JAMA Internal Medicine | Original Investigation

Cannabidiol and Liver Enzyme Level Elevations in Healthy Adults
A Randomized Clinical Trial

Jeffry Florian, PhD; Pablo Salcedo, MD; Keith Burkhart, MD; Aanchal Shah, MS, MBA; Lakshmi Manasa S. Chekka, PharmD, PhD; Dro Keshishi, PharmD; Vikram Patel, PhD; ShanChao Yang, PharmD; Melanie Fein, MD; Ryan DePalma, PhD; Murali Matta, PhD; David G. Strauss, MD, PhD; Rodney Rouse, PhD, DVM, MBA

IMPORTANCE The wide use of unregulated cannabidiol (CBD) products among consumers raises safety concerns. Most research on CBD has studied the relatively high doses used by patients taking prescription CBD. However, limited safety data are available at lower doses.

OBJECTIVE To study the effects of 4-weeks of twice-daily CBD use on the liver and endocrine hormones using a dose within the range consumers are taking with unregulated CBD products.

DESIGN, SETTING, AND PARTICIPANTS This randomized double-blinded placebo-controlled trial from January to August 2024, using per protocol analysis, included healthy adults recruited from a clinical pharmacology unit (Spaulding Clinical Research in West Bend, Wisconsin).

INTERVENTIONS Healthy participants were randomized to CBD, 5 mg/kg/d (2.5 mg/kg/d twice daily), or placebo for 28 days with weekly laboratory assessments.

MAIN OUTCOMES AND MEASURES The primary end point was the percentage of participants with an alanine aminotransferase or aspartate aminotransferase level elevation greater than 3 times the upper limit of normal during the study.

RESULTS In 201 healthy participants (median age, 36 years [IQR, 30-43 years]; 89 women [44%]), 8 participants (5.6%; 95% CI, 1.8%-9.3%) in the CBD group and 0 participants (0%; 95% CI, 0%-7.6%) in the placebo group had liver enzyme level elevation greater than 3 times the upper limit of normal. Seven participants met withdrawal criteria for potential drug-induced liver injury, detected at day 21 in 2 participants and day 28 in 5 participants. No differences in change from baseline were observed between the CBD and placebo groups for total testosterone and inhibin B in male participants or thyrotropin, total triiodothyronine, and free thyroxine in all participants.

CONCLUSIONS AND RELEVANCE In this study, the incidence of elevated alanine aminotransferase or aspartate aminotransferase coupled with the finding of increased eosinophilia, underscores the need for further investigation on the long-term effects of CBD use, its impact on various populations, and the safety of lower doses commonly used by consumers.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT06192589

Visual Abstract

Editorial page 1067

Supplemental content

Author Affiliations: Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Florian, Salcedo, Burkhart, Shah, Chekka, Keshishi, Patel, Yang, DePalma, Matta, Strauss, Rouse); Now with Los Angeles General Medical Center (Yang); Spaulding Clinical Research, West Bend, Wisconsin (Fein); Now with Merck, Lansdale, Pennsylvania (Matta); Now with Translational Cures, Washington, DC (Strauss); Now with Nurix Therapeutics, San Francisco, California (Keshishi).

Corresponding Author: Jeffry Florian, PhD, 10903 New Hampshire Ave, WO64-2020, Silver Spring, MD 20993 (jeffry.florian@fda.hhs.gov).

JAMA Intern Med. 2025;185(9):1070-1078. doi:10.1001/jamainternmed.2025.2366
Published online July 7, 2025. Corrected on August 11, 2025.

The availability and consumer use of cannabidiol (CBD) products have increased in recent years.[1-5] The cannabis plant contains bioactive compounds known as cannabinoids; delta-9 tetrahydrocannabinol (psychoactive component) and CBD (nonpsychoactive component) being the most prevalent in most varieties of cannabis.[6] The Agricultural Improvement Act (Farm Bill) of 2018 removed hemp, defined as cannabis and derivatives of cannabis with extremely low concentrations of delta-9 tetrahydrocannabinol, from the definition of marijuana in the Controlled Substances Act.[6] Following this, many unregulated hemp-derived cannabinoid products became widely available to consumers, often containing CBD, a predominant cannabinoid in hemp that is bioactive and raises various safety concerns.[6,7]

Only one CBD human drug product (Epidiolex; Greenwich Biosciences) is approved by the US Food and Drug Administration (FDA) for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.[8] At labeled doses up to 25 mg/kg/d, an increased risk of liver enzyme level elevation was observed.[8,9] Liver enzyme level elevations typically occurred after 2 weeks and were dose dependent. Limited liver safety data available for lower CBD doses are inconsistent regarding the occurrence and severity of liver enzyme level elevations at 200 to 400 mg a day.[9,10] Consumer self-reporting on CBD use indicates upwards of 200 mg daily,[11-14] so additional safety information at these doses is needed. Further, multiple animal studies have reported CBD effects on the endocrine system, but limited human data exist.[15-19]

This study evaluated the effects of daily CBD on liver enzymes with a dosage similar to reported consumer use in unregulated products. The FDA-approved drug was used to avoid confounding effects from contaminants found in unregulated CBD products.[20,21] We selected a dose toward the upper end of reported consumer CBD use with sufficient dosing duration and monitoring to observe liver enzyme level elevations should they occur.

Key Points

Question What are the effects of daily cannabidiol (CBD) use in healthy adults at doses representative of consumer use on liver safety and endocrine hormone levels?

Findings In this randomized clinical trial of 201 healthy participants, 8 of 151 participants in the CBD group and 0 of 50 participants in the placebo group had liver enzyme level elevations greater than 3 times the upper limit of normal. No differences were observed between CBD and placebo groups on endocrine hormones.

Meaning These results document hepatic transaminase elevations and eosinophilia in healthy adults exposed to CBD doses representative of consumer use of unregulated CBD products.

Methods

Study Design, Oversight, and Participants

We conducted a randomized double-blinded placebo-controlled trial in healthy participants at a clinical pharmacology unit (Spaulding Clinical Research in West Bend, Wisconsin) evaluating the effects of daily CBD use on liver enzyme level elevations and endocrine measures at a dose within the reported range of consumers use with unregulated CBD products from January 2024 through August 2024. This study was approved by the local institutional review board (Advarra). All participants provided written informed consent. The authors designed and implemented the trial, managed all aspects of data collection and analysis, and verified both the completeness and accuracy of the data, as well as adherence to the study protocol. The trial protocol and statistical analysis plan are available in Supplement 1. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

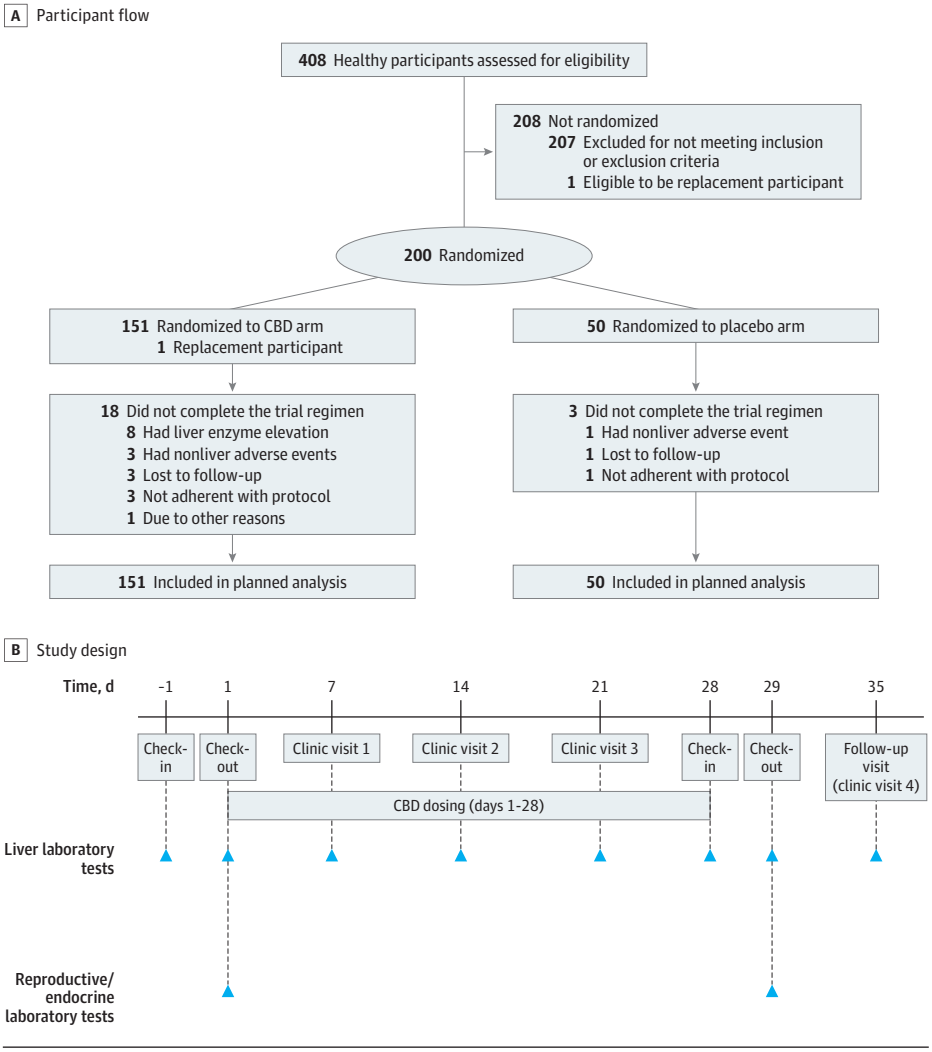
Participants were recruited by standard approaches for healthy volunteer clinical pharmacology studies (ie, online advertising and emails or texts to individuals in the site's database). Key inclusion criteria were age 18 to 55 years (inclusive), nonsmoking, weight of at least 50 kg (110 lb), and normal medical history findings, clinical laboratory results, and physical examination at screening and check-in (eTable 1 in Supplement 2). Negative test results for misuse of drugs and alcohol were required at screening and check-in days. Participants were excluded if they had abnormal liver chemistry test results defined as a serum alanine aminotransferase (ALT) level or aspartate aminotransferase (AST) level greater than 1.5 times the upper limit of normal (ULN), a total bilirubin greater than the ULN, and/or an international normalized ratio greater than 1.3. Participants were excluded if they consumed more than 14 units of alcoholic beverages in preceding 6 months or had a history of alcoholism or drug/substance misuse within 2 years of screening. Participants were also excluded if they used any medications within 14 days of study check-in or could not stop the use of nicotine for the study. Race and ethnicity were self-reported from participants as recommended by FDA guidance.[22] Race and ethnicity were collected for descriptive purposes to characterize the study population; no analyses by race and ethnicity were planned or conducted.

Participants were randomized to 1 of 2 treatments using a random number generator in R statistical software, version 4.1.2 (R Project for Statistical Computing). The study allowed enrollment of additional participants to account for discontinuations.

Study Procedures and Interventions

Oral solution CBD dosage of 2.5 mg/kg twice a day (total 5 mg/kg CBD daily) was administered to 151 participants during this 28-day single-period study. The placebo control group (50 participants) received an inactive oral solution. Participants reported to the study site for screening and returned on day −1 for check-in and baseline assessments. After an overnight stay, participants checked out (day 1) with sufficient take-home doses of oral CBD or placebo solution for 28 days returning on day 28 for a single in-house day with check-out on day 29 (**Figure 1**). Participants had clinic visits (days 7, 14, 21) and a day 35 follow-up visit. The clinical site provided daily reminders to participants during outpatient days. Chemistry and

Figure 1. Participant Flow and Study Design



Panel A shows the flow of participants in the study. Panel B shows the overall study design, including days of cannabidiol dosing and laboratory collection. eTable 1 in Supplement 2 lists inclusion and exclusion criteria failed during screening. CBD indicates cannabidiol.

hematology assessments were performed on days −1, 1, 7, 14, 21, 28, 29, and 35. Endocrine assessments (total testosterone and inhibin B in male participants; thyrotropin, total triiodothyronine, and free thyroxine in all participants) were performed on days 1 and 29. Plasma concentrations of CBD were measured by validated liquid chromatography and tandem mass spectrometry (eMethods 1 in Supplement 2). The approved prescription drug product was used to avoid potential confounders of contaminants.

Outcomes

The primary study end point was the percentage of participants with an ALT or AST liver enzyme level elevation level greater than 3 times the ULN (consensus criteria for elevation: ULN for alanine aminotransferase ALT is 33 U/L for males and 25 U/L for females [to convert ALT and AST to microkatals per liter, multiply by 0.0167]).[23] The secondary liver safety end point was the percentage of participants meeting withdrawal criteria for potential drug-induced liver injury (DILI), which was defined in this study as an ALT or AST greater than or equal to 3 times the ULN with the presence of clinical symptoms and/or eosinophilia (>5%) or an ALT or AST level greater than or equal to 5 times the ULN or an ALP greater than or equal to 2 times the ULN with accompanying elevations of GGT or an ALT greater than or equal to 3 times the ULN and simultaneous elevation of bilirubin concentration exceeding 2 times the ULN.[24] Meeting criteria for potential DILI alone does not translate to clinically apparent liver injury. When potential DILI criteria were met, repeat liver serum levels were collected every 24 to 48 hours until laboratory values stabilized or began a steady decrease, after which laboratory testing was performed weekly until resolution. Due to variations in the time it took for complete liver enzyme level resolution, participants had varying lengths of study follow-up. In addition, viral confounders were evaluated using immunoglobulin and antigen-based viral serological testing.

Additional secondary outcomes included the change from baseline in total testosterone, inhibin B, thyrotropin, total triiodothyronine, and free thyroxine after CBD administration compared with placebo (eMethods 2 in Supplement 2). Mul-

Table 1. Study Participant Demographic and Baseline Characteristics

Characteristic	Cannabidiol (n = 151)	Placebo (n = 50)	Total (N = 201)
Age, median (IQR), y	36 (31-44)	35 (29-41)	36 (30-43)
Sex, No. (%)			
Female	68 (45)	21 (42)	89 (44)
Male	83 (55)	29 (58)	112 (56)
Race, No. (%)[a]			
American Indian	1 (1)	0 (0)	1 (0.5)
Asian	3 (2)	3 (6)	6 (3)
Black or African American	64 (42)	23 (46)	87 (43)
White	77 (51)	22 (44)	99 (49)
More than 1 race[b]	2 (1)	1 (2)	3 (1.5)
Unknown or not reported[c]	4 (3)	1 (2)	5 (2.5)
Hispanic or Latino ethnicity, No. (%)[a]	22 (15)	6 (12)	28 (14)
Body weight, median (range), kg	80.2 (50.6-110.0)	75.9 (53.0-103.0)	79.4 (50.6-110.0)
Height, median (range), m	1.71 (1.53-1.94)	1.72 (1.52-1.87)	1.7 (1.52-1.94)
BMI, median (range)	27.1 (18.6-33.0)	26 (19.2-32.0)	26.9 (18.6-33.0)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Race and ethnicity were self-reported from participants as recommended by US Food and Drug Administration guidance.[41]

[b] For participants who reported more than 1 race: cannabidiol treatment arm (1 American Indian and Black, 1 Asian and White) and placebo arm (1 Black and White).

[c] No further breakdown is available for this category.

Table 2. Primary and Secondary Liver Outcomes

	Outcome			
	Primary: serum ALT or AST >3 × the ULN		Secondary: meeting withdrawal criteria for potential DILI	
Product	Participants, No.	% (95% CI)[a]	Participants, No.	% (95% CI)[a]
Cannabidiol (n = 141)[b]	8	5.6 (1.8-9.3)	7	4.9 (1.3-8.4)
Placebo (n = 47)[b]	0	0 (0-7.6)	0	0 (0-7.6)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal.

[a] Based on Kaplan-Meier estimates.

[b] Number of participants at risk at week 4 of the study.

tiple exploratory outcomes were assessed as specified in the protocol and statistical analysis plan (Supplement 1). Participant safety was monitored with clinical laboratory tests, vital signs, electrocardiograms, and physical examinations.

Statistical Analysis

Sample size was based on the primary end point of percentage of CBD administered participants with an aminotransferase elevation greater than 3 times the ULN. Assuming a true event rate of 6%, the study had a 95% probability of observing 5 or more events. For the secondary end point, assuming the true observed drug-induced liver injury event rate was 2%, the study had a 93% probability of observing 1 or more events. Change from baseline comparisons were performed for various endocrine laboratory measures. Sample size for the study was not powered for any of these comparisons. No adjustments were made for multiplicity for these exploratory end points.

All participants who received at least 1 dose of the study drug and at least 1 laboratory assessment were included in the analyses. The proportions of participants exceeding 3 times the ULN for ALT and AST are summarized. Results are reported as percentages with a 2-sided 95% CI based on a Kaplan-Meier analysis. Separate percentages are reported for both treatment groups. Endocrine end points included the change from baseline in serum total testosterone and inhibin B in males, and in thyroid-stimulating hormone, total triiodothyronine, and free thyroxine in both males and females after CBD administration compared with placebo. Analyses were conducted using a linear mixed-effect model and results are presented as point estimates with associated 95% CIs. Statistical analyses were performed in R version 4.1.2 (R Project for Statistical Computing). Additional liver analysis details are specified in the statistical analysis plan in Supplement 1.

Results

Study Participants

Of the 408 healthy volunteers eligible for screening, 201 participants were enrolled and randomized into 2 groups with 151 participants taking CBD solution and 50 taking matching placebo (median age, 36 years [IQR, 30-43 years]; 89 women [44%]; 87 African American [43%], 6 Asian [3%], 28 Hispanic or Latino ethnicity [14%], 99 White [49%]) (**Table 1**). A total of 188 participants completed the trial (Figure 1).

Primary Outcome

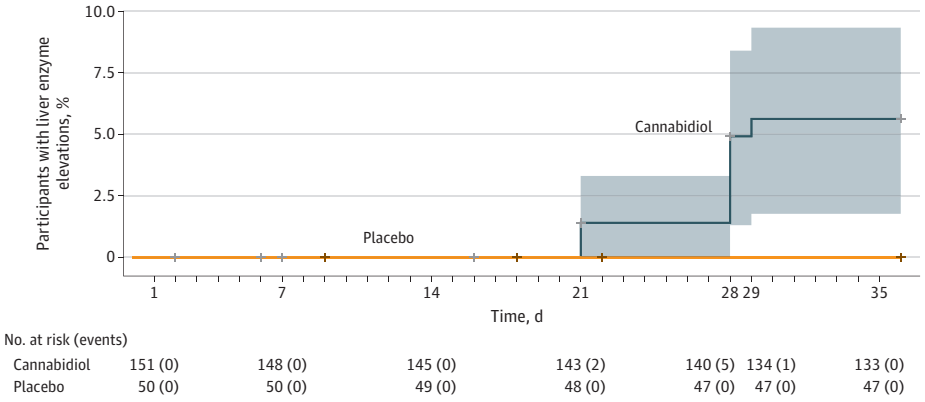
Among participants receiving CBD, 8 (5.6% [95% CI, 1.8%-9.3%]) experienced ALT elevations exceeding 3 times the ULN, as determined by Kaplan-Meier analysis after 4 weeks of CBD dosing (**Table 2**, **Figure 2**). In contrast, no participants in the placebo arm exhibited ALT elevations meeting this threshold (0% [95% CI, 0%-7.6%]).

Secondary Outcomes

Liver Enzymes

Based on Kaplan-Meier analysis, 7 participants (4.9% [95% CI, 1.3%-8.4%]) receiving CBD met withdrawal criteria (Table 2), with discontinuation of CBD dosing occurring on day 21 for 2

Figure 2. Kaplan-Meier Curve for Primary End Point



Kaplan-Meier estimates of liver enzyme level elevations in participants receiving cannabidiol (n = 151) or placebo (n = 50) over the study duration of 35 days. The blue line represents the cannabidiol group with a 95% CI (shaded area), while the orange line represents the placebo group. The risk values show the number of participants at risk and events observed at the following time points: days 1, 7, 14, 21, 28, 29, and 35. Liver enzyme level elevations were first observed in the cannabidiol group on day 21, with occurrences observed in 5.6% of participants by day 35. No events were observed in the placebo group during the study period.

participants and on day 28 for 5 participants. Two of these 7 participants experienced ALT elevations greater than 3 times the ULN but less than 5 times the ULN with accompanying eosinophilia (>5%) and 5 experienced ALT elevations greater than 5 times the ULN with accompanying eosinophilia. No participants in the placebo group (0% [95% CI, 0%-7.6%]) met these criteria.

Endocrine

No substantial differences in change from baseline were observed between the CBD and placebo groups in male participants for total testosterone and inhibin B. Similarly, no substantial differences were observed between the CBD and placebo groups for thyroid stimulating hormone, total triiodothyronine, and free thyroxine in all participants (eTable 2 in Supplement 2).

Exploratory Outcomes

The 8 individuals in the CBD group who experienced ALT elevations greater than 3 times the ULN demonstrated a range of severity with 5 individuals (3.3%) experiencing peak ALT levels greater than 5 times the ULN and 2 individuals (1.3%) with ALT levels greater than 10 times the ULN, with the highest greater than 18 times the ULN (**Figure 3**). One participant (0.7%) experienced an ALT elevation with concurrent symptoms (temporary epigastric discomfort). Three participants (2.0%) in the CBD group and 1 participant (2%) in the placebo group experienced elevations in alkaline phosphatase greater than 1.5 times the ULN (eTable 3 in Supplement 2). Pharmacokinetics from weekly trough samples are summarized in eTable 4 in Supplement 2. Based on all available information, all events were considered probable or definite with regard to the study drug.

Safety

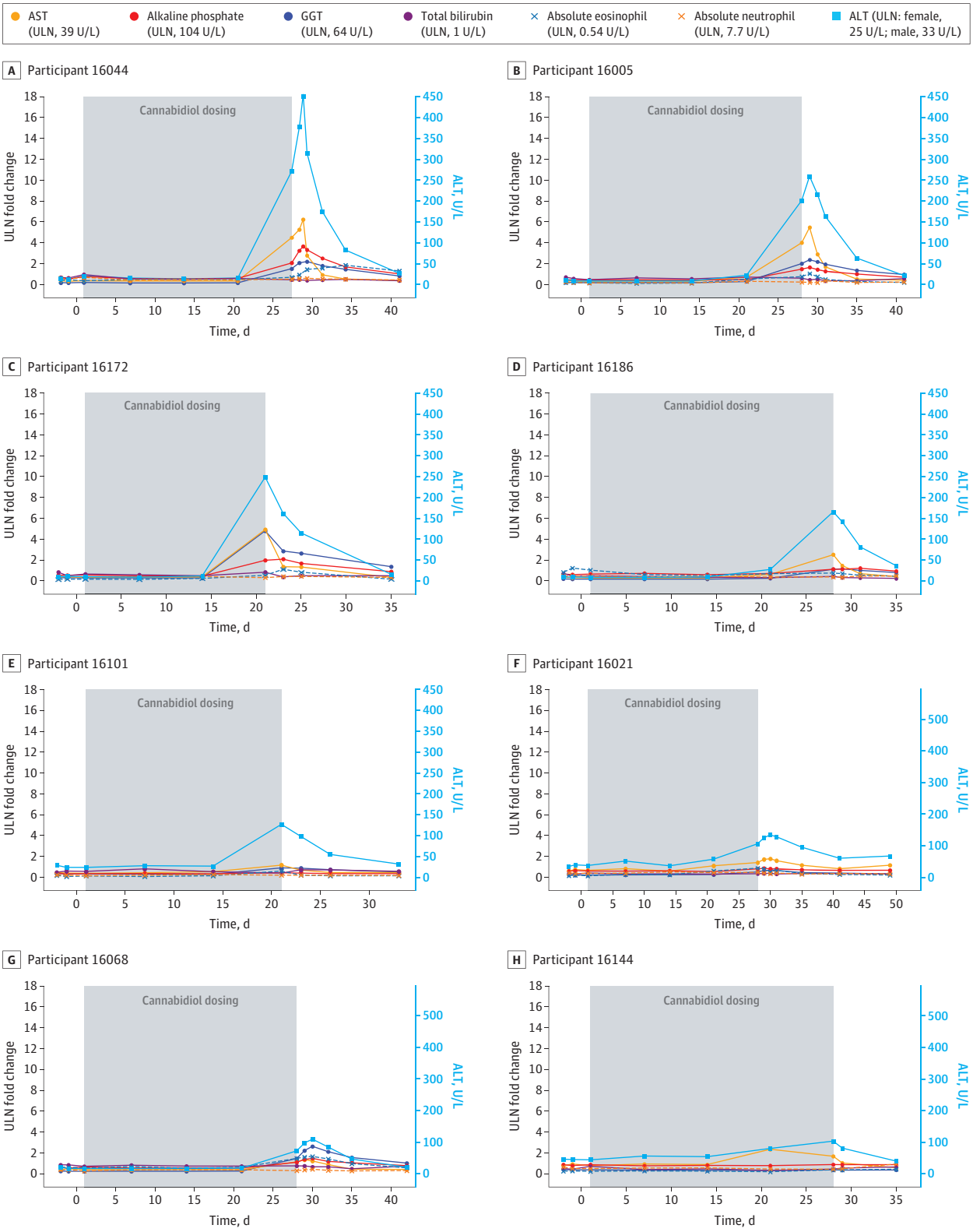
No serious or life-threatening adverse events occurred.[25] A total of 52 participants (26%) experienced undesirable or adverse events: 43 (29%) in the CBD group and 9 (18%) in the placebo group. The most common adverse events in the CBD group were hepatic enzyme increase (11%), eosinophilia (9%), somnolence (8%), and diarrhea (8%) while in the placebo group they were insomnia (27%) and upper respiratory tract infection (18%). eTable 5 in Supplement 2 contains the incidence and number of adverse events. Immunoglobulin and antigen viral serology results revealed prior viral infections among 6 of the 8 participants with elevated liver enzymes: 5 (63%) had prior Epstein-Barr virus exposure, 4 (50%) prior cytomegalovirus infection, and 2 (25%) prior herpes simplex virus 2 infection. None of these infections was active at the time of testing or was considered contributory to enzyme level elevations (eTable 6 in Supplement 2).

Discussion

In this randomized double-blinded placebo-controlled trial, 5.6% of healthy adults administered CBD 5 mg/kg/d for up to 28 days experienced liver enzyme level elevations greater than 3 times the ULN. While hepatic enzyme level elevations were observed, participants did not experience clinical symptoms related to liver function during this 28-day study and hepatic enzymes returned to normal within 1 to 2 weeks following discontinuation.

Rates of consumer use of unregulated CBD-containing products continue to grow. According to the 2022 National Survey on Drug Use and Health (NSDUH), 20% of adults reported using CBD products within the past year.[26] In a 2023 survey of 1142 US adults conducted by the National Opinion Research Center, 21.1% of respondents reported past-year CBD use.[1] While most self-dosing CBD users report consuming 0 to 100 mg per day, many consumers use higher doses.[12-14] A 2023 survey of 5635 CBD users found that 23% reported consuming more than 200 mg daily.[11] Two online surveys on CBD use

Figure 3. Participants Showing Liver Enzyme Level Elevations



Serial liver chemistry values for the 8 participants with ALT ≥3 × the ULN. Eosinophil and neutrophil measurements are also depicted. Participant 16044 experienced epigastric discomfort on day 28. SI conversion factors: To convert ALT and AST to microkatals per liter, multiply by 0.0167. ALT indicates alanine aminotransferase, AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

reported 4.5% and 7.2% of participants consuming more than 200 mg/d.[12,13] An observational study conducted remotely in 1160 self-dosing CBD users reported doses as high as 390 mg/d in some individuals.[14]

There are knowledge gaps surrounding potential health risks associated with CBD at doses consistent with unregulated consumer products, including liver damage and male reproductive harm. In this study, the observed liver enzyme level elevation event rate of 5.6% was consistent with that observed in a previous open-label study with 150 mg twice daily (ie, 300 mg/d) CBD for 4 weeks, where 4 of 59 participants had aminotransferase levels greater than 3 times the ULN (6.8%) and 2 of 59 participants met criteria for DILI.[10] Healthy volunteer studies evaluating CBD doses up to 1500 mg/d over multiple weeks observed aminotransferase levels greater than 3 times the ULN in 7% to 38% of study participants.[27,28] An investigation with doses of 300 to 600 mg daily over 12 weeks did not report any liver enzyme level elevations but included no laboratory analyses.[29] Investigations with lower doses of CBD (less than 50 mg/d) have not reported aminotransferase elevations greater than 3 times the ULN, but sample sizes for these studies may not have been sufficient for observing a lower incidence rate.[9] It is notable that this study's dosage of 5 mg/kg/d (approximately 400 mg/d) falls between the range of higher doses where enzyme level elevations (150-1500 mg/d) were previously reported and lower doses (<50 mg/d) where elevations were not previously observed, suggesting that moderate CBD doses, such as those used in this study, may carry hepatic risks.

Observed liver enzyme level elevations took 3 weeks or more to occur in this study, peaked 1 to 2 days after CBD dosing was discontinued, and returned to baseline within 1 to 2 weeks (Figure 3). Enzyme level elevations did not result in clinically significant liver function changes and were associated with symptoms (abdominal discomfort) in only one case over the 1-month time course of CBD use. This short-term finding does not exclude the potential for hepatic harm or damage with longer-term CBD use at 5 mg/kg/d or lower doses. The delayed onset of liver enzyme level elevation without accompanying symptoms suggests that there is the potential for hepatic harm with CBD use to go undetected without routine clinical monitoring or discontinuation of CBD dosing.

Five of the 8 aminotransferase elevations occurred in females as did the highest observed elevations (eTable 6 in Supplement 2). As the study used weight-based dosing and no differences were observed with CBD or metabolite exposure in males or females, these differences would not be explained by drug exposure and warrant further study. Increased female susceptibility to DILI has been reported in the literature.[30] In a prospective study of 899 individuals conducted from 2004 to 2013 by the DILI Network, a higher prevalence of DILI was observed in females (59% female vs 41% male).[31]

The presence of eosinophilia[24] was observed in 7 of 8 of the elevated ALT cases (88%). Further investigation into this finding of eosinophilia and its potential relationship to hepatic transaminase elevations is warranted, as it could provide more insight into underlying mechanisms. In most patients, the eosinophil counts increased and decreased in parallel with the transaminase levels, with a subset of participants experiencing increases in eosinophil counts immediately preceding transaminase elevations.

Previous animal studies have documented testicular toxic effects, impaired spermatogenesis, and thyroid hormone modulation with CBD exposure.[15,16,32] Lower testosterone and inhibin B levels would be biomarkers of the testes/spermatogenic toxic effects.[33] There was a lack of effect of CBD on endocrine hormones in this study that might be attributed to limited monitoring or the relatively low CBD exposure compared with toxicology studies described above. Further investigation into the impact of CBD on the endocrine system may be warranted.

This clinical trial is part of the FDA efforts to understand the safety of CBD products and inform discussions about safeguards and oversight to manage and minimize risks with CBD products. These findings may have important implications for consumers who may otherwise be unaware of potential safety risks. This study utilized healthy participants without comorbidities or concomitant medication use and therefore may underestimate risk in the general population. Hepatic effects of CBD use may have greater incidence and severity in some populations that use CBD products, including those with neurological disorders, pulmonary conditions, gastrointestinal disorders, and chronic pain.[34] Furthermore, increased occurrence of liver enzyme level elevations may be observed in populations taking concurrent medications or recreational drugs, alcohol, or nicotine.[35,36] CBD has been shown to inhibit cytochrome P450 enzymes and increase in liver enzymes has been documented when CBD is concurrently taken with other medications, such as valproate.[37-39]

Given the growing popularity of unregulated CBD-containing products in the market and the ability of CBD to cause liver enzyme level elevations, inclusion of CBD use as part of routine medical screening could be considered, particularly in patients with existing liver conditions or those taking medications metabolized by the liver. For patients presenting with elevated liver enzymes, CBD use could be considered in the differential diagnosis.[40] Additional research is needed to understand the safety of lower CBD doses typically used by consumers and continued use after initial enzyme level elevations, as well as the effects on endocrine or reproductive systems.

Limitations

The CBD dosing of this study was within the range of reported consumer use, but on the higher end and administered twice daily. While many consumers report taking unregulated CBD more than once daily, most consume it less frequently.[11] In addition, given the reports of inaccurate labeling of some over-the-counter CBD products, it is possible that individuals self-dosing CBD are consuming different doses than expected.[13] The incidence of liver enzyme level elevations may be lower with reduced dosage and less frequent use. The age range of the study's population was 18 to 55 years. Hepatic and endocrine effects in older adult CBD users were not captured,

although CBD is frequently used by older adults, particularly for conditions such as pain, anxiety, insomnia, and arthritis.[41]

Participants were also dosed for 1 month. This duration is not sufficient to inform the potential for longer-term health impacts. Monitoring was not frequent enough to capture initial elevations in all cases. As dosing was discontinued when liver enzyme level elevations were observed, it remains unknown whether these events would have resolved on their own despite continued use or have further escalated. In a systematic review of clinical trials initiating daily CBD treatment, 25% or 32 of 128 cases of liver enzyme level elevations resolved spontaneously with continued CBD use.[9] Furthermore, healthy volunteers were evaluated who were not taking concomitant medications and who had no comorbidities that may increase an individual's susceptibility to hepatic enzyme level elevations. Given this, the study may underestimate hepatic enzyme level elevation in the general population.

Most CBD dosing was self-administered, with daily reminders, a diary to record dosing, and accountability checks. There is a possibility that participants may not have followed instructions. However, pharmacokinetic exposure data fell within the expected range and the study included a placebo control arm where no events were observed increasing confidence that the observed events were related to CBD.

Conclusions

In this randomized double-blind clinical trial of healthy adults administered CBD, 5 mg/kg/d for 28 days, 8 (5.6%) experienced liver enzyme level elevations and 7 (4.9%) met protocol defined criteria for potential DILI. This research has important implications for consumer safety. The findings suggest that CBD use at doses representative of currently available unregulated consumer products can lead to liver enzyme level elevations in healthy adults. As CBD users may not notice these changes on their own, this study highlights the need for caution and potentially routine monitoring in CBD users. The incidence of elevated alanine aminotransferase or aspartate aminotransferase, with a notably higher prevalence among female participants, coupled with the finding of increased eosinophilia, underscores the need for further investigation on the long-term effects of CBD use, its impact on various populations, and the safety of lower doses commonly used by consumers.

ARTICLE INFORMATION

Accepted for Publication: April 25, 2025.

Published Online: July 7, 2025. doi:10.1001/jamainternmed.2025.2366

Correction: This article was corrected on August 11, 2025, to change the license type from an open access CC-BY license to a standard license.

Author Contributions: Dr Florian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Florian, Salcedo, Yang, Matta, Strauss, Rouse.
Acquisition, analysis, or interpretation of data: Florian, Salcedo, Burkhart, Shah, Chekka, Keshishi, Patel, Yang, Fein, DePalma, Matta, Strauss.
Drafting of the manuscript: Florian, Shah, Chekka, Yang, Rouse.
Critical review of the manuscript for important intellectual content: Florian, Salcedo, Burkhart, Chekka, Keshishi, Patel, Yang, Fein, DePalma, Matta, Strauss.
Statistical analysis: Florian, Salcedo, Yang.
Obtained funding: Strauss, Rouse.
Administrative, technical, or material support: Salcedo, Shah, Keshishi, Yang, Fein, Matta, Rouse.
Supervision: Salcedo, Strauss.

Conflict of Interest Disclosures: Dr Fein reported that Spaulding Clinical was paid by the US Food and Drug Administration (FDA) to conduct the clinical study. No other disclosures were reported.

Funding/Support: This study was funded by the US Food and Drug Administration (FDA).

Role of the Funder/Sponsor: The FDA oversaw the design and overall conduct of the study including overseeing the management, analysis, and interpretation of the data. The FDA prepared, reviewed, and approved the manuscript for submission for publication.

Disclaimer: This article reflects the views of the author and should not be construed to represent FDA's views or policies.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We are deeply grateful to the study participants and all the clinical research staff from Spaulding Clinical Research, including Trupti Indurkar, BS, Karrielynn Gerlach, NREMT-P, and Sam Budnik, MS. We also thank Lars Johannesen, PhD, Sreedharan Sabarinath, PhD, Rebecca Racz, PharmD, Kevin Ford, PhD, Paul Hayashi, MD, and Mark Avigan, MD of the FDA. These contributors received no financial compensation outside of their salary.

REFERENCES

1. Wilson-Poe AR, Smith T, Elliott MR, Kruger DJ, Boehnke KF. Past-year use prevalence of cannabidiol, cannabigerol, cannabinol, and Δ8-tetrahydrocannabinol among US adults. *JAMA Netw Open*. 2023;6(12):e2347373. doi:10.1001/jamanetworkopen.2023.47373

2. Caulkins JP. Changes in self-reported cannabis use in the United States from 1979 to 2022. *Addiction*. 2024;119(9):1648-1652. doi:10.1111/add.16519

3. Hasin D, Walsh C. Trends over time in adult cannabis use: A review of recent findings. *Curr Opin Psychol*. 2021;38:80-85. doi:10.1016/j.copsyc.2021.03.005

4. Mattingly DT, Richardson MK, Hart JL. Prevalence of and trends in current cannabis use among US youth and adults, 2013-2022. *Drug Alcohol Depend Rep*. 2024;12:100253. doi:10.1016/j.dadr.2024.100253

5. Williamson EM, Liu X, Izzo AA. Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *Br J Pharmacol*. 2020;177(6):1227-1240. doi:10.1111/bph.14943

6. Food and Drug Administration. *Background materials for the June 14, 2022, meeting of the Science Board to the FDA*. FDA; 2022.

7. Harlow AF, Leventhal AM, Barrington-Trimis JL. Closing the loophole on hemp-derived cannabis products: a public health priority. *JAMA*. 2022;328(20):2007-2008. doi:10.1001/jama.2022.20620

8. Food and Drug Administration. *Cannabidiol (Epidiolex) prescribing information*. FDA; 2018.

9. Lo LA, Christiansen A, Eadie L, et al. Cannabidiol-associated hepatotoxicity: a systematic review and meta-analysis. *J Intern Med*. 2023;293(6):724-752. doi:10.1111/joim.13627

10. Crippa JAS, Zuardi AW, Guimarães FS, et al; Burnout and Distress Prevention With Cannabidiol in Front-line Health Care Workers Dealing With COVID-19 (BONSAI) Trial Investigators. Efficacy and safety of cannabidiol plus standard care vs standard care alone for the treatment of emotional exhaustion and burnout among frontline health care workers during the COVID-19 pandemic: a randomized clinical trial. *JAMA Netw Open*. 2021;4(8):e2120603. doi:10.1001/jamanetworkopen.2021.20603

11. Brightfield Group. *Consumer insights report 2023*. Brightfield Group; 2023.

12. Moltke J, Hindocha C. Reasons for cannabidiol use: a cross-sectional study of CBD users, focusing on self-perceived stress, anxiety, and sleep problems. *J Cannabis Res*. 2021;3(1):5. doi:10.1186/s42238-021-00061-5

13. Binkowska AA, Jakubowska N, Redeł A, Laskowska S, Szlufik S, Brzezicka A. Cannabidiol usage, efficacy, and side effects: analyzing the impact of health conditions, medications, and cannabis use in a cross-sectional online pilot study. *Front Psychiatry*. 2024;15:1356009. doi:10.3389/fpsyt.2024.1356009

14. Kaufmann R, Bozer AH, Jotte AK, Aqua K. Long-term, self-dosing CBD users: indications,

dosage, and self-perceptions on general health/symptoms and drug use. *Med Cannabis Cannabinoids*. 2023;6(1):77-88. doi:10.1159/000531666

15. Patra PB, Wadsworth RM. Quantitative evaluation of spermatogenesis in mice following chronic exposure to cannabinoids. *Andrologia*. 1991;23(2):151-156. doi:10.1111/j.1439-0272.1991.tb02520.x

16. Rosenkrantz H, Fleischman RW, Grant RJ. Toxicity of short-term administration of cannabinoids to rhesus monkeys. *Toxicol Appl Pharmacol*. 1981;58(1):118-131. doi:10.1016/0041-008X(81)90122-8

17. Mandal TK, Das NS. Testicular toxicity in cannabis extract treated mice: association with oxidative stress and role of antioxidant enzyme systems. *Toxicol Ind Health*. 2010;26(1):11-23. doi:10.1177/0748233709354553

18. Huang HF, Nahas GG, Hembree WC III. Effects of marihuana inhalation on spermatogenesis of the rat. *Adv Biosci*. 1978;22-23:419-427.

19. Dixit VP, Gupta CL, Agrawal M. Testicular degeneration and necrosis induced by chronic administration of cannabis extract in dogs. *Endokrinologie*. 1977;69(3):299-305.

20. Gidal BE, Vandrey R, Wallin C, et al. Product labeling accuracy and contamination analysis of commercially available cannabidiol product samples. *Front Pharmacol*. 2024;15:1335441. doi:10.3389/fphar.2024.1335441

21. Johnson E, Kilgore M, Babalonis S. Cannabidiol (CBD) product contamination: Quantitative analysis of Δ^9-tetrahydrocannabinol (Δ^9-THC) concentrations found in commercially available CBD products. *Drug Alcohol Depend*. 2022;237:109522. doi:10.1016/j.drugalcdep.2022.109522

22. US Food and Drug Administration. Collection of race and ethnicity data in clinical trials. October 26, 2016. Accessed June 2, 2025. https://www. fda.gov/media/75453/download

23. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol*. 2017;112(1):18-35. doi:10.1038/ajg.2016.517

24. Food and Drug Administration. Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. July 2009. Accessed April 4, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

25. US Dept of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. November 17, 2017. Accessed May 29, 2025. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

26. Choi NG, Marti CN, Choi BY. Prevalence of cannabidiol use and correlates in US adults. *Drug Alcohol Depend Rep*. 2024;13:100289. doi:10.1016/j.dadr.2024.100289

27. Watkins PB, Church RJ, Li J, Knappertz V. Cannabidiol and abnormal liver chemistries in healthy adults: results of a phase I clinical trial. *Clin Pharmacol Ther*. 2021;109(5):1224-1231. doi:10.1002/cpt.2071

28. Taylor L, Crockett J, Tayo B, Checketts D, Sommerville K. Abrupt withdrawal of cannabidiol (CBD): a randomized trial. *Epilepsy Behav*. 2020;104(Pt A):106938. doi:10.1016/j.yebeh.2020.106938

29. Gundugurti PR, Banda N, Yadlapalli SSR, et al. Evaluation of the efficacy, safety, and pharmacokinetics of nanodispersible cannabidiol oral solution (150 mg/mL) versus placebo in mild to moderate anxiety subjects: A double blind multicenter randomized clinical trial. *Asian J Psychiatr*. 2024;97:104073. doi:10.1016/j.ajp.2024.104073

30. Amacher DE. Female gender as a susceptibility factor for drug-induced liver injury. *Hum Exp Toxicol*. 2014;33(9):928-939. doi:10.1177/0960327113512860

31. Chalasani N, Bonkovsky HL, Fontana R, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. 2015;148(7):1340-52.e7. doi:10.1053/j.gastro.2015.03.006

32. Porcella A, Marchese G, Casu MA, et al. Evidence for functional CB1 cannabinoid receptor expressed in the rat thyroid. [published correction appears in Eur J Endocrinol 2002 Sep;147(3):434]. *Eur J Endocrinol*. 2002;147(2):255-261. doi:10.1530/eje.0.1470255

33. Pierik FH, Burdorf A, de Jong FH, Weber RF. Inhibin B: a novel marker of spermatogenesis. *Ann Med*. 2003;35(1):12-20. doi:10.1080/07853890310004084

34. Nguyen C, Moeller KE, McGuire M, Melton BL. Consumer perception, knowledge, and uses of cannabidiol. *Ment Health Clin*. 2023;13(5):217-224. doi:10.9740/mhc.2023.10.217

35. Alatalo P, Koivisto H, Puukka K, et al. Biomarkers of liver status in heavy drinkers, moderate drinkers and abstainers. *Alcohol Alcohol*. 2009;44(2):199-203. doi:10.1093/alcalc/agn099

36. Jang ES, Jeong SH, Hwang SH, et al. Effects of coffee, smoking, and alcohol on liver function tests: a comprehensive cross-sectional study. *BMC Gastroenterol*. 2012;12:145. doi:10.1186/1471-230X-12-145

37. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP; UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia*. 2017;58(9):1586-1592. doi:10.1111/epi.13852

38. Gilmartin CGS, Dowd Z, Parker APJ, Harijan P. Interaction of cannabidiol with other antiseizure medications: a narrative review. *Seizure*. 2021;86:189-196. doi:10.1016/j.seizure.2020.09.010

39. Chen S, Kim JK. The role of cannabidiol in liver disease: a systemic review. *Int J Mol Sci*. 2024;25(4):2370. doi:10.3390/ijms25042370

40. Eadie L, Lo LA, Boivin M, Deol JK, MacCallum CA. Clinical guidance for cannabidiol-associated hepatotoxicity: A narrative review. *J Gastroenterol Hepatol*. 2024;39(12):2522-2532. doi:10.1111/jgh.16730

41. Porter B, Marie BS, Milavetz G, Herr K. Cannabidiol (CBD) use by older adults for acute and chronic pain. *J Gerontol Nurs*. 2021;47(7):6-15. doi:10.3928/00989134-20210610-02