

Article – Coffee and Liver Disease

Manav Wadhawan¹, Anil C Anand².

1. Senior Consultant, Fortis Escorts Liver and Digestive Diseases Institute, Delhi.
2. Senior Consultant Hepatology and Gastroenterology Indraprastha Apollo Hospital, Delhi
President, Indian Society of Gastroenterology
Quondam: President's Honorary Surgeon
Chief Consultant (Gastroenterology), AFMS as Lieutenant General
Director General Medical Services (Navy) as Surgeon Vice Admiral
Professor and Head of Department (Gastroenterology and Hepatobiliary Unit Army Hospital R and R, Delhi)

Correspondence:

Manav Wadhawan

Senior Consultant

Fortis Escorts Liver and Digestive Diseases Institute, Delhi.

manavwadhawan@gmail.com

Abstract

Coffee is the most popular beverage in the world. Consumption of coffee has been shown to benefit health in general, and liver health in particular. This article reviews the effects of coffee intake on development and progression of liver disease due to various causes. We also describe the putative mechanisms by which coffee exerts the protective effect. The clinical evidence of benefit of coffee consumption in Hepatitis B, C as well as NAFLD and Alcoholic liver disease has also been presented. Coffee consumption is associated with improvement in liver enzymes (ALT, AST and GGTP), especially in individuals with risk for liver disease. Coffee intake more than 2 cups per day in patients with preexisting liver disease has been shown to be associated with lower incidence of fibrosis and cirrhosis, lower HCC rates as well as decreased mortality.

Introduction

Coffee is the most commonly consumed beverage in the world. Recently, a lot of interest has been generated in the overall beneficial effects of coffee consumption in reducing total and cause specific mortality.^{1,2} Coffee is a very rich source of antioxidants and the protective effects of coffee have been proposed in a variety of conditions ranging from heart disease to stroke to type 2 diabetes as well as Parkinson disease.³⁻⁶ There is increasing evidence in favor of protective effects of coffee consumption in development and progression of liver disease. This article will analyze the effects of coffee on liver disease in details and also briefly mention other effects on health.

Pharmacology of Coffee

Coffee fruits (cherries) are harvested and undergo pulp extraction to obtain green coffee seeds, which can then be either roasted or processed for decaffeination. It is only through roasting that the seeds gain the characteristic aroma and flavor of coffee. Another factor that can affect the chemical composition of coffee is the method of brewing, which can be percolation, boiling, French press or electric coffee

maker, espresso machine or Italian coffee maker.⁷ Instant coffee production typically involves treating ground-roast coffee with hot water and use of high pressure to extract the water-soluble compounds. This soluble material is then cooled and sometimes centrifuged, again concentrated by heating, and dried through freeze-drying to reduce moisture to approximately 5%. The basic chemical composition of green coffee depends primarily on genetic aspects (species of plant), and on physiologic aspects such as degree of maturation. Chemical composition on an average and proposed beneficial effects of coffee are shown in Table-1 and 2 respectively. Most studies on pharmacology of coffee have focused on the effects of caffeine (1,3,7-trimethylxanthine), a purine alkaloid, which is just one of the myriads of chemicals that are contained in coffee. Diterpenes, cafestol and kahweol have also been studied to varying extent. Diterpenes have been blamed for coffee induced rise in cholesterol levels in human studies.^{8,9} There are at least 30 organic compounds that have been shown to impact the typical aroma of coffee. A detailed review of chemical constituents of coffee is outside the purview of this paper and has been discussed elsewhere.¹⁰

Mechanism of action

The exact mechanism of beneficial effects of coffee is not clear. Coffee contains more than 1000 substances, including caffeine, diterphenolic alcohols, potassium, niacin, magnesium, and the anti-oxidants chlorogenic acid (CGA) and tocopherols.¹¹ It should be noted that caffeine may not be the most important component, as other caffeinated drinks do not provide similar protection against liver disease. The polyphenols (CGA, etc.) may be responsible for the positive metabolic effects of coffee. There is experimental evidence that coffee with high CGA concentrations can modulate glucose intolerance and improve/decrease NAFLD development in obese rats.¹²

Coffee is a rich source of dietary antioxidants. The antioxidant capacities of both hydrophilic components (like caffeine and CGA) as well as hydrophobic components (like cafestol, kahweol and trigonelline) have been extensively investigated using both chemical assays as well as biological systems, including cell culture, animal and human studies.¹³ Maillard reaction products (MRP) that provide the aroma, flavor and color of different brewed coffees are generated during the roasting process and significantly contribute to its antioxidant activity.^{14,15}

There are various studies linking the lower circulating levels of inflammatory biomarkers in coffee drinkers. A recently published study used luminex based bead assays to measure 77 immune and inflammatory markers in more than 1700 adults. This trial reported significantly lower levels of IFN- γ , CX3CL1/fractalkine, CCL4/MIP-1b, FGF-2 and sTNFRII in coffee drinkers than non-coffee drinkers.¹⁶ Another European nested case control study has suggested an inverse association of coffee intake with HCC risk that was partly accounted for by biomarkers (IL-6, etc.) of inflammation and hepatocellular injury.¹⁷ The role of biomarkers in protection provided by coffee against various diseases requires further investigation.

Recently, autophagy has gained a lot of attention as a global health-promoting and anti-ageing property. Autophagy is a lysosomal degradation pathway responsible for the selective renewal of cytoplasmic organelles. Autophagy preferentially targets damaged proteins and organelles (such as dysfunctional mitochondria), thus contributing to getting rid of aged structures in the cytoplasm. Hence, autophagy is responsible for renewal of non-nuclear portions of the cell. There is some evidence to suggest that coffee may be acting partially by inducing autophagy in vivo.¹⁸

Effect of coffee on evolution of liver disease has also been attributed to its anti-fibrotic effects. In a rat model, coffee has been shown to attenuate thioacetamide induced liver inflammation and fibrosis.¹⁹ Animal studies have shown that coffee decreases expression of transforming growth factor- β and connective tissue growth factor, thus contributing to reduced fibrosis.²⁰ Furthermore, in rat models of alcohol

induced liver injury, caffeine has been shown to be protective against alcohol-induced liver fibrosis by dampening the cAMP/PKA/CREB pathway in rat hepatic stellate cells.²¹

Clinical Impact of Coffee on Liver Diseases

Coffee and Liver functions tests

Coffee consumption has been associated with lower liver enzyme levels (AST, ALT and GGTP). The first study to demonstrate this effect was published from Norway in 1986, GGTP levels were reported to be lower in coffee drinkers.²² Subsequently a number of studies have demonstrated a similar effect on AST, ALT as well as GGTP levels.²³⁻³² Many of these are population based studies, published from all parts of the world (Italy, Mexico, US, Japan, etc.), thus validating the findings and giving more strength to the reported association. The effect of lowering enzymes is even more pronounced in patients at highest risk of liver injury (overweight patients, significant alcohol intake, impaired glucose metabolism, viral hepatitis).^{33,34,22,27,28}

Coffee and Hepatitis B/C

The data on association between hepatitis B and coffee consumption is very limited. There are at least two experimental studies linking the coffee constituents to inhibition of hepatitis B virus in vivo and in vitro.^{35,36} One study showed lower HBsAg and HBV DNA levels in HEP G2 cell lines as well as duck hepatitis B virus infection models. The other study showed inhibition of replication of HBV in HBx(+) hepatocytes by downregulating PGE2 synthesis. However, there is only one study evaluating the clinical effect of coffee in HBV positive patients.³⁷ This study found no influence of coffee on the severity of hepatitis B as measured by transient elastography. However, this trial had several limitations. First, significant alcohol consumption was much higher in the coffee consumers; the results may have been confounded against coffee by this fact. Secondly, the value of transient elastography in patients with raised transaminases is in question. Considering the positive effects

of coffee in almost all types of liver disease, the association with hepatitis B is worthy of further investigation.

The interplay between coffee and hepatitis C virus is much better studied than hepatitis B. Caffeine has been shown to inhibit replication of hepatitis C virus in Huh-7.5 cell lines in a dose dependent manner at non-cytotoxic concentrations.³⁸ Freedman et al in the HALT-C cohort of hepatitis C patients treated with peg-interferon and ribavirin first showed the beneficial effect of coffee on disease progression in hepatitis C patients.³⁹ The coffee drinker cohort in this trial had higher consumption of alcohol as well smoking. Moreover, non-coffee drinkers had higher serum insulin levels as well higher insulin resistance. Despite that the incidence of advanced fibrosis as well as cirrhosis was lower in coffee drinkers as compared to non-coffee drinkers. Also the degree of steatosis (grade 3-4) was lower in the coffee drinkers. The same authors in the follow-up retrospective analysis in the same cohort further validated this protective effects of coffee against hepatitis C.⁴⁰ The HCV RNA levels were significantly lower in the coffee drinkers, the SVR rates on treatment were significantly higher in the coffee drinkers. On multivariate analysis, coffee consumption was significantly predictive of SVR in this cohort. Cardin et al demonstrated a reduced oxidative DNA damage, increased apoptosis, and reduced procollagen III deposition in HCV patients who drink coffee compared to non-coffee drinkers.⁴¹ Modi et al evaluated the relationship of coffee intake and liver fibrosis in patients undergoing liver biopsy for hepatitis C.⁴² One hundred and twenty eight patients undergoing liver biopsy completed a detailed caffeine questionnaire on three occasions over a 6-month period. The investigators showed that coffee consumption more than 2 coffee-cup equivalents per day, was associated with less severe hepatic fibrosis. There are a number of other trials showing a beneficial effect of coffee on evolution of chronic hepatitis C with or without treatment as well as better tolerability of therapy with interferon and ribavirin.⁴²⁻⁴⁵

Coffee and Non-Alcoholic Fatty Liver Disease (NAFLD)

The available experimental as well clinical evidence suggests that coffee consumption has protective effects against metabolic syndrome as well as development of NAFLD. In rat models of experimental studies, coffee has been shown to decrease inflammatory cytokines, modify adipose tissue gene expression, protect against development of adverse metabolic profile, as well as decrease liver fat and collagen deposition.⁴⁶⁻⁴⁹

The clinical evidence for beneficial effect of coffee against NAFLD is also overwhelming. There are published population based case-control studies; population based cohort as well as cross-sectional studies supporting the usefulness of coffee in NAFLD. The first evidence came from Japan that coffee is associated with lower incidence of metabolic syndrome.⁵⁰ This was followed by a case control study published by Catalano et al, which showed lower fatty liver severity in coffee drinkers. These authors also showed an inverse association of coffee consumption with obesity and insulin resistance. Subsequently, a number of clinical trials from across the globe showed that coffee protects against metabolic syndrome as well as NAFLD/NASH.⁵¹⁻⁵⁵ Many of these trials were histology based and showed a protective effect of coffee consumption on development of hepatic fibrosis. A very important community based cohort study investigated the effect of dietary behavior on NAFLD utilizing four continuous cycles of the National Health and Nutrition Examination Surveys (NHANES 2001–2008).⁵⁴ Multivariate analysis found five factors independently associated with NAFLD – Race, male gender, obesity, caffeine intake and total plain water consumption. Their analysis showed that caffeine intake is independently associated with a lower risk for NAFLD. Another very recent cross-sectional, multicentric, prospective population based study has shown a protective effect of coffee consumption on fibrosis development in NAFLD patients.⁵⁶ This trial demonstrated no association between coffee consumption and new onset NAFLD. However, in patients with NAFLD, the severity of fibrosis was inversely related to coffee consumption on a multivariate regression analysis.

Coffee and fibrosis/cirrhosis

Experimental studies validating the role of coffee in fibrosis prevention have already been discussed above. The clinical evidence for the same has been recently reviewed in a meta-analysis.⁵⁷ Of 1657 citations concerning fibrosis and/or cirrhosis with coffee, 16 were selected. Of these, there were 7 case-control studies,^{45, 58-63} and 9 cohort studies.^{31,37,39,42,43,64-66} Seven of these studies measured association between coffee consumption and liver fibrosis, eight measured association with cirrhosis and 1 reported association with both liver fibrosis and cirrhosis. The majority of these studies had either alcoholic or NAFLD or HCV patients. The pooled analysis indicated that coffee consumers were less likely to develop liver fibrosis as well cirrhosis compared to those who do not consume coffee (OR 0.73 and 0.61, respectively). This effect was seen across the high coffee consumption and low to moderate coffee consumption groups. This effect of fibrosis prevention has further been proven in a prospective, multicentric, population based study in NAFLD patients.⁵⁶ In this cross-sectional study, high coffee consumption was associated with a lower proportion of clinically significant fibrosis (8.8% vs 16.3%, $p=0.038$). In this study, coffee consumption was the strongest predictor for significant fibrosis.

Coffee and Hepatocellular carcinoma

The relationship of coffee consumption and cancers in general and HCC in specific has been under investigation for a long time.^{34,67-70} La Vecchia et al were the first group to analyze the effect of coffee on digestive tract and liver cancers.⁶⁷ This was a case control study with almost 2000 patients with various cancers. This was a negative study showing no association of coffee intake with HCC. Subsequently the inverse relation of coffee with HCC has been shown by many studies. A meta-analysis published in 2013 reported a 40% protective effect of coffee consumption on development of HCC (RR-0.60).⁷¹ The protection was higher in high consumption (≥ 3 cups/day, RR 0.44), versus low consumption (1-2 cups/day, RR 0.72). For each increment of 1 cup of coffee per day, the RR decreased by 0.80. More recently, two large population based cohort studies have been published from a US and European

multiethnic population.^{72,73} In the European cohort, 201 HCC cases were identified out of 486799 men/women, after a median follow-up of 11 years. HCC incidence was calculated in relation to categories of coffee intake. This cohort study reported that incremental coffee consumption is associated with lower HCC risk. Coffee consumers in the highest compared to the lowest category of consumption had lower HCC risk by 72%. The US cohort study association of coffee intake with HCC was evaluated in 162,022 African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the US Multiethnic Cohort (MEC). In addition to reduced risk of HCC in coffee drinkers, this study also showed an association of coffee consumption with lower mortality in CLD patients. Coffee consumption 2–3 cups per day reduced the risk of HCC by 38% (RR 0.62); ≥ 4 cups per day had a 41% reduction in risk of HCC (RR 0.59). Similarly, 2–3 cups coffee per day gave a 46% reduction in risk of death from CLD (RR 0.54) and ≥ 4 cups per day had a 71% reduction (RR 0.29). These two important studies further strengthen the evidence for role of coffee in prevention of HCC in liver disease patients.

How much coffee and a word of caution

The beneficial effects of coffee are reported for ≥ 2 cups/day. One cup is equivalent to 10 gm of whole bean coffee and 5 gm of instant coffee. Incremental beneficial effects have been reported up to 4-6 coffee cups a day. However, coffee drinking in pediatric age group should be discouraged in view of side effects of caffeine in form of anxiety, restlessness, etc. Up to 400 mg of caffeine a day is considered safe.⁷⁴ However young people consuming large amount of coffee should always be warned about possible side effects such as headaches and insomnia and potential risk of dependence. Caffeine use disorder is identified as a research diagnosis in DSM-5 (e.g. meant to encourage studies but not be used in clinical settings). Several case studies demonstrate that high caffeine intake can lead to dependence in a manner similar to other psychoactive substances.⁷⁵ Excessive coffee can also have other untoward effects. In an observational study of 217 people (median age 17) who used caffeinated energy drinks recreationally, 87 percent had adverse effects

(palpitations, tremor, agitation, and gastrointestinal upset).⁷⁶ Twenty-one individuals demonstrated serious neurologic or cardiac signs (arrhythmias, ischemia, seizures, hallucinations). More than 125 were hospitalized for adverse effects, and of these, 57 consumed caffeinated energy drinks alone. Also, there is some data that coffee drinking beyond 300ml/day may be associated with increased cardiovascular complications.⁷⁸

The data provided in favor of coffee consumption in liver disease patients may seem to be overwhelming. However, it should be understood that most of the trials listed above have either been retrospective, observational and/or cross sectional point prevalence studies. In the absence of significant prospective data, conclusive comments can only be made about the association between coffee drinking and better liver health. In other words, we need more interventional, prospective trials before we can say that coffee drinking causes less liver disease.

Summary

Coffee is beneficial for health in general and particularly for patients with liver disease. Consumption of coffee ≥ 2 cups/day protects against progression of almost all forms of liver disease. Usual mechanisms involved are prevention of fibrosis, carcinogenesis and antioxidant effect. The incidence of advanced fibrosis and cirrhosis is lower among coffee drinkers. The risk of hepatocellular carcinoma also is lower in coffee drinkers compared non-coffee consuming population. The protective effects are irrespective of etiology of liver disease, and more pronounced in alcohol related liver disease. However, in view of retrospective nature of data, more interventional trials are required before coffee finds its way in the regular prescription in liver disease patients.

Table-1: A representative composition per 100 mL of coffee brew from medium roasted coffee. Composition of coffee varies according to blend, roasting degree, grid, and method of preparation. (Modified from Farah A. et al⁷)

Constituent	Amount
Caffeine	50-380 mg
Melanoidins	500-1500 mg
Soluble fibre	200-800 mg
Protein	100 mg
Niacin	10 mg
Lipids	0.8 mg
Trigonelline	40-50mg
Chlorogenic acids	35-500 mg
Minerals	250-700 mg

Table – 2: Proposed mechanisms of main beneficial effects of coffee on the liver
(Modified from Saab et al⁷⁷)

Effect on Liver	Site of action	Chemical involved	Mechanisms
Anti-fibrotic	Hepatic Stellate Cell (HSC)	Caffeine	Inhibit focal adhesion kinase (FAK) and actin synthesis
			Increase HSC apoptosis and intracellular F-actin and cAMP expression
			Inhibit procollagen type 1C and alpha-SMA Expression
	Hepatocyte	Caffeine	Decrease transforming growth factor beta (TGF-B)
			Stimulate ARE-regulated signaling
Cancer prevention	Hepatocyte	Cafestol and Kehweol	Inhibit phase I activating enzyme expression and activity
			Induce phase II detoxifying enzymes(i.e.- glutathione S-transferase)
			Stimulate antioxidant responsive element (ARE)-regulated signaling
			Induction of Gamma-glutamyl Cysteine

			Synthetase (GCS)
Antioxidant effect	Hepatocytes	Hydrophilic (Caffeine and Polyphenols such as chlorogenic acids); Hydrophobic (cafestol, kahweol and trigenolline)including Maillard reaction products	Preventing inflammatory reaction Downregulation of Immune and inflammatory markers such as Interferon Gamma (IFN- γ), chemokine coded by CX3CL1 or fractalkine, chemokine ligand4 or CCL4 also called macrophage inhibitory protein (MIP-1b), fibroblast growth factor-2 (FGF-2) and tumou necrosis factor receptors (sTNFRII)

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