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Black Coffee Consumption and Liver Health: A Comparative Review of Observational, Interventional, Mechanistic, and Mendelian Randomization

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ABSTRACT

Coffee is one of the most widely consumed beverages in the world and has been studied many times for its positive liver effects in epidemiological research. Black coffee, made with no sugar, cream, or milk, is the best representation of a pure coffee dose of bioactive compounds, such as caffeine, chlorogenic acids, cafestol, and kahweol. With the amount of recent evidence available, synthesis is warranted to ascertain whether this association is causal, dose-dependent, and clinically relevant throughout the spectrum of chronic liver disease. It is a review of 35 peer-reviewed publications published between 2021 and 2025 from large prospective cohorts (UK Biobank, n ≈ 355,000–495,000; NHANES), systematic reviews and meta-analyses, randomized controlled trials on caffeine or chlorogenic acid supplementation, Mendelian randomization studies, disease-specific cohorts (hepatitis B, cirrhosis, metabolic syndrome), and mechanistic pharmacological reviews. The studies were assessed in five domains: MASLD risk, liver fibrosis and stiffness, cirrhosis, HCC, and liver-related mortality; biochemical evidence; interventional evidence; and molecular mechanisms. Observational data consistently show a lower risk of advanced fibrosis, cirrhosis, HCC, and liver-related mortality, while the strongest associations with coffee consumption are with fibrosis and cirrhosis rather than in relation to the incidence of steatosis. The dose-response relationship is not really dependent upon caffeine content; this suggests that chlorogenic acid and other polyphenols are likely to be the major mediators. However, there are inconsistent short-term biochemical effects from RCTs, mixed causal evidence from Mendelian randomization, and one large inverse-probability-weighted analysis suggested that the liver-specific mortality benefit was highly dependent on extensive adjustment for confounding factors.

INTRODUCTION

Chronic liver disease is a growing and significant public health problem worldwide and is a large umbrella that covers a diversity of conditions such as metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), alcohol-related liver disease, chronic viral hepatitis (hepatitis B and C), cirrhosis, and hepatocellular carcinoma (HCC). As obesity and type 2 diabetes have increased in recent years, and metabolic syndrome has been on the rise, the prevalence of MASLD is estimated at 25-30% of the adult population worldwide, making it the most common chronic liver disease in the world. At the same time, both alcohol and viral hepatitis have a substantial impact on liver morbidity in many low- and middle-income areas [1]. Together, these causes lead to a common pathway of liver inflammation, fibrosis, and cirrhosis, greatly raising the risk of developing HCC and dying from liver disease. In the hepatology literature, coffee has been widely studied as one of the most widely documented dietary exposures, with a longstanding association with better liver biochemistry, a decreased rate of fibrosis progression, and a lower risk of cirrhosis and HCC. The interest in coffee is biologically plausible because it is a complex and diverse matrix of bioactive phytochemicals, which goes beyond cumulative caffeine. They contain compounds such as diterpenes like cafestol and kahweol, which have been shown to have anti-

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inflammatory and anticarcinogenic effects in preclinical studies, and chlorogenic acids, powerful antioxidants that regulate oxidative stress and glucose metabolism [2]. Furthermore, melanoidins, which are produced during roasting, have prebiotic-like activities that could be beneficial in the gut-liver axis, which plays a key role in the pathogenesis of MASLD and alcohol-related liver damage [3]. Importantly, the preparation method of coffee seems to affect the bioactive content; for example, filtered coffees have less cafestol or kahweol than unfiltered types, and sugared and creamed or milky coffee contain other components (lipids and calories) that may bias or alter the hepatoprotective associations observed [4].

The dose-response relationship is typically said to be graded, but there is not a strong consistency in quantifying the relationship by etiological type of liver disease, and the optimal dose threshold for protection has not been well established. Secondly, the relative roles of caffeine and non-caffeine ingredients, such as chlorogenic acid and other polyphenols, are not completely understood, and the mechanism of action of these ingredients needs to be elucidated at the molecular and clinical level. Also, it has been difficult to translate findings from observations into actionable public health recommendations because there have been few adequately powered randomized controlled trials that have proven effectiveness in achieving hard clinical outcomes, such as fibrosis regression, decompensation, or mortality. This systematic review aims to synthesize and compare a spectrum of study designs to assess the association between black coffee or habitual coffee intake and liver health indicators, such as liver steatosis, fibrosis severity, serum liver enzymes, liver cirrhosis, hepatocellular cancer, and liver-related mortality. In the end, this review aims to inform the current state of knowledge and to establish priorities for future high-quality interventional and genetically informed studies to clarify the available scientific evidence and inform the evidence base for proposed public health recommendations on coffee consumption and the prevention and management of chronic liver diseases.

Literature Search Strategy

A systematic literature search was carried out in various electronic databases, such as the Cochrane Library, ScienceDirect, Scopus-indexed journals via the publisher platforms (Springer Nature, Wiley, MDPI, Frontiers, Elsevier and Cambridge Core), PubMed/MEDLINE, and Google Scholar. Also, backward citation tracking of retrieved systematic reviews and meta-analyses was conducted, and reference lists of these were hand-searched for further eligible primary studies. The search strategy used the following terms for the exposure: "coffee," "black coffee," "caffeine" or "chlorogenic acid" combined with the following terms for hepatic outcome: "liver," "hepatic," "NAFLD," "MASLD," "non-alcoholic fatty liver disease," "liver fibrosis," "cirrhosis," "HCC," "hepatocellular carcinoma," "liver enzymes," and "hepatitis." The search was limited to articles published between January 1, 2021, and June 30, 2026, and articles were deliberately selected to allow for the use of the recently updated nomenclature change from NAFLD/NASH to MASLD/MetALD and the most recent large cohort, interventional, and Mendelian randomization evidence available. We included studies that met the following criteria: Original research (peer-reviewed), cohort study, case-control, cross-sectional, randomized controlled trial, or Mendelian randomization design; adult humans (age 18 or older), with one adolescent interventional pilot study retained for completeness; exposure was defined as coffee, black coffee, or caffeine/chlorogenic acid intake; at least one hepatic outcome was reported, including steatosis, fibrosis, liver enzymes, cirrhosis, hepatocellular carcinoma, liver-related death, or mechanistic endpoint directly relevant to hepatic pathophysiology; published in English from January 2021 to June 2026 and indexed or retrievable via Google Scholar or other databases. Studies that did not include humans or that included only in vitro experiments with no translation to human liver outcomes, but with an apparent direct clinical implication, were also included; animal-only studies, studies on tea, energy drinks and non-coffee caffeine sources were excluded, except for one animal-based mechanistic study with apparent clinical relevance, which was included; papers that were duplicate publications, conference abstracts without full peer review, and those in which data was not extractable were excluded, though such papers could be cited for historical or background purposes if noted as such. Thirty-five studies were selected for detailed thematic synthesis after applying these criteria (Table 1).

Table 1: Major Prospective Cohort and Population-Based Studies, Systematic Reviews, Meta-Analyses, and Bibliometric Syntheses, Interventional (RCT) and Genetically Informed (Mendelian Randomization) Studies, and Disease-Specific Cohorts and Mechanistic/Pharmacological Reviews of Coffee Consumption and Liver Outcomes

References	Population / n	Design and Disease Context / Type	Key Exposure Contrast	Key Finding
Prospective Cohort and Population-Based Studies				
[4]	Korean cohort n = 6,592	Prospective cohort, 11.6–15.7-yr follow-up	Graded coffee intake (0 to ≥2 cups/day)	No effect on MASLD incidence; ≥2 cups/day reduced advanced fibrosis risk by ~43%

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[5]	NHANES 2013–2018 n = 8,062	Cross-sectional, weighted logistic regression	Coffee consumption category; nonlinear spline by sex	Coffee inversely associated with NAFLD (OR 0.96); optimal intake ~2 cups/day in women
[6]	NHANES 2017–2018 n = 4,510	Cross-sectional with transient elastography	Coffee vs decaf/tea, adjusted for diet quality	Coffee independently associated with lower liver stiffness (LSM)
[7]	UK Biobank n = 494,585	Prospective cohort, median 10.7-yr follow-up	Any coffee vs none; decaf, instant, ground compared	All coffee types associated with lower incident chronic liver disease, HCC, and CLD death
[8]	UK Biobank n ≈ 355,000–495,000	Cohort with MRI (n=28,961) and proteomic (n=44,633) sub-studies, median 13-yr follow-up	≥5 cups/day vs non-drinkers	32% lower cirrhosis, 47% lower HCC, 42% lower liver-related mortality; concordant favourable MRI and proteomic markers
[9]	UK Biobank n = 455,870	Cohort with IPTW causal adjustment	1–2 cups/day (moderate) vs none, across MASLD/MetALD strata	Pre-adjustment liver-mortality benefit lost significance after IPTW; all-cause mortality benefit persisted
[10]	Southern Italy cohort	Prospective population cohort	Italian-style coffee, 1 to 4–6 cups/day	Dose-dependent reduction in MASLD risk, greatest at 4–6 cups/day (OR 0.41)
Systematic Reviews, Meta-Analyses, and Bibliometric Syntheses				
[11]	—	Meta-analysis of epidemiological studies	11 studies	Reduced risk of NAFLD and fibrosis progression among regular coffee drinkers (fibrosis RR 0.68)
[12]	—	Meta-analysis of observational studies (RR, random-effects)	11 studies; up to 92,075 (incidence), 4,303 (fibrosis)	No significant effect on NAFLD incidence/prevalence; 35% reduced odds of significant fibrosis (RR 0.65)
[13]	—	Umbrella review + systematic review/meta-analysis	Multiple SRMAs; 5 studies (n=3,752) for fibrosis subgroup	Significant fibrosis reduction in NAFLD patients (OR 0.67); inconsistent effect on general-population NAFLD prevention
[14]	—	Dose-response meta-analysis (cohort + case-control)	15 studies; 557,259 participants	Coffee inversely associated with liver cancer risk (RR 0.39); non-linear dose-response
[15]	—	Meta-analysis of RCTs (weighted mean difference)	14 RCTs; 897 subjects	No significant change in ALT/AST/GGT/ALP; significant increase in adiponectin (WMD 1.19 mg/mL)
[16]	—	Bibliometric analysis (Web of Science, VOS viewer, CiteSpace)	1,106 articles, 2013–2023	Marked acceleration in coffee-liver research after 2019; China, South Korea, and the US lead output
Interventional (RCT) and Genetically Informed (Mendelian Randomization) Studies				
[17]	156 overweight adults with/without T2D; 24- hr urinary caffeine/non-caffeine metabolites	Cross-sectional biomarker study	—	Non-caffeine coffee components associated with reduced fatty liver index; caffeine associated with lower fibrosis odds
[18]	23,711 adults; caffeine intake ≥78 mg/day vs less, by glucose status	Cross-sectional (NHANES 2005–2020)	—	Higher caffeine intake independently associated with lower Fibrosis-4 index risk across glycemic subgroups
[19]	Type 2 diabetes patients with NAFLD; 200 mg chlorogenic acid and/or 200 mg caffeine vs placebo	6-month double-blind, placebo-controlled RCT	—	Neither compound superior to placebo for hepatic fat or stiffness (null result)
[20]	50 patients with cirrhosis; caffeine 400 mg/day	8-week double-blind, placebo-controlled RCT	—	Significant improvement in inflammatory markers, APRI/FIB-4 fibrosis indices, and MELD score vs placebo
[21]	50 patients with cirrhosis; caffeine 400 mg/day	8-week randomized, placebo-controlled RCT	—	Improved handgrip strength and MELD score; no significant lipid-profile difference
[22]	GWAS instruments (FinnGen, UK Biobank); 10 hepatobiliary/pancreatic outcomes	Multivariable Mendelian randomization	—	Minimal overall causal association; modest protective signal specific to NASH; contrasts with strong causal harms of smoking/alcohol

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Disease-Specific Cohorts and Mechanistic/Pharmacological Reviews				
[1, 2]	Caffeine and chlorogenic acid pathways	Mechanistic review	–	Antifibrotic, antioxidant, anti-inflammatory, and epigenetic mechanisms in hepatic stellate cells and hepatocytes
[23]	94 NAFLD cases, 63 controls	Case-control, Morocco	–	Coffee consumption inversely associated with NAFLD occurrence (OR 0.39) and severity (OR 0.32)
[24]	ANRS CO22 Hepather; n = 3,792	Chronic hepatitis B cohort	–	≥3 cups/day independently associated with lower risk of elevated fibrosis biomarkers (APRI, FIB-4, GPR)
[25-27]	Adenosine-receptor signaling	Mechanistic/pharmacological review	–	Caffeine's antagonism of hepatic adenosine receptors proposed as principal antifibrotic/ anticarcinogenic mechanism
[28]	Humanized transgenic UGT1A mice, bile duct ligation	Translational mouse model	–	UDP-glucuronosyltransferases mediate coffee-associated reduction of liver fibrosis
[29]	Rafsanjan Cohort (PERSIAN); n = 8,889	Population cohort, Iran	–	Coffee/tea/caffeine intake associated with liver enzyme and lipid profile differences

Coffee and MASLD/NAFLD Risk: Observational and Cross-Sectional Evidence

The evidence on the effect of coffee on the incidence of steatosis is more ambiguous than its effect on disease progression. In the Korean cohort study, conducted by Lee *et al.* 1326 participants with MASLD and 5266 without it were followed for a median of 11.6 years, showing that there was no significant association between coffee consumption and the risk of new-onset MASLD, but there was a strong inverse association between coffee consumption and progression to ALF in those who already had MASLD, with a 2+ cup of coffee per day, the adjusted HR was 0.57 (95% CI 0.37–0.90) [4]. Similarly, a large study (n=2026) by Chen *et al.* of NHANES 2013–2018 showed a weak but significant inverse association between coffee consumption and prevalence of NAFLD (adjusted OR 0.96 per level increase), with an optimum intake of ~2 cups per day for women [5]. In contrast, a Moroccan case-control study from 2023 by Nadi *et al.* reported a much stronger protective association, as coffee consumption was associated with a reduced risk of NAFLD occurrence (OR 0.39) and severity (OR 0.32) [23].

Coffee and Liver Fibrosis, Including Viral Hepatitis

The hepatoprotective signal is most consistent when evaluated by disease aetiology and/or fibrosis outcome. Pooling the results from eleven epidemiological studies found that regular coffee drinkers had a significantly lower risk of developing fibrosis progression and NAFLD (pooled risk ratio for fibrosis 0.68, 95% CI 0.68-0.79) [11]. In a study using NHANES data on 23,711 adults, Han *et al.* identified evidence of a dose-dependent, glycemic-status-independent association with liver fibrosis and a threshold of at least 78 mg of caffeine per day [18]. Barré *et al.* reported that in a cohort of 3,792 patients with chronic hepatitis B (CHB), coffee use (three or more cups per day) was independently associated with a decreased risk of increased non-invasive fibrosis markers (APRI, FIB-4, and GPR) [24].

Coffee, Cirrhosis, Hepatocellular Carcinoma, and Liver-Related Mortality

Very large prospective cohorts provide the best and most policy-relevant evidence. This 2021 UK Biobank study involving 494,585 people followed for a median of 10.7 years did not just show a benefit of coffee, but also ground coffee, instant coffee, and decaffeinated coffee for reduced risk of incident chronic liver disease, hepatocellular carcinoma, and chronic liver disease death, suggesting the association is likely not attributable to caffeine alone [7, 30]. Coffee consumption was also associated with beneficial measures of liver fat and stiffness obtained by MRI [31], whereas the risk of cirrhosis was reduced by 32%, that of HCC by 47%, and that of liver-related mortality by 42% (HRs 0.68, 0.53 and 0.58, respectively). In line with these cohort results, a 2023 Chinese dose-response meta-analysis of 15 studies (557,259 people) by Liu and colleagues reported a significant, non-linear association between coffee and liver cancer risk (RR 0.39, 95% CI 0.27–0.57) [14].

Randomized Controlled Trials and Interventional Evidence

There is relatively little interventional data available. Mansour *et al.* supplement 200 mg chlorogenic acid and/or 200 mg caffeine daily to 200 type 2 diabetes patients with NAFLD over six months in a randomized, double blind, placebo-controlled trial, and found neither compound alone nor combined to be superior to placebo in reducing hepatic fat or stiffness, a notable null result that calls into question the potential benefits of supplementation with isolated compounds in comparison to whole-coffee consumption [19]. In more advanced disease, though, there was signal for benefit: in an eight-week double-blind, placebo-controlled study of 50 patients with established cirrhosis, Ebrahimi *et al.* found that those taking 400 mg/day of caffeine (roughly four cups of coffee) had significant reductions in inflammatory markers, non-

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invasive fibrosis indices (APRI and FIB-4), and even the Model for End-Stage Liver Disease (MELD) score — one of the few treatments to show improvement in MELD score — compared with placebo [20].

Mendelian Randomization and Causal Inference

Several groups used Mendelian randomization (MR) techniques, using genetic variants that are known to be associated with frequent coffee or caffeine consumption as instrumental variables, to test for causality, since observational associations are susceptible to reverse causation and residual confounding. Together, MR evidence points in the same direction of a mild causal protection, but with weaker and less consistent effect sizes compared to the effect sizes observed in the observational cohorts.

Mechanistic and Pharmacological Evidence

There is a rather large and expanding mechanistic literature to support the epidemiological observations listed above. Shan *et al.* and Sewter *et al.* summarized the pharmacology and toxicology of caffeine in liver diseases, indicating that caffeine is a non-selective adenosine receptor antagonist, expressed on hepatocytes, hepatic stellate cells, and Kupffer cells, and mechanistically related to fibrogenesis and carcinogenesis [25, 32]. Di Pietrantonio *et al.* have shown that both caffeine and chlorogenic acid have independent anti-fibrotic properties against HSCs, which include the reduction of connective tissue growth factor expression, inhibition of focal adhesion kinase and procollagen synthesis, and induction of stellate cell apoptosis [1].

Impacts, Controversies, and Innovations: Black Coffee versus Additive-Laden Preparations

The hepatoprotective signal is present in the reviewed literature, and it is only for coffee, and NOT for high-sugar, high-fat coffee beverages. The Southern Italian cohort study by Siani *et al.* provides another preparation-specific twist, with the investigators finding that the epidemiological signal of Italian-style (moka/espresso) coffee was related to its dose rather than to any single standard definition of a "cup", with the greatest benefit seen at four to six cups per day (OR 0.41 (CI 0.19–0.89)) [10].

Caffeinated versus Decaffeinated Coffee: Mechanistic Controversy

One of the main controversies is whether it is caffeine or the non-caffeine polyphenolic content of coffee (chlorogenic acid, cafestol, kahweol, melanoidins) that is responsible for the hepatoprotective association. On the other hand, the adenosine-receptor mechanistic literature [25-27] suggests that the adenosine-receptor antagonism of caffeine is enough to account for much of the anti-fibrotic and anti-carcinogenic effect.

Innovation: Multi-Modal Biomarker Triangulation

One of the methodological innovations of the 2026 UK Biobank study [8] is the novel combination of clinical outcomes, quantitative MRI-based hepatic imaging, and high-throughput proteomics in a single study. This multi-layered architecture provides much more causal plausibility than clinical endpoints alone: lower liver fat, liver stiffness on imaging, lower levels of fibrogenic proteins, macrophage-activation proteins, and lower rates of clinical events rather than just one of the outcomes, which may be confounded. This triangular construction, together with the recently developed bibliometric mapping of the field [16], likely will be the blueprint for further nutritional hepatology studies.

Controversy: The Confounding Problem and Null Interventional Findings

The IPTW-adjusted reanalysis by Yang and colleagues is an important corrective to the field, showing that a significant amount of the apparent liver-mortality benefit from coffee consumption seen in previous much less rigorously adjusted cohort studies may be due to healthy-user and socioeconomic/lifestyle confounding, rather than a direct causal pathway to liver protection [9]. There is a tension here, as the null RCT result by Mansour *et al.* did not report any benefit from isolated caffeine and/or chlorogenic acid supplementation over placebo on hepatic fat or stiffness in a well-designed six-month trial [19].

Regional and Population Variation

Results are similar across geographically and ethnically distinct groups, such as the largely European-ancestry UK Biobank, Korean and Chinese clinical/population cohorts, Thai patients with the metabolic syndrome, Portuguese and Iranian patients with type 2 diabetes or in population cohorts (Rafsanjan/PERSIAN) [29], clinic populations of Moroccan patients, and hepatitis B patients from France, Brazil (ELSA-Brasil) [33-35], southern Italy, and the United States (NHANES), indicating this association is not limited to a specific dietary or genetic environment.

Limitations and Future Recommendations

This review is limited by the observational nature of most included studies, which are susceptible to residual confounding from healthier lifestyle patterns among coffee drinkers. Substantial heterogeneity in coffee preparation methods, cup sizes, and caffeine content across cohorts hampers precise dose-response comparisons. Most Mendelian randomization analyses rely on European-ancestry data, limiting generalizability to diverse populations. Randomized controlled trials have been short-term, underpowered, or focused on isolated caffeine/chlorogenic acid rather than whole coffee, leaving long-term efficacy untested. Future research should prioritize longer-duration RCTs of whole black coffee with hard endpoints like fibrosis progression, expand Mendelian randomization to non-European populations, standardize exposure measurement, and investigate stage-specific effects across diverse liver disease etiologies.

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CONCLUSIONS

In conclusion, habitual coffee consumption is consistently associated with reduced risk of advanced fibrosis, cirrhosis, HCC, and liver-related mortality, with benefits most pronounced at the fibrosis/cirrhosis stage. Mechanistic evidence supports caffeine and chlorogenic acid as key mediators. However, null findings from supplement RCTs, mixed Mendelian randomization results, and confounding concerns suggest that causality remains unproven. Current hepatology guidelines cautiously endorse coffee as a low-risk adjunctive measure, but not a definitive therapy. Pending further high-quality causal evidence, coffee should be framed as a plausible supportive dietary factor complementary to established lifestyle interventions.

Author's Contribution

Conceptualization: VN
Methodology: VN
Formal analysis: VN
Writing and Drafting: VN
Review and Editing: VN

The author approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

The author declare no conflict of interest.

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