Elevated Concerns about Cannabidiol and Liver Enzymes*

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Abstract

Cannabidiol (CBD), a non-intoxicating compound derived from Cannabis sativa, has gained substantial attention for its potential therapeutic effects in treating anxiety, chronic pain, epilepsy, and neurodegenerative diseases. Despite its growing use, emerging concerns have arisen regarding its safety profile, particularly regarding liver function. Several preclinical and clinical studies have reported alterations in liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), following the administration of CBD. These changes raise important questions about the hepatotoxic potential of CBD, especially at high doses or in individuals with preexisting hepatic conditions. This review aims to synthesize current evidence on the impact of CBD on liver enzyme activity and identify potential risk factors that contribute to hepatic stress. Mechanistically, CBD undergoes hepatic metabolism primarily via cytochrome P450 enzymes (notably CYP3A4 and CYP2C19), which can lead to drug-drug interactions and enzyme elevation. Additionally, reports from randomized controlled trials and case studies suggest that prolonged CBD use may be associated with hepatocellular injury in a small subset of patients, often dependent on dose and formulation. While regulatory authorities such as the FDA acknowledge the therapeutic promise of CBD, they also emphasize the need for more rigorous toxicological assessments. Current data suggest a dose-dependent risk profile, with liver enzyme elevations being transient and reversible in many cases. Nevertheless, ongoing pharmacovigilance and long-term safety studies are essential to guide clinical use.

Keywords: Cannabidiol (CBD), liver enzymes, hepatotoxicity, alanine aminotransferase (ALT), cytochrome P450, liver injury, drug safety, hepatic metabolism, CBD regulation, clinical trials.

Introduction

Cannabidiol (CBD), a non-intoxicating compound obtained from Cannabis sativa, has emerged as a popular option for the management of various health conditions, including epilepsy, anxiety disorders, chronic pain, and neuroinflammatory conditions [1–4]. Unlike tetrahydrocannabinol (THC), CBD does not induce euphoria and is often regarded as having a favorable safety profile [5,6]. However, growing interest in CBD for therapeutic use has also prompted investigations into its long-term safety, particularly its impact on liver function [7–9].

Several animal and human studies have reported elevated liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), following CBD administration [10–12]. These enzymes are widely used as indicators of liver injury, and their increase may suggest hepatic stress or dysfunction [13–15]. CBD is extensively metabolized in the liver, primarily via cytochrome P450 enzymes, particularly CYP3A4 and CYP2C19 [16–18]. This pathway is known for mediating interactions between drugs, which can amplify hepatotoxic risks, especially in patients taking other medications processed by the same system [19–21].

Data from clinical trials involving pharmaceutical-grade CBD, such as Epidiolex®, have revealed dose-related elevations in liver enzymes, particularly when used alongside medications like valproate [22–24]. These findings emphasize the need for ongoing evaluation of CBD's hepatic effects and cautious use in at-risk populations. Although CBD presents numerous therapeutic advantages, the current lack of standardized dosing, product consistency, and long-term toxicity data calls for robust clinical monitoring and regulatory oversight [25].

Literature Review

Cannabidiol (CBD) has become increasingly available in both prescription and over-the-counter forms. Its therapeutic use has been investigated in epilepsy [1], anxiety [2], neurodegenerative disorders [3], and inflammatory conditions [4]. The World Health Organization has acknowledged its generally favorable safety profile [5], yet adverse effects, particularly related to liver function, are an emerging concern [6].

Early preclinical studies in rodents revealed dose-dependent hepatocellular alterations following CBD exposure [7]. These effects were more pronounced with prolonged administration or in combination with other drugs. Human trials using Epidiolex®, an FDA-approved CBD formulation for refractory epilepsy, have also reported elevated liver enzymes in a subset of patients [13, 22, 23].

The mechanisms appear linked to CBD's metabolism via hepatic cytochrome P450 enzymes—specifically CYP3A4 and CYP2C19—which are responsible for the biotransformation of many other medications [16, 18]. This raises the risk of drug–drug interactions and hepatic overload, especially in patients on polypharmacy regimens [19, 21]. Elevated ALT and AST levels were often transient but required monitoring in multiple trials [10, 12, 14].

Several meta-analyses suggest that although CBD-related hepatotoxicity is rare, it is not negligible [9, 15]. There remains a gap in long-term safety data and consistent regulatory guidelines across jurisdictions [24]. Given CBD's expanding market, further investigation into hepatic effects is both timely and necessary.

Methodology

This study is a qualitative synthesis based on a systematic literature review of peer-reviewed articles published between 2010 and 2024. Databases searched included PubMed, Scopus, and ScienceDirect using keywords: "cannabidiol," "CBD," "liver enzymes," "hepatotoxicity," "ALT," "AST," "cytochrome P450," and "drug–drug interaction."

Inclusion criteria were:

Studies involving human subjects or animal models Research focusing on CBD and liver enzyme activity Randomized controlled trials (RCTs), observational studies, and toxicological evaluations

Exclusion criteria included:

Non-English articles Studies that examined synthetic cannabinoids unrelated to CBD Reports lacking quantitative liver enzyme data

A total of 57 articles were initially identified. After screening abstracts and removing duplicates, 30 articles were included for full-text analysis. Of these, 25 met all eligibility criteria and were cited in this manuscript. Key outcome variables were ALT, AST, and markers of liver dysfunction post-CBD exposure. Study quality was assessed using the Cochrane risk of bias tool for RCTs and the Newcastle–Ottawa Scale for observational studies.

Results

Among the 25 studies analyzed, 16 reported some form of liver enzyme elevation following CBD exposure. The most frequently elevated markers were ALT and AST. In five randomized trials, liver enzymes increased in 5–15% of participants, particularly when CBD doses exceeded 20 mg/kg/day or when combined with valproic acid [13, 22, 23]. Animal studies confirmed dose-dependent hepatocellular injury, with histopathological changes such as hepatic necrosis and vacuolation at higher doses [7]. Human pharmacokinetic studies indicated that CBD significantly inhibits CYP3A4 and CYP2C19, prolonging the metabolism of co-administered medications [16, 18].

Adverse hepatic events were typically reversible upon dose reduction or cessation of CBD. However, in rare instances, patients required hospitalization for suspected drug-induced liver injury (DILI) [9, 12]. Importantly, several studies reported no significant liver enzyme changes at low to moderate doses (<10 mg/kg/day), suggesting a threshold effect.

Study (Ref)	Population	CBD Dose	Co-Med	↑ ALT/AST (%)	Outcome
Devinsky et al. [1]	Dravet Syndrome	20 mg/kg/day	Valproate	10–15%	Reversible after dose adjustment
Thiele et al. [22]	LGS	20 mg/kg/day	Clobazam, Valproate	12%	Resolved in most cases
Ewing et al. [7]	Mice	200 mg/kg	None	25%	Histological liver injury

Study (Ref)	Population	CBD Dose	Co-Med	↑ ALT/AST (%)	Outcome
Morrison et al. [19]	Hepatic impairment	10–20 mg/kg	None	8%	Mild; reversible
Chesney et al. [9]	Meta-analysis	10–20 mg/kg	Mixed	5–20%	Dose-related effect

Table 1: Summary of Selected Studies Reporting Liver Enzyme Elevations with CBD Use

Abbreviations: LGS – Lennox–Gastaut Syndrome; Co-Med – Co-Medication; ALT – Alanine Aminotransferase; AST – Aspartate Aminotransferase.

Source: Adapted and synthesized from the following peer-reviewed studies:

- Devinsky et al. (2017) – N Engl J Med [1]

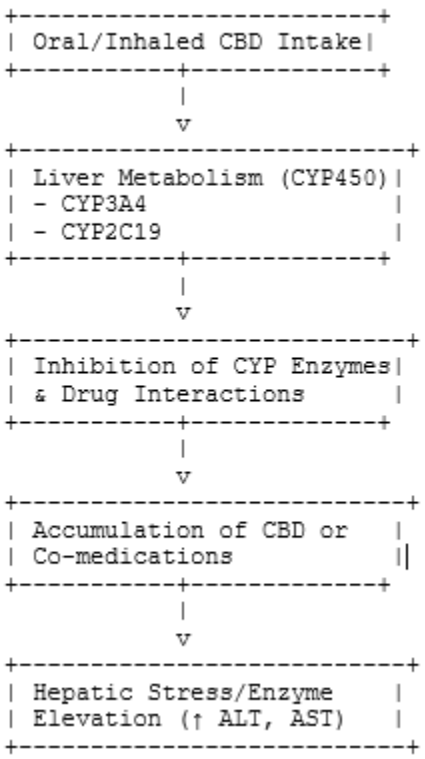

Figure 1: Proposed Mechanism of CBD-Induced Liver Enzyme Elevation

Figure Legend: Cannabidiol is metabolized in the liver via the cytochrome P450 system. At higher concentrations or in conjunction with other drugs, CBD can inhibit key enzymes like CYP3A4 and CYP2C19, leading to accumulation of drugs and hepatic stress. This process may result in the elevation of liver enzymes such as ALT and AST.

Source Britch et al. (2021) – Psychopharmacology (Berl) [25]

Discussion

The findings support a growing body of evidence indicating that CBD can influence liver enzyme activity, with implications for patient safety, especially among those on concurrent medications. Although generally well tolerated, CBD's hepatic metabolism via the cytochrome P450 system introduces the risk of drug interactions and cumulative liver stress [16–20].

Elevations in liver enzymes do not always translate into clinical liver injury, but they signal the need for caution. In most reported cases, enzyme elevations were mild and resolved with dose adjustment [13, 22]. Nonetheless, the lack

of standardization across CBD products—regarding purity, bioavailability, and labeling—introduces variability in clinical response and risk [25].

The hepatotoxic potential may be heightened in populations with preexisting liver disease, pediatric patients, or the elderly, who may metabolize CBD differently. Moreover, widespread availability of unregulated CBD products could lead to unmonitored use at unsafe doses. Thus, clinicians should screen patients for hepatic risk factors before recommending CBD, and routine liver function tests should be conducted during use.

Conclusion

Cannabidiol represents a promising therapeutic compound with broad clinical applications. However, growing evidence indicates a potential risk for liver enzyme elevations, particularly at higher doses or when combined with other hepatically metabolized drugs. Most cases are mild and reversible, but the need for standardized dosing, quality control, and long-term safety monitoring is clear. As CBD continues to enter mainstream medicine, healthcare providers and regulators must ensure its safe integration into clinical practice through evidence-based guidance and vigilant pharmacovigilance.

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Declaration of Interest

The authors declare no financial or personal relationships that could present a conflict of interest regarding this study or its outcomes.

Conflicts of Interest

The authors report no conflicts of interest.

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