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Potential Therapeutic Value of Cannabis Extract in Liver Fibrosis: A Systematic Review and Meta-Analysis of Preclinical Studies

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Yang, QL; Zhang, XJ; Zhao, YW; Min, HH; Li, D; Zhang, X; Nie, G.

Corresponding author:
Ge Nie

yql1298092911@163.com

Author Affiliation:
Liuyang Hospital of Traditional Chinese Medicine.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 July 2026 and was last updated on 13 July 2026.

INTRODUCTION

Review question / Objective P (Population): Animal models of liver fibrosis (rats or mice), with no limitations regarding sex, age, or modeling methods.
I (Intervention): Cannabis-derived extracts, including CBD, THC, THCA, hemp seed oil, and beta-caryophyllene, without restrictions on dosage, administration route, or treatment duration.
C (Comparison): Control groups administered equivalent volumes of placebo substances, such as normal saline, sesame oil, olive oil, or Tween-80 solution.
O (Outcomes): Serum ALT and AST levels, liver index, hepatic collagen-positive area (CPA), alpha-SMA immunohistochemical expression, and alpha-SMA protein expression by Western blot.
S (Study design): Randomized controlled animal experiments.

Condition being studied Liver fibrosis is a pathological process characterized by excessive deposition of extracellular matrix (ECM) during the wound-healing response to chronic hepatic injury, leading to progressive connective tissue remodeling. Although histologically reversible at early stages, untreated fibrosis may progress to cirrhosis and significantly increases the risk of hepatocellular carcinoma. Cirrhosis attributable to fibrotic progression accounts for approximately 50% of liver disease-related mortality. Current therapeutic strategies primarily focus on etiological control, symptomatic management, and anti-fibrotic interventions, including antiviral agents, antioxidants, and immunomodulatory drugs.

METHODS

Participant or population Animal models of liver fibrosis, including mice and rats, without restrictions regarding sex, age, or weight. Both chemical-induced fibrosis models (e.g., carbon tetrachloride [CCl4], thioacetamide [TAA]) and diet-

induced models (e.g., methionine-choline-deficient [MCD] diet) were eligible for inclusion.

Intervention Cannabis-derived extracts, including cannabidiol (CBD), Delta-9-tetrahydrocannabinol (THC), Delta-9-tetrahydrocannabinolic acid (THCA), hemp seed oil, and beta-caryophyllene. The interventions were administered via intraperitoneal injection or oral gavage, without restrictions on dosage, administration route, or treatment duration.

Comparator Control groups received placebo substances administered via the same route as the intervention groups, including normal saline, sesame oil, olive oil, or Tween-80 solution, without any active cannabis-derived compounds.

Study designs to be included Study design (S): only randomized controlled animal experiments were eligible.

Eligibility criteria Inclusion criteria:
Only randomized controlled animal experiments were eligible.
No restrictions were applied regarding publication date or language.
Exclusion criteria:
Studies with insufficient or unavailable data that precluded extraction and quantitative analysis.
Non-animal experimental designs, including in vitro studies, cell-based experiments, reviews, abstracts, letters, or conference proceedings.
Studies in which the control groups also received cannabis-derived extracts.
Studies in which the primary active component was not derived from cannabis or cannabis-related extracts.

Information sources A comprehensive literature search was conducted in the following electronic databases from inception to March 16, 2026: PubMed, Embase, the Cochrane Library, Web of Science, and CNKI (China National Knowledge Infrastructure). In addition, the reference lists of all included studies were manually screened to identify potentially relevant articles that might have been missed in the electronic search. No restrictions were applied regarding publication date or language.

Main outcome(s) The primary outcomes of this systematic review and meta-analysis included the following indicators:
Serum alanine aminotransferase (ALT) levels — a marker of liver injury.
Serum aspartate aminotransferase (AST) levels — a marker of liver injury.
Liver index (liver-to-body weight ratio) — an indicator of hepatomegaly.
Hepatic collagen-positive area (CPA) — a measure of collagen deposition.
Alpha-smooth muscle actin (alpha-SMA) expression assessed by immunohistochemistry (IHC) — a marker of hepatic stellate cell (HSC) activation.
Alpha-SMA protein expression assessed by Western blot (WB) — a quantitative measure of HSC activation.
All continuous outcomes were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs) using a random-effects model.

Quality assessment / Risk of bias analysis Methodological quality of the included animal studies was assessed using the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool. This instrument evaluates six domains:
Selection bias — random sequence generation, baseline characteristics, and allocation concealment.
Performance bias — random housing and blinding.
Detection bias — random outcome assessment and blinding.
Attrition bias — incomplete outcome data.
Reporting bias — selective outcome reporting.
Other sources of bias.
Each item was rated as "low risk," "unclear risk," or "high risk." The assessment was independently performed by two reviewers, with any disagreements resolved through discussion or consultation with a third reviewer.

Strategy of data synthesis Statistical analyses were performed using RevMan 5.4 and Stata 16.0 software. For continuous outcomes, effect sizes were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Given the expected methodological and biological heterogeneity among animal studies, a random-effects model was applied. Heterogeneity was assessed using the I-squared (I^2) statistic to quantify between-study variability. Meta-regression, subgroup analyses, and sensitivity analyses were further conducted to explore potential sources of heterogeneity. Publication bias was evaluated following the Cochrane Handbook recommendation, with funnel plots constructed when at least 10 studies were available.

Subgroup analysis Subgroup analyses were planned to explore potential sources of heterogeneity based on the following variables: animal species (mice vs. rats), type of cannabis-

derived extract (CBD, THC, THCA, hemp seed oil, beta-caryophyllene), dosing regimen, administration route (intraperitoneal injection vs. oral gavage), and liver fibrosis modeling method (CCl4, TAA, MCD diet). However, due to the limited number of included studies (n = 10), formal subgroup analyses could not be performed for all variables.

Sensitivity analysis Sensitivity analyses were conducted to evaluate the robustness of the pooled effect estimates by sequentially omitting individual studies (leave-one-out analysis) to assess the influence of each study on the overall results. This approach helped to identify whether any single study disproportionately contributed to the observed heterogeneity or effect size.

Country(ies) involved China.

Keywords cannabis-derived extracts; liver fibrosis; meta-analysis; systematic review.

Contributions of each author

Author 1 - Qiongliang Yang - Literature search, study selection, risk-of-bias assessment, and drafting of the initial manuscript.
Email: 598789133@qq.com
Author 2 - Xiaojuan Zhang - Literature search, study selection, risk-of-bias assessment.
Author 3 - Yingwu Zhao - Consultation for bias evaluation disagreements.
Author 4 - Hanhui Min - Data extraction, interpretation, figure preparation, data visualization.
Author 5 - Dong Li - Data extraction and interpretation.
Author 6 - Xu Zhang - Overall supervision, critical revision of manuscript.
Author 7 - Ge Nie - Overall supervision, critical revision of manuscript.