study in rats using highly purified CBD rather than enriched *Cannabis* extracts is needed, enabling the determination of hepatic as well as other tissue effects and potential margin of safety.

Keywords

Cannabidiol, hepatoprotection, hepatotoxicity, neuroprotection, adverse events

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Introduction

Cannabidiol (CBD) is a nonpsychoactive cannabinoid derived from the plant *Cannabis sativa* and has been the subject of much discussion and marketing in recent years. It is a major component of Epidiolex[®], a drug approved for the treatment of drug-resistant seizure disorders.^{1–5} However, there is great interest in its use either as a dietary supplement or as an over-the-counter product for a wide range of health benefits including pain management, relaxation and stress relief, sleep aid, antidepressant, antioxidant, anti-inflammatory, neuroprotective, and other indications.⁶

Typical doses of CBD that have been used for seizure disorders and psychotic conditions are in the range of 10–20 mg/kg/day, with the higher dose being most commonly used.^{1–5,7} At these doses, the most common adverse events have included somnolence, diarrhea, decreased appetite, fatigue, and, less frequently, elevated serum aminotransferases.^{1–4,8,9} Several animal studies have raised questions regarding the potential hepatotoxicity of CBD.^{10–12} However, these studies may have generated more questions than they have answered, as will be discussed below.

Furthermore, a number of animal studies have demonstrated that CBD is hepatoprotective,^{13–18} adding to the confusion regarding hepatic effects.

To this end, is CBD safe and free of serious adverse events, including hepatotoxicity, at the doses that are commonly and widely used in dietary supplements and foods? These supplements and food-related doses are typically in the range of 25–100 mg/day as compared to doses of approximately 1000–1400 mg/day for a 70 kg (154 lb.) human for neurological disorders. These questions will be addressed, and both human and animal studies related to hepatic effects are reviewed.

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Human studies

A number of human studies have addressed the safety, including hepatotoxic potential of the CBD drug product Epidiolex in conjunction with its efficacy in seizure and psychotic disorders. A primary issue in assessing safety and the potential existence of adverse events of CBD in these studies is the concurrent use of one to five other medications for neurological disorders. One of the most prominent of these other drugs is valproic acid which is known for its hepatotoxicity.^{19,20} As a consequence, based on human studies, it is unclear whether adverse hepatic effects are due to the valproic acid or caused or potentiated by high doses of CBD.

In an open label study involving 162 patients with treatment-resistant epilepsy, all the subjects were given oral doses of 2–5 mg/kg/day of CBD for 12 weeks.¹ It was noted that 7% of the patients experienced slightly elevated transaminases, with one patient being withdrawn from the study due to high levels. All patients were concomitantly taking valproic acid.

In a 14-week study, 120 children with drug-resistant Dravet syndrome were given CBD orally at a dose of 20 mg/kg/day.² Elevated aminotransferase levels occurred in 12 patients. All patients were taking valproic acid. In nine cases in which the patient continued the trial, the enzyme levels returned to normal while receiving CBD.

An open-label extension trial involving long-term CBD treatment of Dravet syndrome patients was conducted.³ A total of 264 patients were enrolled and completed a median treatment duration of 274 days with a modal CBD dose of 21 mg/kg/day. Patients also received a median of three concomitant antiepileptic drugs. Twenty-two of them were also on valproic acid, who experienced elevated serum aminotransferase levels greater than three times upper limits of normal.

In a placebo-controlled double-blind study involving treatment-resistant Lennox-Gastaut syndrome,⁴ 76 patients received CBD at a dose of 20 mg/kg/day and 73 patients received 10 mg/kg/day for 14 weeks. Increases in serum aminotransferase levels greater than three times the upper limit occurred in 11 patients at the high dose and 3 patients at the low dose. Of these 14 patients, 11 were also receiving valproic acid. The elevated serum enzyme levels resolved spontaneously during treatment (five patients), after reducing the dose of CBD, CBD discontinuation, or reducing the dose of another antiepileptic drug (nine patients).

An open-label study was conducted in 55 epilepsy patients with CDKL5 deficiency disorder and Dup15q and Doose syndromes.⁵ The average CBD oral dose at 48 weeks of treatment was 28.9 mg/kg/day. All patients were receiving other antiepileptic medications. Four patients withdrew from the study stating adverse events as the reason. The most frequently noted adverse events were diarrhea (29%), fatigue (22%), somnolence (22%), convulsions (9%), status epilepticus (9%), and respiratory infections

(5%). No mention was made of elevated serum aminotransferase enzymes or hepatotoxicity. Taken together, the above studies indicate a low level of hepatic effects with resolution upon continued use of the product in some cases, and only several subjects being withdrawn from the studies as a result thereof.

Animal studies

A paucity of published, peer-reviewed, well-designed animal safety studies involving orally administered highly purified CBD devoid of tetrahydrocannabinol (THC) exists. Marx et al.¹⁰ conducted a 14-day oral dose range-finding study in rats treated with 1000, 2000, and 3000 mg/kg/day of a *Cannabis* supercritical fluid extract that contained 25% CBD. The product also contained 61% fatty acids; 13% combination of plant sterols, triterpenes, and tocopherols; and less than 1% of the psychoactive THC. The authors were unable to determine a no-observed-adverse-effect-level (NOAEL). One animal died after several doses of 4000 mg/kg of the extract. No median lethal dose (LD₅₀) was determined.

In male rats, the increase in serum alanine transaminase (ALT) was not significant even at the highest dose, while a twofold increase in ALT occurred in female rats at the 2000 and 3000 mg/kg doses.¹⁰ Small, less than twofold increases occurred in serum alkaline phosphatase (ALP) levels at 3000 mg/kg dose in both male and female rats. Greatest increases were observed in serum gamma-glutamyl transferase (GGT) levels at all doses of the extract in both male and female rats in this 14-day study. Taken together, the results indicate mild hepatotoxic effects at high doses of the 25% CBD extract.

These authors also conducted a 90-day repeated dose toxicity study in rats that orally received 100, 360, or 720 mg/kg/day of the extract containing 25% CBD.¹⁰ No increases were observed in this 90-day study in serum ALT or aspartate transaminase (AST) levels in either male or female rats at any of the doses. No increases in serum ALP levels were observed in male rats and less than a threefold increase in ALP in female rats at the 720 mg/kg dose. An increase of less than three-fold occurred in serum GGT in male rats at the 720 mg/kg dose, while a less than five-fold increase in serum GGT was observed in female rats at this highest dose. Levels of all these serum parameters returned to normal or were approaching normal at the end of the 28-day recovery period. These results indicated that the hepatic effects of this extract in rats were mild and reversible at doses as high as 180 mg of CBD (720 mg of the extract)/kg for 90 days.

Ewing et al.¹¹ conducted an acute hepatotoxicity study of a CBD-rich *Cannabis* extract in mice. The extract contained about 58% CBD and approximately 4.8% other cannabinoids including 1.69% THC. Approximately one-third of the components in the extract were not identified. Doses of CBD were based on the CBD content of the extract. In an

acute toxicity study, mice were treated with 0, 246, 738, or 2460 mg/kg of CBD as a single oral dose. No animals died after a single dose up to and including 2460 mg/kg of CBD. At the highest dose, no effects were observed for ALP or GGT, while less than three-fold increases were observed for serum ALT, AST, and total bilirubin. Small increases in liver-to-body weight ratios were also observed.

These authors¹¹ also conducted a 14-day study with daily oral doses of 0, 61.5, 184.5, or 615 mg/kg of CBD. Hepatic effects were observed only with the highest dose, with less than three-fold increases occurring in serum AST and ALT. Total bilirubin was also increased. No effects of any dose of CBD were observed for ALP and GGT. A dose-dependent increase in liver-to-body weight ratios was observed. At the 615 mg/kg dose, more than 50 hepatic genes were differentially modulated, including genes linked with oxidative stress, lipid metabolism, and drug metabolism. However, no significant differences in serum glutathione (GSH) were noted at any dose of CBD, suggesting a lack of oxidative stress. Based on these studies, it is clear that the authors have reported suboptimal liver injury but have claimed CBD-induced hepatotoxicity.

Ewing et al.¹² also published a second study using the CBD-rich (58%) *Cannabis* extract. Mice were gavaged daily for 3 days with 116 mg/kg. CBD-treated animals were given 400 mg/kg acetaminophen (APAP) intraperitoneally (i.p.) on day 4 to induce hepatotoxicity, resulting in a 37.5% mortality. No animals died with APAP alone. GSH depletion and oxidative stress were confirmed by microscopic examination. However, when mice were treated orally for 3 days with 290 mg/kg of CBD followed by APAP on day 4, no mortality occurred with no GSH depletion and no histopathological effects were observed. Thus, the high (290 mg/kg) dose of CBD appeared to be hepatoprotective with respect to a lethal dose of APAP. These disparate effects may have been due to the antioxidant/prooxidant properties of CBD and will be discussed below. The authors emphasized that their results highlighted the potential for CBD/drug interactions.

The adverse effects associated with the administration of CBD to healthy dogs at a dose of 10 and 20 mg/kg/day for 6 weeks have been reported.¹³ The dogs were treated with CBD in a topical cream, a capsule form, or in an oil. The only significant change in a biomarker during the study was an increase in serum ALP, which occurred in about one-third of the dogs. All dogs experienced diarrhea regardless of dose or formulation. The authors reported no evidence of short-term hepatotoxicity with bile acid levels remaining normal throughout the study and suggested that longer term studies were warranted. As with other studies, the products used in this study contained various amounts of THC as well as other cannabinoids and therefore uncertainties regarding the cause of the observed effect on ALP.

These authors also studied the effect of administering the same three CBD products (CBD in a topical cream, a

capsule form, or in an oil) in addition to conventional anti-epileptic treatment on the frequency of seizures in dogs with idiopathic epilepsy for 12 weeks.¹⁴ As was the case in healthy dogs,¹³ the primary adverse finding was a significant elevation in serum ALP. Whether the elevation was related to an effect of CBD or other components in the products on bone, liver, intestine, or another organ was not known. No adverse behavioral effects were noted.

Several studies have been reported by Magen et al.^{15,16} regarding the ability of CBD to ameliorate toxicity caused by bile duct ligation in mice, a model of chronic liver disease. In the initial study,¹⁵ bile duct-ligated mice were given either the vehicle or 5 mg/kg of CBD i.p. daily for 4 weeks. The ligated mice exhibited cognitive and locomotor impairment, increased the expression of *tumor necrosis factor- α 1 (TNF- α 1) receptor* gene, and reduced the expression of the *brain-derived neurotrophic factor (BDNF)* gene. In CBD-treated mice, cognitive impairment and locomotor function improved, while CBD reduced TNF- α 1 gene expression and increased BDNF gene expression.

In a subsequent study,¹⁶ the ability of 5 mg/kg of CBD i.p. for 4 weeks to reverse the effects of bile duct ligation of mice with respect to locomotion, cognitive function, and the expression of genes associated with TNF- α 1 and BDNF was conducted. The authors concluded that the cognitive impairment and decreased locomotion from bile duct ligation resulted from both neuro-inflammation and 5-hydroxytryptamine-A1 (5-HT_{1A}) receptor downregulation. Furthermore, CBD reversed these effects through a combination of anti-inflammatory activity and the activation of the 5-HT_{1A} receptor.

Avraham et al.¹⁷ studied the effects of CBD on mice with experimentally induced liver failure, which was induced by treating the mice with 200 mg/kg of thioacetamide i.p. The mice were treated one day after the thioacetamide with either 5 mg/kg of CBD i.p. or the vehicle. Neurological and motor functions were evaluated 2 or 3 days after the liver failure, respectively. Cognitive and neurological functions of the mice were severely impaired, while 5-hydroxytryptamine (5-HT) levels were enhanced following the thioacetamide treatment, and these functions were restored and normalized by CBD treatment. The decreased locomotor functions produced by thioacetamide were partially restored by CBD. The authors also showed that CBD at 5 mg/kg dose gave a maximal effect as compared to doses of 1 and 10 mg/kg.

The ability of CBD to protect against hepatic toxicity and seizures in mice produced by cocaine was demonstrated by Vilela et al.¹⁸ CBD was given i.p. 30 min prior to the administration of 75 mg/kg of cocaine i.p. CBD reduced acute liver damage and prevented seizures induced by the cocaine. A dose of 30 mg/kg of CBD provided greater protection than 60 and 90 mg/kg. A previous study by these authors showed that CBD inhibited hyperlocomotion produced by D-amphetamine (5 mg/kg) and ketamine (60 mg/kg).¹⁹ CBD was given in doses of 15–60 mg/kg

immediately after the two psychomimetic drugs with 30 mg/kg providing the optimal dose. All substances were given i.p.

CBD was shown to attenuate alcohol-induced hepatic steatosis, metabolic dysregulation, inflammation, and neutrophil-mediated injury in mice.²⁰ Mice were fed a liquid diet containing 5% ethanol for 10 days and on day 11 were gavaged with a single dose of 5 g/kg ethanol. The mice had been given CBD at a dose of 5 or 10 mg/kg i.p. or the vehicle for the 11 days of ethanol exposure. CBD treatment significantly attenuated the ethanol-induced elevation of serum AST and ALT levels and the liver-associated increases in triglycerides, fat droplet, protein 3-nitrotyrosine and 4-hydroxynonenal formation, lipid peroxidation, inflammation (increased messenger RNA expressions of interleukin-6 and other mediators of inflammation), and neutrophil accumulation.

Discussion

Concerns have been raised regarding the potential hepatotoxicity of CBD.^{9–13} In conjunction with assessing the efficacy of CBD in various neurological diseases, the potential hepatic effects have been determined in human subjects who received CBD in daily doses of 10–29 mg/kg.^{1–5} In addition to the high doses of CBD, essentially all patients in these studies were taking at least one antiepileptic medication, with the most common being valproic acid, a drug well known to be associated with hepatotoxicity.^{21,22}

Many variables are involved, which impact the assessment and comparison of human and animal studies that have been conducted relative to hepatotoxicity versus hepatoprotection of CBD. Pharmacokinetic differences, metabolic differences, condition of the liver, doses, duration of studies, purity of product, concurrently administered drugs, and healthy versus disease states as well as paucity of published studies complicate the assessment picture. However, some information can be gleaned from the extant literature.

It is noteworthy that with few exceptions, the hepatic effects in these human studies were mild with small, less than three-fold increases in AST and ALT. In several studies, it was noted that the elevated plasma levels of AST and ALT returned to normal for some subjects during the study^{2,4} and after reducing the dose of another antiepileptic drug, reducing the dose of CBD, or discontinuation of the CBD.⁴ In one study, it was stated that although AST and ALT were modestly elevated, no hepatic damage occurred.¹

Based on these human studies which are limited in number, it can be concluded that the incidence of hepatotoxicity was low due to CBD, and in only several cases, aminotransferases were sufficiently elevated to warrant withdrawal of the subjects from the study. It appears that the increased AST and ALT levels may have been due most frequently to the augmentation by CBD of the hepatic

effects of the antiepileptic medications, although effects due to the high dose of CBD cannot be ruled out.

The concurrent use of valproic acid and/or other antiepileptic drugs known to cause hepatotoxicity constitutes a major confounding factor in these studies. To determine the actual incidence of adverse hepatic effects due to CBD, studies are needed where CBD is given without the concomitant administration of antiepileptic drugs as valproic acid.

The hepatotoxicity of valproic acid in patients with epilepsy has been reviewed.²³ These authors summarized the available mechanistic literature regarding formation of valproic acid reactive metabolites, excess oxidative stress, altered fatty acid metabolism, and genetic variants of some enzymes such as glutathione transferases, uridine diphosphate (UDP)-glucuronosyltransferases, superoxide dismutase, and mitochondrial polymerase gamma.

Both CBD and valproic acid are known to undergo metabolism, and a metabolite of valproic acid (2-ene-valproic acid) has been shown to be hepatotoxic.^{23,24} Because here are some structural similarities between the metabolites of CBD and valproic acid, CBD may potentiate the hepatotoxicity of valproic acid via this mechanism.²⁴

Several animal studies have specifically addressed the potential hepatotoxic effects of CBD-containing products.^{10–15} Unfortunately, in one case, the product contained approximately 25% CBD,¹⁰ and in the other cases, it contained approximately 58% CBD.^{11,12} As a consequence, it is not possible to attribute the observed effects to CBD, recognizing that the other constituents in the products could have attenuated, enhanced, or had no effect on the hepatic outcomes. Although NOAELs were determined for male and female rats in the study of Marx et al.,¹⁰ because the extract contained only 25% CBD, it is not known how these values would relate to a product that would contain pure CBD. The authors did follow standard Organization for Economic Cooperation and Development (OECD) 407 and OECD 408 protocols for their 14-day and 90-day studies, respectively.

The study of Ewing et al.¹¹ in mice in addition to using a product that contained only 58% CBD presents a number of additional issues. The authors did not determine an LD₅₀, although a single dose of 2460 mg/kg of CBD was not lethal. As points of comparison, the LD₅₀ of table salt (sodium chloride) is about 3000 mg/kg in rats and 4000 mg/kg in mice, while the LD₅₀ of caffeine is about 200 mg/kg in rats and 150 mg/kg in mice. The authors failed to determine the no-observed-effect-level (NOEL) and NOAEL, which enable the determination of margins of safety. If one assumes based on the data provided that the NOAEL in mice was 61.5 mg/kg and this is directly extrapolated to a 60 kg human per Food and Drug Administration (FDA) guidelines, this would represent a single dose of 3690 mg of CBD in humans as compared to 1200 mg for a 20 mg/kg dose, which is commonly used in seizure disorders^{1–5,7} The authors concluded that “CBD exhibited clear

signs of hepatotoxicity” and “it poses a risk for liver injury” but failed to emphasize that the doses required to do so.¹¹ One can also conclude that the potential for hepatotoxicity is vastly overstated by the authors and draw the opposite conclusion based on the data provided.

In the second study of Ewing et al.¹² in mice, a CBD dose of 116 mg/kg was shown to enhance the hepatotoxicity of APAP, while a dose of 290 mg/kg protected the liver against the toxicity of APAP. The high-dose protective response of CBD might be explained based on having an appropriate dose that prevented oxidative damage due to the free radicals and reactive oxygen species produced by the metabolism of APAP. The CBD and/or other constituents in the extract may have acted as free radical scavengers, antioxidants, and anti-inflammatory,²⁵ therefore prevented hepatotoxicity due to APAP.

It is not known whether the enhanced toxicity at the lower dose was due to CBD or other constituents in the extract. Unless pure CBD is used, it is not possible to attribute the enhanced toxicity of the extract to CBD. The antioxidant and anti-inflammatory properties of CBD are well known and the associated mechanisms have been extensively reviewed.²⁶ However, as with other antioxidants, CBD may act as a prooxidant under certain conditions,²⁷ which may have been the case with the lower dose of CBD in conjunction with the APAP toxicity.¹² Finally, the authors of the hepatotoxicity studies in rats¹⁰ and mice^{11,12} failed to review studies that have shown effects that are contradictory to their own findings.

A series of studies have demonstrated that pure CBD can be hepato- and neuroprotective in mice against bile duct ligation^{15,16} as a model of hepatic encephalopathy, thioacetamide-induced fulminant hepatic failure as a model of hepatic encephalopathy,¹⁷ cocaine-induced hepatotoxicity and seizures,¹⁸ and alcohol-induced hepatic steatosis, metabolic dysregulation, inflammation, and neutrophil-mediated injury.²⁰ In addition, CBD inhibited hyperlocomotion produced by D-amphetamine and ketamine.²¹

Pure CBD and not an enriched extract was administered i.p. in all of the above hepatoprotective studies.^{15–20} An effective CBD dose of 5 mg/kg/day reversed the adverse effects of bile duct ligation^{15,16} and thioacetamide-induced liver failure.¹⁷ A CBD dose of 30 mg/kg was most effective against the effects of cocaine,¹⁸ D-amphetamine, and ketamine,¹⁹ while a 5 and 10 mg/kg dose response effect of CBD was observed against alcohol-induced hepatic steatosis, metabolic dysregulation, inflammation, and neutrophil-mediated injury in mice.²⁰

As compared to the i.p. administration of 5–30 mg/kg hepatoprotective doses of CBD,^{15–20} the oral administration of 290 mg/kg protected against the hepatotoxic effects of APAP.¹² Again, it should be noted that this latter extract product was only 58% CBD. In a pharmacokinetic study, when mice were given 120 mg/kg of CBD orally and i.p.,²⁸ the i.p. administration yielded plasma maximum concentration and area under the curve values that were 6.45- and

6.30-fold higher, respectively, than when the CBD was administered orally. These observations can be extrapolated to the APAP study where 290 mg/kg of CBD given orally provided protection.¹² Recognizing that this may not have been the optimal dose, this dose would translate into an i.p. dose of CBD of approximately 45 mg/kg. Conversely, a dose of 30 mg/kg of CBD given i.p. that provided hepatoprotection could translate into an oral dose of approximately 190 mg/kg,^{18,19} indicating that the results between the various studies involving i.p. administration are within the range of the oral dose used in the APAP study.¹²

It is important to know whether CBD causes hepatotoxicity at therapeutic doses. However, for the general public, the question is whether CBD causes hepatotoxicity at the much lower doses that are more widely and commonly used in the form of dietary supplements and food products, that is, to deal with common ailments, such as pain management, relaxation and stress relief, sleep aid, and depression. As previously noted, the doses of CBD that are commonly used therapeutically as a drug to treat resistant neurological disorders such as seizures are about 20 mg/kg or 1200 mg for a 60 kg individual. The doses of CBD that may be appropriate when used for providing relief for aches and pains, headaches, insomnia, and so on, are in the range of 25–100 mg/day. Taken together, this suggests that CBD-induced hepatotoxicity reported in mice in the recent literature is not pharmacologically relevant.¹²

Based on the data provided, if one assumes that the NOAEL for CBD in mice was 184.5 mg/kg,¹¹ and this is extrapolated to a 60 kg human per FDA guidelines, this would represent a single dose of 11,070 mg of CBD in humans. If one assumes a typical daily dose of 50 mg of CBD, this yields a margin of safety of 221. This factor should be kept in mind when designing animal experiments and clinical trials with human subjects.

Based on the available data, it may be concluded that there is a higher probability of serious hepatotoxicity at the high therapeutic doses that are used, particularly when used in conjunction with other antiepileptic drugs such as valproic acid, and a much lower risk of adverse hepatic effects and the potential for hepatoprotection at the lower doses commonly used in dietary supplements and food products. However, a safety study in rats using a highly purified CBD rather than enriched *Cannabis* extracts is needed. Studies should include an assessment of the LD₅₀ and a 90-day subchronic toxicity study that enables the determination of hepatic as well as other tissue-specific effects, NOEL, NOAEL, and potential margins of safety.

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References

- Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label intervention trial. *Lancet Neurol* 2016; **3**: 270–278.
- Devinsky O, Cross JH and Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Eng J Med* 2017; **377**: 699–700.
- Devinsky O, Nabbut R, Miller I, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial. *Epilepsia* 2018; **60**: 294–302. DOI: 10.1111/epi.14628.
- Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Eng J Med* 2018; **378**: 1888–1897.
- Devinsky O, Verducci C, Thiele E, et al. Open-label use of highly purified CBD (Epidiolex[®]) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q and Doose syndromes. *Epilepsy Behav* 2018; **86**: 131–137.
- Crippa JA, Guimaraes FS, Campos AC, et al. Translational investigation of the therapeutic potential of cannabidiol (CBD): toward a new age. *Front Immunol* 2018; **9**: 2009.
- Millar SA, Stone NL, Bellman ZD, et al. A review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol* 2019; **85**: 1888–1900.
- Lattanzi S, Brigo F, Trinka E, et al. Efficacy and safety of cannabidiol in epilepsy: a systematic review and meta-analysis. *Drugs* 2018; **78**: 1791–1804.
- Huestis MA, Solimini R, Pichini S, et al. Cannabidiol adverse effects and toxicity. *Curr Neuropharmacol* 2019; **17**: 974–989.
- Marx TK, Reddeman R, Clewell R, et al. An assessment of the genotoxicity and subchronic toxicity of a supercritical fluid extract of the aerial parts of hemp. *J Toxicol* 2018; 8143582. DOI: 10.1155/2018/8143582.
- Ewing LE, Skinner CM, Quick CM, et al. Hepatotoxicity of a cannabidiol-rich cannabis extract in the mouse model. *Molecules* 2019; **24**(9): E1694.
- Ewing LE, McGill MR, Yee EU, et al. Paradoxical patterns of sinusoidal obstruction syndrome-like liver injury in aged female CD-1 mice triggered by cannabidiol-rich cannabis extract and acetaminophen co-administration. *Molecules* 2019; **24**(12): E2256.
- McGrath S, Bartner LR, Rao S, et al. A report of adverse effects associated with the administration of cannabidiol in healthy dogs. *J Am Holistic Vet Med Assoc* 2018; **52**: 34–38.
- McGrath S, Bartner LR, Rao S, et al. Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *J Am Vet Med Assoc* 2019; **254**: 1301–1308.
- Magen I, Avraham Y, Ackerman Z, et al. Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation. *J Hepatol* 2009; **51**: 528–534.
- Magen I, Avraham Y, Ackerman Z, et al. Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT_{1A} receptor activation. *Br J Pharmacol* 2010; **159**: 950–957.
- Avraham Y, Grigoriadis NC, Poutahidis T, et al. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. *Br J Pharmacol* 2011; **162**: 1650–1658.
- Vilela LR, Gomides LF, David BA, et al. Cannabidiol rescues acute hepatotoxicity and seizures induced by cocaine. *Med Inflamm* 2015: 523418. DOI: 10.1155/2015/523418.
- Moreira FA and Guimãres FS. Cannabidiol inhibits the hyperlocomotion induced by psychomimetic drugs and mice. *Eur J Pharmacol* 2005; **512**: 199–205.
- Wang Y, Mukhopadhyay P, Cao Z, et al. Cannabidiol attenuates alcohol-induced liver steatosis, metabolic dysregulation, inflammation and neutrophil-mediated injury. *Sci Rep* 2017; **7**: 12064.
- Cotariu D and Zaidman JL. Valproic acid and the liver. *Clin Chem* 1988; **34**: 890–897.
- Nanau RM and Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem* 2013; **46**: 1323–1338.
- Guo HL, Jing X, Sun JY, et al. Valproic acid and the liver injury in patients with epilepsy: an update. *Curr Pharm Des* 2018; **25**: 343–351.
- Ujvary I and Hanus L. Human metabolites of cannabidiol: a review on their formation, biological activity, and relevance in therapy. *Cannabis Cannabidiol Res* 2016; **1**: 90–101.
- Pellati F, Borgonetti V, Brighenti V, et al. *Cannabis sativa* L. and non-psychoactive cannabinoids: their chemistry and role against oxidative stress, inflammation and cancer. *Biomed Res In* 2018; **2018**: 1691428.
- Atalay S, Jarocka-Karpowicz I and Skrzydlewska E. Antioxidant and anti-inflammatory properties of cannabidiol. *Antioxidants* 2019; **9**(1): E21.
- Usami N, Yamamoto I and Watanabe K. Generation of reactive oxygen species during mouse hepatic microsomal metabolism of cannabidiol and cannabidiol hydroxyquinone. *Life Sci* 2008; **83**: 717–724.
- Deiana S, Watanabe A, Yamasaki Y, et al. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarin (CBDV), Δ^9 -tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behavior. *Psychopharmacology* 2012; **219**: 859–873.