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Review Article

# Cannabis in Patients with Liver Disease; A Concise Review of Recent Data

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## Abstract

The endocannabinoid system has emerged as a new and important player in liver physiology and disease. *In vitro* and animal studies suggested a fibrogenic and steatogenic role for the cannabinoid receptors CB1 and the opposite for CB2 receptors. In contrast, the effect of the psychoactive plant *Cannabis sativa* in patients with liver disease is less clear. Smoking cannabis is not uncommon in patients with liver disease e.g. alcoholic liver disease and chronic hepatitis C. Studies that investigated the effect of the herb in subjects with liver disease have yielded contradictory results. Chronic users of cannabis exhibited increased serum levels of liver enzymes and bilirubin, suggesting hepatotoxicity and smoking cannabis has been shown to accelerate the progression of fibrosis and steatosis in patients with chronic hepatitis C. Other studies, however, failed to demonstrate a harmful effect for cannabis while more recent studies suggested a benefit for smoking cannabis in liver disease. The review aims to provide an updated overview on the human studies pertaining to the use of cannabis in hepatic patients and its effect on the disease process.

***Keywords:*** *Cannabis sativa; Cannabinoid Receptors; Endocannabinoids; Liver; Hepatitis C Virus; Liver Steatosis; Liver Fibrosis*

## Introduction

Psychoactive cannabis from the plant *Cannabis sativa* remains the most widely used illicit substance worldwide. It was estimated in 2016 that 193 million people have used the drug for at least one time in the preceding year [1]. The most commonly used preparations of cannabis are marijuana or the flowering tops and leaves of the female plant and hashish which is the compressed resin secreted by the plant glands [2]. The term cannabinoids refers to a group of terpenophenolic compounds present in the plant [3] and among them delta-9-tetrahydrocannabinol ($\Delta^9$-THC) have been identified as the agent responsible for the psychotropic effects of *Cannabis sativa* [4]. Other cannabinoids such as cannabidiol, cannabinol, cannabigerol, and cannabichromene are not psychoactive and exert pharmacological effects distinct from and even antagonistic to that of the main psychoactive compound $\Delta^9$-THC [5-7]. In the fresh plant, cannabinoids exist in their inactive carboxylic acids; decarboxylation into active cannabinoids occur during storage, drying or heating (smoking) [3]. Cannabis is usually smoked in cigarettes or "joints" and in water pipes but can also be eaten or consumed in the form of herbal tea [8,9]. Cannabis produces euphoria and relaxation. There is also intensification of ordinary sensory experiences and time distortion when using cannabis [8,10]. Cannabinoids are highly lipophilic, and are distributed rapidly throughout the body tissues, accumulate in fatty tissues and are released slowly thereafter. Cannabinoids are metabolized in the liver and metabolites excreted in urine, intestine and bile [10].

Cannabinoids bind specific receptors which belong to the superfamily of G protein coupled receptors. Cannabinoid receptors are expressed in different tissues in the body with CB1 receptors being mainly expressed in the brain but also in the periphery. CB2 receptors are predominantly expressed on the cells of the immune system in the periphery [11]. Endogenous ligands or "endocannabinoids" also exist e.g. arachidonoyl ethanolamide or anandamide, 2-arachi donoylglycerol, and noladin ether. These are derivatives of arachidonic acid and are produced "on demand" from their membrane lipid precursors [12].

Apart from its recreational uses, cannabis is also widely prescribed to treat a variety of medical conditions, the so called "medicinal cannabis". It is used to alleviate pain in patients with arthritis, neuropathy [13,14], sickle cell disease [15] and fibromyalgia [16]. It is used in the form of an oromucosal spray of the whole plant extract (Sativex) to treat spasticity and bladder disorders in multiple sclerosis [17]. A synthetic $\Delta^9$-THC (Nabilone) is also available for reducing nausea and vomiting due to chemotherapy [14].

Drug abuse is a common health problem in patients with liver disease [18-20] and smoking cannabis is frequent among patients with chronic liver disease [21,22] including those who are candidates for liver transplantation [20,23,24]. Subjects coinfected with hepatitis C virus /human immune-deficiency virus are also more likely daily users of cannabis including medically prescribed compared with those with only hepatitis C virus [22].

Several studies have attempted to investigate the effects of cannabis/marijuana in patients with liver disease but with inconclusive or contradictory data [25]. The aim of this review is to provide an update on the clinical data pertaining to the use of cannabis in hepatic patients and its effect on the disease process.

## Cannabinoid receptor expression in hepatic disease

There is increased expression of cannabinoid receptors in liver disease. In their study on cirrhosis associated with non-alcoholic fatty liver disease, Julien., *et al.* [26] reported increased expression of CB2 receptors at the vicinity of fibrous septa. In contrast, CB2 receptors were not detected in the normal liver. Cultured hepatic myofibroblasts and activated hepatic stellate cells expressed CB2 receptors. In patients with non-alcoholic steatosis and steatohepatitis, CB2 receptors were expressed by hepatocytes, cholangiocytes and hepatic stellate cells, even in absence of significant fibrosis. CB2 receptor expression was not detected in the normal liver tissue [27]. In the liver of patients with alcoholic liver disease, CB1 receptors were expressed in areas with advanced fibrosis [28]. CB1 receptors were also up-regulated in hepatocytes and biliary epithelial cells in primary biliary cirrhosis while hepatocytes and in cholangiocytes expressed CB2 receptors [29]. There was also increased expression of CB1 and CB2 receptors in liver cirrhosis and hepatocellular carcinoma [30]. In chronic hepatitis C, CB1 expression levels were 6-fold up-regulated than in controls. CB1 expression increased with the increase in viral load, fibrosis stage and with steatosis grade. CB1 expression also increased in chronic hepatitis B compared to controls, but to much lower degree compared with hepatitis C infected individuals [31]. In patients with hepatitis B infection, the expression of CB1 and CB2 receptors increases as fibrosis progresses. CB1 receptors were expressed by hepatic stellate cells [32]. The activation of this cell type is central to the development and progression of liver fibrosis and its inhibition is one strategy to prevent fibrosis progression [33]. Studies also indicated an increase in endogenous cannabinoids in patients with liver disease. Increased plasma anandamide levels were detected in cirrhotic patients [34] and both anandamide and 2-arachidonoyl glycerol were increased in plasma of patients with hepatitis C infection but not in liver tissue [35]. Collectively, the above data implicate the endocannabinoid system in liver disease.

## Cannabis and changes in serum liver enzymes and ammonia

The effects of recreational cannabis on serum liver enzymes as indicators of hepatocellular injury have been investigated by several authors [36-40]. In their study, Borini., *et al.* [36] evaluated 323 subjects using illicit substances for changes in serum alanine aminotransferase, aspartate aminotransferase, bilirubin, γ-glutamyl transferase and enlargement of liver and spleen on clinical examination. The study included 123 subjects who were users of only cannabis, 26 users of cannabis and crack in addition to 14 individuals who use cannabis and alcohol. In users of only cannabis or cannabis/alcohol, there were elevations in serum alanine aminotransferase, and aspartate aminotransferase, alkaline phosphatase. Serum γ-glutamyl transferase increased in cannabis/alcohol users. Hepatomegaly, splenomegaly and hepatosplenomegaly were observed in 57.7%, 73.1% and 46.2%, respectively, of users of only cannabis. Toson., *et al.* [37] conducted a study on a group of cannabis smokers (duration 5 - 10 years) with no history of liver disease. The study included 90 subjects aged 20 - 30 years who tested negative for hepatitis C and B viruses. The authors reported that compared with healthy individuals, cannabis users exhibited increased serum activities of γ-glutamyl transferase, alkaline phosphatase, and aspartate aminotransferase as well as increased serum bilirubin and total bile acids. Quraishi., *et al.* [38] in a study on 51 cannabis users (mean duration of cannabis use: 9.53 ± 8.06 years) found raised serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin in; 33.3%, 15.6%, 37.2%, and 17.6% of subjects, respectively. Eosinophil counts were raised in 5.8% while the relative monocyte count was lower in 92% of cases. In contrast, Bonnet., *et al.* [39] in another study on 42 cannabis-dependent subjects seeking treatment, the authors reported no increase in serum alanine aminotransferase, and aspartate aminotransferase or bilirubin in 32/42 (76.2%) subjects. No significant

association was observed between levels of serum alanine aminotransferase, and aspartate aminotransferase, bilirubin and $\Delta^9$-THC and its major metabolites. In a study in healthy individuals with self-reported daily use of cannabis for a median of 9.5, plasma levels of alanine aminotransferase, and aspartate aminotransferase did not differ but alkaline phosphatase levels were significantly higher compared with non-smokers of cannabis [40]. One study in healthy cannabis users, found that either smoking (6.9% THC cigarettes or vaporized cannabis) or eating cannabis was associated with increased plasma ammonia levels. In this translational study, cannabis given to mice increased both plasma and striatal ammonia concentrations and decreased striatal glutamine synthase activity [41].

### Cannabis in patients with chronic hepatitis C virus infection

Chronic hepatitis C infection is the major cause of chronic liver disease worldwide. It is estimated that 80 million people are infected with the virus (RNA +ve) all over the World, most of them are adults (62 - 89 million) [42]. It is the leading cause of end-stage liver disease, liver transplantation, hepatocellular carcinoma and liver disease-related deaths in the Western World [43]. The disease runs a silent and progressive course once infection is acquired with persistent liver inflammation and ultimately ending in the development of liver cirrhosis in 10 - 20% of infected individuals over 20 - 30 years [44]. In chronic hepatitis C, the progression of fibrosis is influenced by host, environmental and viral factors such as older age at onset of infection, male gender, alcohol intake, cigarette smoking, insulin resistance, obesity, the presence of hepatic steatosis, and co-infection with other viruses e.g. hepatitis B virus and human immunodeficiency virus [44,45].

Several studies have attempted to determine the influence of smoking cannabis on the severity of liver fibrosis and disease progression [21,22,46,48,49]. Hezode., *et al.* [46] investigated the effect of smoking cannabis on the fibrosis stage and fibrosis progression rate in 270 patients with untreated chronic hepatitis C and no history of other illicit substances use. Patients were classified as daily users of cannabis, occasional users and non-users. The study identified daily cannabis usage as a predictor of both the severity and rapid fibrosis progression rate. Similarly, Ishida., *et al.* [22] found that daily use of cannabis was significantly associated with moderate-severe fibrosis when compared to non-daily users. Daily users of cannabis had nearly 7-fold higher odds of moderate-severe fibrosis when compared to non-daily users. The study included 204 chronic hepatitis C infected individuals who did not receive antiviral treatment. Studies indicated that in chronic hepatitis C, steatosis is significantly associated with genotype 3 infection and high body mass index. Steatosis is also an independent risk factor associated with severe fibrosis [47]. A steatogenic role for cannabis has also been suggested. Hezode., *et al.* [48] found that marked steatosis was more frequent in daily users of cannabis as compared to occasional and non-users. It was found that 33% of daily cannabis users exhibited marked steatosis compared with 16% of non-users. The study included 315 patients with chronic hepatitis C infections who did not receive treatment. A meta-analysis of three cohort studies that included 898 patients with chronic hepatitis C infection, found that the risk for the progression of hepatic fibrosis increased in those who use cannabis compared with non-users. These results, however, did not reach statistical significance [49].

Other studies, however, failed to demonstrate a harmful effect for smoking cannabis in patients with hepatitis C. One study concluded that users of cannabis did not have more advanced fibrotic stage, higher inflammatory grade or even increased steatosis on liver biopsy compared with non-users of cannabis. Sustained virological response following interferon therapy did not differ between users and non-users of cannabis (51.7% vs. 61%). Moreover, cannabis did not influence the likelihood of completing antiviral treatment or led to premature treatment interruption [21].

Beneficial effects for cannabis in patients with chronic liver disease have also been reported. In the era of interferon-based antiviral therapy, smoking cannabis was used to improve the tolerability to antiviral drugs [50]. In this study, Sylvestre., *et al.* [50] found that modest cannabis users adhere more to antiviral treatment as compared with non-users, resulting in an increase in the treatment duration and more sustained virological response compared with non-cannabis users ((54%) vs. 18%). A small study conducted on patients with cholestatic liver disease who had intractable pruritus unresponsive to conventional and also unconventional treatments reported improvement of their pruritus and sleep after treatment with a synthetic $\Delta^9$-THC. These patients were also able to return to work after the improvement of their symptoms [51].

In their study, Adejumo., *et al.* [52] used data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) database in order to determine the relationship between cannabis usage and non-alcoholic fatty liver disease. The discharge records

of patients ≥ 18 years were analyzed. Patients were divided into non-cannabis users, non-dependent cannabis users and dependent cannabis users. Using cannabis was found associated with a significant decrease in the prevalence of non-alcoholic fatty liver disease as compared to non-users. A 15% and 52% lower prevalence was observed in non-dependent and dependent users, respectively. These findings were supported by Kim., *et al.* [53] in their analysis of the National Health and Nutrition Examination Survey data from 2005-2014. The prevalence of non-alcoholic fatty liver disease was found to be inversely correlated with using cannabis compared to non-users. Current heavy cannabis use was associated with a 28% prevalence of non-alcoholic fatty liver disease compared with a prevalence of 30.5% and 38% for current light and past users and a prevalence of 40.7% for those who never used the herb.

In another study, Adejumo., *et al.* [54] analysed the hospital discharge records of subjects (≥ 18 years) who are past or current abusers of alcohol. Data were obtained from the 2014 Nationwide Inpatient Sample (NIS) database. It was found that alcoholic users of cannabis whether dependent or non-dependent had significantly lower odds of developing steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatic cancer. Similarly, Adejumo., *et al.* [55] evaluated hospital discharge records of adults with hepatitis C infection (from 2007 - 2014) and found decreased prevalence of liver cirrhosis among users of cannabis. There was also a decrease in costs of total health care in cannabis users compared to patients who did not use the herb. Moreover, cannabis usage did not affect the incidence of hepatocellular carcinoma in these patients.

### Cannabis in human immune-deficiency/ hepatitis C virus co-infected patients

Brunet., *et al.* [56] in a multicenter longitudinal study of human immunodeficiency virus (HIV)/hepatitis C virus coinfected individuals found no effect for smoking cannabis on progression to fibrosis or cirrhosis. Kelly., *et al.* [57] in a study conducted on women coinfected with human immunodeficiency virus (HIV)/HCV found no effect for occasional cannabis use on fibrosis progression. In this study 67% were abstaining from cannabis or using less than weekly and 6% reported daily use for the entire duration of follow-up (10 - 11 years). In their study, Marcellini., *et al.* [58] investigated the relationship between liver stiffness and cannabis use. The authors used data of 824 co-infected patients from ANRS CO13 HEPAVIH cohort study (French nationwide multicentre cohort of HIV-HCV-co-infected patients), 92% of them were receiving antiretroviral treatment with undetectable HIV viral load in 75% of patients. The study reported no significant association was found between cannabis use and transient elastography measures. One other study conducted in the same population found daily cannabis use to be independently associated with a reduced prevalence of liver steatosis on ultrasound examination (after adjusting for body mass index, excessive intake of ethanol, and current or lifetime use of the antiviral drugs lamivudine/zidovudine) [59].

### Cannabis: many constituents and diverse effects in the liver

Studies that investigated the role of cannabis in liver disease relied on self-reported cannabis use and at best the number of cannabis cigarettes "joints" smoked but there was no information as regards the type, quality and dose of the used cannabis. The potency of smoked cannabis has increased dramatically over the last decades. This increase in the potency of cannabis led to marked increase in amount of $\Delta^9$-THC in the cannabis joint from 10 mg in the early 1970s to 60 - 150 mg or more [10]. The mean $\Delta^9$-THC increased from 1.5% in 1980 to 4.2% in 1997. This is due to improved breeding techniques, indoor cultivation and ease of exchange of seeds from high potency strains in the internet era [3]. The reported median $\Delta^9$-THC content of the unpollinated female cannabis ('sinsemilla') grown indoor was 13.9% [60].

Cannabis has a complex chemistry with over one hundred cannabinoids, terpenoids, and flavonoids e.g. flavocannabiside or flavosativaside [3,5,61]. Strains that contain balanced amounts of cannabidiol and $\Delta^9$-THC or cannabidiol rich strains are likely to exert different effects compared with $\Delta^9$-THC-rich preparations. Cannabinoids differ in their receptor pharmacology e.g. $\Delta^9$-THC acts as a partial agonist of CB1 and CB2 receptors, while cannabidiol displays CB2 receptor inverse agonism [6,7]. In experimental models of liver injury, a profibrogenic role has been suggested for CB1 receptor stimulation as opposed to CB2 receptor-mediated antifibrotic effect [26,62,63]. CB1 receptors mediate profibrogenic events for their inhibition blocked hepatic stellate cell proliferation and the expression of fibrosis-mediated genes procollagen α1(I) and matrix metalloproteinase-13 [28], reduced the expression of hepatic transforming factor beta [62] and activation of 5-lipoxygenase and cyclooxygenase enzymes [64]. In contrast, CB2 receptor stimulation exert anti-inflammatory and antifibrotic effects by reducing the activation or inducing apoptotic cell death of hepatic stellate cells [26,65]. In rats, $\Delta^9$-THC rich extracts of cannabis have been shown to cause hepatic deoxyribonucleic acid fragmentation, fibrosis, vacuolar degeneration, portal cellular infiltration, increase caspase-3 expression and to exacerbate histological liver damage and fibrosis induced by hepatotoxicants e.g. carbon tetrachloride, acetaminophen and thioacetamide [66-68].

Studies have shown no difference in CB1 expression between patients with chronic hepatitis C with a history of cannabis use in the last year and non-users [31]. Thus, the effect of cannabis on the progression of fibrosis and/or steatosis process in patients with liver disease will depend on the relative proportions of the main cannabinoids present $\Delta^9$-THC and cannabidiol.

Cannabis appear to have provided symptomatic relief, helping patients to withstand the interferon-based therapy, thereby increasing the number of patients who had sustained virological response. The study reported adherence to antiviral therapy in 86% of cannabis users as compared to 59% of non-users. Sustained virological response was achieved in 54% of cannabis users vs. 18% of the non-users [50]. Interestingly, there are studies that indicate an antiviral activity for cannabidiol against hepatitis C virus (though not against hepatitis C virus) *in vitro*. Viral replication was inhibited by 86.4% at cannabidiol concentration of 10 μM [69]. Other researchers reported inhibition of hepatitis C virus replication by the CB1 receptor antagonist AM251 [70]. Moreover, studies in simian immunodeficiency virus-infected rhesus macaques treated with $\Delta^9$-THC indicated increased survival, lower plasma viral loads and lower viral replication in lymph nodes [71,72].

Cannabinoids have different immunomodulatory effects and therefore could modulate fibrogenesis and steatosis progression in patients with hepatitis C infection by suppressing antiviral immune response [73]. The endocannabinoids anandamide and 2-arachidonoyl glycerol are increased in plasma in patients with hepatitis C infection [35] or liver cirrhosis [34]. These endocannabinoids appear to modulate the inflammatory and immune response in hepatitis C infection. Anandamide and 2-arachidonoyl glycerol were shown to inhibit the production of inflammatory cytokines interferon-γ, and α, and of interleukin-2 in peripheral blood mononuclear cells from non-infected and hepatitis C -infected patients. On the other hand, 2-arachidonoyl glycerol induced the expression of cyclo-oxygenase-2 and of interleukns-6, -10, -17A, -32 in hepatocytes, and enhanced hepatic stellate cells activation [35]. Anandamide has also been shown to inhibit hepatic stellate cells proliferation and induce their death, suggesting an antifibrogenic role for this endocannabinoid [74].

There could be also role for functional polymorphism of cannabinoid receptors in disease progression in alcoholic hepatitis or hepatitis C infection. A study by Rossi., *et al.* [75] in obese children with steatosis found CB2 Q63R variant to be associated with the severity of inflammation and the presence of non-alcoholic steatohepatitis. One other study reported that the CB2 receptor variant CB2-63QQ was associated with increased severity of liver disease in hepatitis C infected patients (HCV-RNA +ve). This variant was associated with higher serum values of liver aminotransferases and higher histologic activity index (increased inflammation and hepatocellular necrosis). This was ascribed to increased inhibition of T cells by endocannabinoids and consequently a reduction in the immune response against hepatitis C virus [76].

In liver disease, hyperglycaemia, diabetes mellitus, and obesity are independent risk factors for steatosis and fibrosis progression [44,45,77]. The metabolic effects of cannabis could also have a role in modulating live fibrosis and steatosis in chronic liver disease. These metabolic effects, however, are a subject of controversy, either suggesting lower prevalence of diabetes in marijuana users [78] or lower adipose tissue insulin resistance [40] and lower levels of fasting insulin and insulin resistance [79]. The nutritional status of cannabis users is also important. Users of cannabis differ from non-users in higher carbohydrate intake and higher percentage calories from carbohydrate sources [40]. Finally, users of cannabis often try other illicit substances [18,19] and probably receive treatments for other disease processes including antiviral therapy which could modify liver disease progression.

## Conclusion

It is too early to draw a conclusion from human studies on the impact of smoking cannabis on the progression of liver disease. It is clear that there is a need for more carefully designed studies taking into account the type of cannabis used, the relative amounts of the different cannabinoids present, the serum levels of $\Delta^9$-THC and cannabidiol as well as that of endocannabinoids.

## Conflicts of Interests

The author declares that there are no conflicts of interest.

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