REVIEW ARTICLE

Impact of coffee on liver diseases: a systematic review

Sammy Saab[1,2], Divya Mallam[3], Gerald A. Cox II[2] and Myron J. Tong[1,2,4]

1 Department of Medicine, David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, CA, USA
2 Department of Surgery, David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, CA, USA
3 The Department of Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA
4 The Huntington Medical Research Institutes, Pasadena, CA, USA

Abstract

Coffee is one of the most commonly consumed beverages in the world. Its health benefits including improved overall survival have been demonstrated in a variety of disease states. To examine the association of coffee consumption with liver disease, a systematic review of studies on the effects of coffee on liver associated laboratory tests, viral hepatitis, nonalcoholic fatty liver disease (NAFLD), cirrhosis and hepatocellular carcinoma (HCC) was performed. Coffee consumption was associated with improved serum gamma glutamyltransferase, aspartate aminotransferase and alanine aminotransferase values in a dose dependent manner in individuals at risk for liver disease. In chronic liver disease patients who consume coffee, a decreased risk of progression to cirrhosis, a lowered mortality rate in cirrhosis patients, and a lowered rate of HCC development were observed. In chronic hepatitis C patients, coffee was associated with improved virologic responses to antiviral therapy. Moreover, coffee consumption was inversely related to the severity of steatohepatitis in patients with non-alcoholic fatty liver disease. Therefore, in patients with chronic liver disease, daily coffee consumption should be encouraged.

Coffee is a commonly consumed beverage worldwide. In the United States, over 50% of Americans consume coffee on a daily basis (1).The commonly cited reasons for coffee consumption are its stimulatory effects, taste and aroma (2, 3). Recent data suggests that coffee consumption may have health benefits in a number of medical ailments. Long-term coffee drinkers may be at a decrease risk for type II diabetes, symptomatic gallstone disease, Parkinson's disease, heart disease and stroke (2, 4–7). Moreover, coffee consumption is associated with decreased all-cause mortality (8, 9). In a recent analysis of the NIH-AARP Diet and Health Study data, a dose-dependent inverse association between coffee consumption and total mortality was described (9). Men and women who drank 6 or more cups daily had a 10% and 15% decreased risk of death, respectively.

Chronic liver disease is major health burden in the United States, ranking 12th amongst the leading causes of death and accounting for over 30 000 deaths in 2009 alone (10). Chronic liver disease affects approximately 15% of the US population and is a major economic strain through direct healthcare expenditures as well by indirect costs related to lost income due to premature death or disability (11, 12). Treatments for liver disease is often viewed with suspicion, and many patients often seek alternative therapies for their liver disorders (13–15).

Given the potential health benefits in a variety of medical conditions and its impact on survival, we explored the impact of coffee consumption on patients with liver ailments. A systematic, comprehensive review on the interaction between coffee consumption and liver associated tests, viral hepatitis, nonalcoholic Fatty Liver Disease (NAFLD), cirrhosis and hepatocellular carcinoma (HCC) was performed and is presented herein.

Methods

We searched MEDLINE and PubMed for all studies published on coffee and liver diseases from 1986 to September 2012. We used a combination of the keywords 'coffee', 'caffeine', 'liver disease', 'cirrhosis', 'fibrosis', 'hepatitis B', 'hepatitis C', 'non-alcoholic fatty liver disease', 'fatty liver', 'hepatocellular carcinoma', 'liver cancer', 'alcoholic liver disease', and 'alcoholic hepatitis'. We analyzed all studies published in scientific journals including observational studies and case-controlled studies. Bibliographies of identified studies were searched for relevant articles.

Liver-associated laboratory tests

A number of studies noted a beneficial effect of increased coffee consumption on liver-associated laboratory tests. This benefit was reported in a variety of populations at risk for liver disease, including those with excessive alcohol intake, obesity, smokers, and those with chronic viral hepatitis. These studies demonstrated that increased coffee consumption was associated with aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), and Gamma-glutamyltransferase (GGT) levels in a dose-dependent manner.

The first studies to demonstrate a relationship between coffee intake and liver-associated test values were two Norwegian reports which revealed an inverse association between coffee consumption and serum GGT values (16, 17). The results were further illustrated in a 7 year longitudinal study of a subset of the Tromsø Study by Nilssen *et al.* (18). Their findings have since been confirmed in multiple population studies in Japan (19–22), Italy (24, 25), and Finland (26) (Table 1). Another study from Norway also found coffee consumption inversely related to serum GGT (26). The results of a randomized study, however, showed that cafetière increased liver enzymes (28).

In one of the largest studies including over 12 000 health examinees in Japan, Tanaka *et al.* described that increased coffee consumption had a strong and independent association with decreased GGT activity in male alcohol drinkers ($P < 0.0001$) (19). However, consumption of coffee was only weakly associated with lowered GGT levels among women. Using the data from the Self-Defense Forces Fukuo Hospital, Honjo *et al.* further confirmed earlier observations which demonstrated that coffee consumption was associated with lowered serum GGT levels (20–22).

Population studies in Italy, Japan, and the United States also have reported an inverse relation of coffee consumption with serum aminotransferase levels. In a cohort study of over 2000 Italian patients aged 65 or older, Casiglia *et al.* observed that ALT values were 10.3% lower in those who drank three or more cups of coffee daily ($P = 0.0160$) (24). In a Japanese study of 12 020 middle-aged and elderly male participants, a strong inverse association between coffee consumption and elevated ALT values also were noted (29).

The results of the third National Health and Nutrition Examination Survey (NHANES) found that coffee consumption and caffeine were associated with a decreased risk of elevated ALT levels amongst persons at high risk for liver injury in the United States, such as persons who were overweight, had viral hepatitis, impaired glucose metabolism, iron overload or excessive alcohol intake (30). In an unadjusted analysis, a lowered ALT activity was associated with an increasing consumption of coffee ($P = 0.001$) and caffeine ($P = 0.001$).

Chronic liver disease and cirrhosis

Chronic liver disease

Coffee intake has also been associated with a decreased incidence of chronic liver disease (Table 2). The histologic benefit of coffee was first demonstrated by Modi *et al.* who examined the association between daily caffeine intake and severity of hepatic fibrosis amongst persons with chronic liver diseases (31). The authors described that daily caffeine intake above two cups of

Table 1. Studies assessing impact on coffee on liver related health outcomes - *Liver Enzymes*

Reference	Year	Design	Population	Country	Findings
Pintus et al[25]	1996	Cross-Sectional	4803	Italy	Coffee consumption is inversely related to serum GGT in men
Nilssen et al[17]	1990	Cross-Sectional	21 782	Norway	Coffee consumption is inversely related to serum GGT
Nilssen et al*[19]	1994	Prospective Cohort	2438	Norway	Coffee consumption is inversely related to serum GGT in women
Skurtveit et al[27]	2002	Cross-Sectional	16 805	Norway	Coffee consumption is inversely related to serum GGT
Honjo et al†[22]	2001	Cross-Sectional	7313	Japan	Coffee decreases AST/ALT values
Nakanishi et al†[23]	2000	Cross-Sectional	1353	Japan	Coffee consumption is inversely related to serum GGT
Poikolainen et al[27]	1997	Cross-Sectional	6010	Finland	Boiled coffee elevated GGT values more often that filtered or instant coffee
Urgert et al[28]	1996	Randomized Controlled Trial	46	Netherlands	Cafetière coffee increases serum ALT level
Casiglia et al[24]	1993	Prospective Cohort	2240	Italy	Liver enzymes consistently lower in coffee drinkers
Ikeda et al[29]	2010	Cross-Sectional	12 020	Japan	Inverse association between coffee and ALT values, particularly among men
Ruhl et al[30]	2005	Cross-Sectional	5944	USA	Coffee associated with lower ALT values
Tanaka et al[19]	1998	Cross-Sectional	12 687	Japan	Coffee associated with lower GGT, particularly among alcohol drinkers

ALT, Alanine-aminotransferase; AST, Aspartate-aminotransferase; GGT, Gamma-glutamyltransferase.

*Longitudinal subset of previously published study (17).

†The most recent study was included in Table if data was duplicated in more than one study.

Table 2. Studies assessing impact on coffee on liver related health outcomes – *Cirrhosis*

Reference	Year	Design	Cohort*		Country	Findings
Corrao *et al.*(35)	1994	Case-Control	Cases	115	Italy	Protective effect of coffee on alcohol cirrhosis
			Controls	167		
Corrao *et al.*(33)	2001	Case-Control	Cases	274	Italy	Coffee, but not othercaffeine containing
			Controls	458		beverages, may prevent Alcohol cirrhosis
Gallus *et al.*(34)	2002	Case-Control	Cases	101	Italy	Inverse association between coffee and cirrhosis
			Controls	1538		
Tverdal & Skurtveit (39)	2003	Retrospective Cohort		51 306	Norway	Inverseassociationbetween coffee and cirrhosis
Klatsky *et al.*† (38)	2006	Retrospective Cohort		125 580	USA	Coffee protects against cirrhosis, particularly
						alcoholic cirrhosis
Ruhl *et al.*(32)	2005	Retrospective Cohort		9849	USA	Coffee and tea decrease risk of chronic liver
						disease among patients at increased risk of
						liver disease

*Cases were patients with cirrhosis.
†The most recent study was included in Table if data was duplicated in more than one study.

coffee was associated with lower rates of hepatic fibrosis (OR 0.33, 95% CI .14–0.8, $P = 0.015$). The observed protective relationship persisted after controlling for age, sex, race, liver disease, BMI, alcohol intake, and hepatitis C viral infection (HCV) infection. Of note was the fact that caffeine intake from non-coffee sources was not associated with decreased hepatic fibrosis. In a large cross sectional US study, intake of regular ground coffee and caffeine intake was associated with a decreased risk of chronic liver disease (32). Persons included in the report were those with hepatitis B, hepatitis C, iron overload, impaired glucose metabolism, and excessive alcohol intake (>2 alcoholic beverages per day). In the study, participants were followed for a median of 19 years, and those who drank greater than two cups of coffee daily had less than half the rate of chronic liver disease than those who drank less than one cup daily.

Cirrhosis and mortality

In addition to the decreased risk of chronic liver disease, coffee consumption has been associated with a decreased risk of cirrhosis (Table 2). Two Italian hospital-based case-control studies found that coffee may delay the development of cirrhosis. The first study by Corrao *et al.* found a dose-dependent inverse relationship between caffeine intake and risk of cirrhosis (33). The odds ratios of cirrhosis development decreased from 1.0 (lifetime non-coffee drinkers) to 0.47 (95% CI 0.2–1.10), 0.23 (0.10–0.53), 0.21 (0.06–0.74), and 0.16 (0.05–0.50) in those ingesting 1, 2, 3, and 4 or more cups of coffee daily respectively. A longer term follow up in the same cohort confirmed earlier observations (35). The second study by Gallus *et al.* found an inverse relationship between coffee consumption and cirrhosis [odds ratio (OR) 0.54 for coffee drinkers compared to non-coffee drinkers; OR 0.29 for 3 or more cups daily]. An inverse relationship with duration of coffee consumption and cirrhosis also was observed (OR 0.45 for 40 years or more of coffee consumption) (34).

The results of a large 10-year cohort follow-up study in the US revealed that coffee may be protective against both hospitalization and death from alcoholic cirrhosis (36). Subsequently, Klatsky *et al.* reported that coffee consumption may lead to a decreased mortality risk from nonalcoholic and alcoholic cirrhosis; the relative risk per cup of coffee daily was 0.77 (95% CI 0.67, 0.89) (37). Further expanding upon their original cohort study from 1992, Klatsky *et al.* presented a 22-year follow-up report in which they provided further evidence that increased coffee intake led to a decreased risk of alcoholic cirrhosis; with greater coffee intake associated with a lower relative risk of cirrhosis [1–3 cups, 0.6 (95% CI, 0.4–0.8; $P < 0.001$; 4 or more cups, 0.2 (95% CI, 0.1–0.4, $P < 0.001$)] (38). There was no relationship between tea intake and the development of alcohol-related cirrhosis.

The inverse association between coffee intake and mortality from cirrhosis also was supported by a Norwegian cohort study by Tverdal *et al.* (39). In the study, mortality rates were lower for persons drinking 3 or more cups of coffee daily compared to those drinking 2 or less cups. After adjusting for age, sex, alcohol use and other cardiovascular risk factors, similar benefits of coffee were also observed among patients with alcoholic cirrhosis. The relative risk of cirrhosis associated with an increase of two cups of coffee was 0.6 (95% CI, 0.5–0.8) (39).

Chronic hepatitis B and hepatitis C

There are limited published data on the association between caffeine consumption and chronic viral hepatitis (Table 3). Only one report assessed the association in chronic hepatitis B, and found no benefit from coffee consumption on severity of hepatitis B as measured by transient elastography (40). Since most participants who consumed alcohol were also mostly coffee drinkers, the benefit of caffeine intake may have been confounded by the deleterious effects of alcohol consumption. Further-

Table 3. Studies assessing impact on coffee on liver related health outcomes – *Hepatitis B and C*

Reference	Year	Design	Cohort	Country	Findings
Ong *et al.*(40)	2011	Cross-Sectional	1045	China	Caffeine not associated with decreased fibrosis HBV-infectedpatients
Costentin *et al.*(44)	2011	Cross-Sectional	238	France	Caffeine consumption greater than 3 cups or more a day is associated with reduced histological activity
Freedman *et al.*† (42)	2009	Retrospective Cohort	766	USA	Coffee decreases rate of HCV disease progression in HCV
Freedman *et al.*† (43)	2011	Retrospective Cohort	885	USA	Coffee predictor of improved virologic response to peginterferon plus ribavirin for HCV
Modi *et al.*(31)	2010	Retrospective Cohort	177	USA	Caffeinated coffee consumption associated with lowerodds of liver fibrosis in HCV patients
Carrieri *et al.*(45)	2012	Prospective Cohort	106	France	Coffee consumption alleviated pegylated interferon and ribavirin adverse effects

HBV, hepatitis B viral infection; HCV, hepatitis C viral infection.
†Studies from similar database.

more, the use of transient elastography, while proven to be accurate in diagnosing histological advanced fibrosis in chronic Hepatitis B viral infection (HBV)-infected patients, may be of limited utility in patients with elevated serum transaminase levels (41).

Several studies have examined the impact of coffee consumption on fibrosis severity in patients with chronic hepatitis C (Table 3). Modi *et al.* demonstrated the beneficial impact of coffee consumption on fibrosis severity in patients with hepatitis C (OR 0.19, 95% CI 0.05–0.66, $P = 0.009$) (31). The patients in this study completed detailed caffeine questionnaires on three occasions over a six-month period of time. Freedman *et al.* also found that regular coffee intake was associated with decreased rates of liver disease progression amongst chronic hepatitis C patients enrolled in the HALT-C Trial (42). The rates of liver disease progression declined with increasing coffee intake ($P = 0.0011$). Compared to non-coffee drinkers, the relative risks for reaching pre-defined endpoints indicating disease progression were 1.11 for less than 1 cup daily (CI 0.76–1.61), 0.7 for 1 to <3 cups daily (CI 0.48–1.02), and 0.47 for 3 or more cups daily (CI 0.27–0.85, $P = 0.0003$). Utilizing data from the HALT-C trial, Freedman *et al.* also explored the relationship between

coffee consumption and response to antiviral therapy (43). The authors demonstrated that greater than 3 cups of coffee daily was an independent predictor of improved virologic response to retreatment with peg-interferon plus ribavirin in patients with hepatitis C who failed initial treatment. Consumption of 3 or more cups daily was associated with a higher tolerance for the full dose of peg-IFN (60.6% compared to 50.4% of non-coffee drinkers).

A prospective cohort study done in France by Costentin *et al.* evaluated the effect of coffee consumption on treatment-naïve chronic hepatitis C patients (44). In the report, multivariate analysis showed that daily caffeine consumption equivalent to 3 cups of coffee was associated with a decreased necroinflammatory activity [OR 0.32, Confidence Interval (CI) 0.12–0.85]. Of note, caffeine intake in this study was not limited to coffee alone, but included caffeinated coffee, tea, and caffeine-containing sodas. Carrieri *et al.* evaluated whether coffee intake improved the tolerability of peginterferon alfa-2a and ribavirin in HIV-HCV co-infected patients (45). The authors found that those patients drinking 3 or more cups of coffee daily were less likely to report adverse effects compared to coffee nondrinkers (OR 0.19, CI .05–0.78, $P = 0.02$). These findings remained

Table 4. Studies assessing impact on coffee on liver related health outcomes – *Non-alcoholic fatty liver disease*

Reference	Year	Design	Cohort*		Country	Findings
Anty *et al.*(50)	2012	Cross-Sectional		195	France	Regular but not espresso coffee protective against liver fibrosis in patients with NAFLD
Birerdinc *et al.*(46)	2011	Cross-Sectional		1782	USA	Caffeine associated with a lower risk of NAFLD
Catalano *et al.*(47)	2010	Case- Control	Cases	157	Italy	Coffee inversely related to severity of NAFLD
			Controls	153		
Gutièrrez-Grobe *et al.*(48)	2012	Case-Control	Cases	57	Mexico	Coffee protectiveagainstNAFLD
			Controls	73		
Molloy *et al.*(49)	2012	Cross-Sectional		306	USA	Coffee caffeine associated with a significant reduction in risk of fibrosis among NASH patients

NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis.
*Case were patients with non-alcoholic fatty liver disease

significant after adjustments for gender, age, cirrhosis, and history of opioid use.

Nonalcoholic fatty liver disease

Several studies have assessed the association between coffee consumption and NAFLD (Table 4). In an analysis of four continuous cycles (2001–2008) of the Nat-ional Health and Nutrition Examination Survey (NHANES), a dietary intake questionnaire collected by the National Center for Health Statistics of the Centers for Disease Control and Prevention revealed that caffeine intake was independently associated with a decreased risk of development of NAFLD (OR 0.931, CI 0.900–0.964) (46).

Two case–control studies have suggested the beneficial effect of coffee on the risk of NAFLD as defined by abdominal imaging (47, 48). Catalano *et al.* found that a decrease in fatty liver severity in coffee drinkers as compared to non-coffee drinkers ($\beta = -2.585$, $P = 0.011$, CI -0.133 to 0.018). Also, coffee drinking was inversely associated with obesity and insulin resistance (47). A case control study performed in Mexico showed similar results with a dose-dependent reduction in coffee intake with increasing severity of hepatic steatosis (48). In addition, a cross-sectional study demonstrated that coffee consumption was associated with a significant decrease in the risk of hepatic fibrosis among patients with nonalcoholic steatohepatitis (NASH) (49). In the study, an inverse relationship was found between coffee consumption and hepatic fibrosis ($r = -9.215$, $P = 0.035$). There was a significant difference between coffee consumption in patients with bland steatosis/not-NASH ($P = 0.005$), NASH Stage 0–1, and between NASH stage 0–1 and NASH stage 2–4 ($P = 0.005$).

Table 5. Studies assessing impact on coffee on liver related health outcomes – *Hepatocellular carcinoma*

Reference	Year	Design	Cohort†		Country	Findings
La Vecchia *et al.*‡ (51)	1989	Case Control	Cases	151	Italy	No association between coffee and liver cancer
			Controls	1944		
Ohfuji *et al.*(67)	2006	Case-Control	Cases	73	Japan	Inverse association between coffee drinking and HCC incidence
			Controls	253		
Ohishi *et al.*(57)	2008	Case-Control	Cases	224	Japan	Daily consumption associated with decreased risk for HCC
			Controls	644		
Gelatti *et al.*(54)	2005	Case Control	Cases	250	Italy	Inverse association between coffee and HCC incidence
			Controls	500		
Gallus *et al.*(53)	2002	Case-Control	Cases	501	Italy	Inverse association between coffee and HCC incidence
			Controls	1552		
Johnson *et al.*(62)	2011	Retrospective Cohort		61 321	China	Coffee may reduce risk of HCC
Kuper *et al.*‡ (52)	2000	Case-Control	Cases	333	Greece	Coffee not positively associated with HCC incidence
			Controls	360		
Shimazu *et al.*(58)	2005	Prospective Cohort 1		22 404	Japan	Dose-dependent inverse association between coffee and HCC incidence
		Prospective Cohort 2		38 703		
Montella *et al.*(56)	2007	Case-Control	Cases	185	Italy	Inverse association between caffeinated coffee and HCC
			Controls	412		
Tanaka *et al.*(55)	2007	Case-Control	Cases	209	Japan	Dose-dependent inverse association between coffee use particularly among community and CLD controls
			Controls	1308		
			Community	275		
			Hospital CLD	381		
Hu *et al.*(61)	2008	Prospective Cohort		60 323	Finland	Dose-dependent inverse association with risk of HCC
Inoue *et al.*† (59)	2009	Prospective Cohort		18 815	Japan	Coffee consumption may reduce the risk of liver cancer regardless of HCV and HBV
Leung *et al.*(63)	2011	Case-Control	Cases	109	Hong Kong	Moderate coffee consumption in HBV carriers reduce risk of HCC
			Controls	125		
Wakai *et al.*(66)	2007	Case-Control	Cases	96	Japan	Coffee associated with decreased risk of death from HCC in patients with hepatitis C
			Control (HCV+)	420		
			Control (HCV−)	3024		

HBV, Hepatitis B viral infection; HCV, Hepatitis C viral infection; HCC, hepatocellular carcinoma; CLD, Chronic liver disease. Case were patients with hepatocellular carcinoma.
†The most recent study was included in Table if data was duplicated in more than one study.
‡Data reanalyzed by Gallus *et al.* (53) above.

The results of a recent European study provided further evidence regarding the protective effects of coffee in morbidly obese persons with NAFLD (50). Regular coffee consumption was associated with decreased liver fibrosis in morbidly obese women with NAFLD undergoing bariatric surgery (OR 0.752, CI 0.578–0.98, $P = 0.035$) (50). However, regular filtered coffee, but not espresso coffee, was found to be associated with the decreased likelihood of fibrosis.

Hepatocellular carcinoma

Decreased risk of hepatocellular carcinoma

The relationship between coffee and the development of HCC was initially unsettled (Table 5). Two early case-control studies found no association between coffee consumption and the risk of HCC (51, 52). However, the results of a follow up study combining both data sets indicated that coffee was indeed protective against HCC (51–53). Additional more recent reports indicate a potential benefit of coffee on the incidence of hepatocellular carcinoma. Several case-control studies also demonstrated that coffee drinking was associated with decreasing HCC risk with a dose-effect relationship. Gelatti *et al.* found that compared to non-coffee drinkers, the odds ratio for HCC development was 0.4 (95% CI 0.2–0.8) for those consuming 3–4 cups daily regardless of the underlying liver disease cause (54). Tanaka *et al.* reported on coffee use either during the last 1–2 years or 10 years using three different control groups (hospital, community, and patients with chronic liver disease) (55). Coffee use during the last 1–2 years was associated with decreased risk of HCC against all three control groups. Coffee use over the last 10 years was associated with decreased risk of HCC in reference to community controls or patients with chronic liver disease. The results of another case-control study by Montella *et al.* also found a dose-effect relationship between coffee intake and risk for HCC for persons who consumed 4 or more cups daily (OR = 0.4, 95% CI 0.2–1.1); the inverse relationship was maintained amongst both HBV and HCV-infected individuals (56).

Several studies support the hypothesis that coffee consumption leads to decreased risk of liver cancer (57). In a Japanese pooled analysis of two prospective cohort studies, a significant inverse relationship was found between coffee consumption and risk of liver cancer in patients with liver disease (58). Compared to nondrinkers, those with coffee intake of 1 or more cups daily had a relative risk 0.58 (CI 0.36–0.96) (58). Another Japanese prospective cohort of 18 815 subjects with 110 incident cases of liver cancer found increased coffee consumption to be associated with reduced liver cancer risk (hazard ratio for <1, 1–2, 3 or more cups daily 0.67, 0.49, 0.54, p trend 0.025) (59, 60). A similar risk tendency was observed in patients with HBV and/or HCV infections.

The results of a large population-based cohort study by Hu *et al.* performed in Finland supported the finding that coffee drinking led to a decreased liver cancer risk in a dose-response manner (61). Multivariable-adjusted hazards ratios of liver cancer in participants who drank 0–1, 2–3, 4–5, 6–7, and 8 or more cups of coffee daily were 1.00, 0.66, 0.44, 0.38, and 0.32 ($P = 0.003$), respectively. The operational definition of 'liver cancer' in the study included a diagnosis of HCC, cholangiocarcinoma, adenocarcinoma, and primary liver cancer of unspecified etiology.

A Japanese cohort study also showed that those who drank coffee on a daily or almost daily basis had a lower HCC risk than those who almost never drank coffee with a dose-response effect [HR for 3–4 cups daily: 0.48 (95% CI 0.28–0.83)] (60). The risk of HCC in subjects who never or occasionally drank coffee was 547.2 cases per 100 000 over 10 years, but was 214.6 cases per 100 000 in those who drank coffee regularly. Findings from a Singapore prospective cohort study found that compared with coffee non-drinkers, persons who drank 3 or more cups of coffee daily had a 44% risk reduction of HCC (HR 0.56, 95% CI 0.31–1.00, $P = 0.049$), after adjustment for confounding variables and tea intake (62). A Hong Kong case-control study found that moderate coffee intake led to a reduction in HCC risk by almost half in daily coffee drinkers with chronic HBV infection compared to non-drinkers (OR 0.54, 95% CI 0.3–0.97), with a dose-response effect ($P = 0.02$) (63).

The results of several studies analyzing data from the Japan Collaborative Cohort Study indicated the beneficial effects of coffee consumption on the incidence of HCC deaths (64–66). All three studies found a statistically significant decrease in risk of death from HCC in persons consuming one or more cups of coffee daily. Kurozawa *et al.* found that in persons aged 60–79 with a history of liver disease, drinking one or more cups of coffee daily had a significant inverse relationship with mortality due to HCC (men: HR 0.44, CI 0.19–0.90, women: 0.30, 0.10–0.89). No significant relationship was found for men and women aged 40–59 (64). In another case-control study by Kurozawa *et al.*, coffee was again found to be protective against HCC mortality (65). Hazard ratio for one or more cups per day compared to non-coffee drinkers was 0.5 (95% CI 0.31–0.79). The HCC mortality Hazard Ratio was significantly reduced in men who drank one or more cups of coffee daily, but not in women. The authors did not control for HBV or HCV infection.

In a nested case-control study, the multivariate-adjusted OR(with 95% CI) for HCC mortality in daily coffee drinkers (1 or more cups daily) in contrast to nondrinkers was 0.49(0.25–0.96) in all participants, 0.31 (0.11–0.85) in HCV-positive patients, and 0.75 (0.29–1.92) in HCV-negative patients (66). This study supports previous findings in case-control studies by Gelatti *et al.* and Ohfuji *et al.* that coffee has a protective effect amongst HCV-infected persons (54, 67). However,

another report did not find a protective effect of coffee consumption among HCV-infected individuals (56).

Discussion

Coffee is one of the most commonly consumed beverages in the world (2). There is increasing evidence that daily consumption of 2–3 cups of coffee has significant health benefits. Not only has coffee been associated with a decrease in a number of liver diseases, but its consumption may also decrease mortality (9). Thus, coffee appears to have 'hepatoprotective' health benefits (68). Coffee is composed of over one hundred compounds, any of which could be responsible for its beneficial effects (50). It is possible not one compound in particular, but the synergistic effect of multiple compounds, which provides the health benefits described.

Not all types of coffee may be beneficial in liver disease. Numerous studies have shown a hepatoprotective role for filtered coffee, and a potentially deleterious effect for unfiltered coffee (26, 28). It was postulated that this difference is due to the presence of kahweol and cafestol, which are caffeine diterpenes that are released from ground coffee beans but removed by paper filters (28, 69). Moreover, another study found that espresso coffee had no beneficial effect on liver disease, particularly in NAFLD (50). In the US, filtered coffee is one of the main types of coffee consumed, whereas in Europe, espresso coffee is more commonly consumed (50). Anty *et al.* postulated that perhaps espresso coffee was not found to be beneficial in NAFLD because of the sucrose added to the coffee (50). Sucrose is composed of glucose and fructose, and fructose has been associated with increased severity of hepatic fibrosis in NASH (79).

There are a number of proposed mechanisms for the hepatoprotective effects of caffeine (Table 6). In rat studies, methylxanthine caffeine has been implicated in the hepatic fibrinogenesis pathway by (i) downregulating transforming growth factor beta-1 (TGFB-1)-induced connective tissue growth factor (CTGF) production in hepatocytes via promotion of breakdown of SMAD2 (a TGF-B effector protein), (ii) inhibition of SMAD3 phosphorylation, and (iii), by upregulation of the PPAR-gamma receptor (70). The antioxidant hepatoprotective effects of coffee may also be induced by UDP glucoronosyltransferases (UGT1A) (71). Caffeine has also been implicated to have antifibrotic effects via its influence on hepatic stellate cells (HSC) through inhibition of focal adhesion kinase (FAK) and actin synthesis, stimulation of HSC apoptosis, induction of intracellular F-actin and cAMP expression, and via inhibition of procollagen type 1C and alpha-smooth muscle actin expression (72).

Caffeine as well as cafestol and kahweol may have anticarcinogenic effects by upregulation of antioxidant-responsive element (ARE)-regulating signaling (Table 6) (73, 74). The ARE sequence plays a key role in carcinogenesis as it has been found on the promoter of numerous genes involved in detoxification processes. Furthermore, animal models and in-vitro studies indicate that kahweol and cafestol may deregulate enzymes involved in detoxification of carcinogens (75, 76). These compounds also induce glutathione-S-transferase and gamma-glutamylcysteine synthetase (GCS), leading to protection against mutagenesis, and inhibit N-acetyltransferase (77, 78).

Although caffeine is a major component of coffee, studies evaluating non-coffee caffeinated sources have revealed inconsistent evidence of hepatoprotective effects (30, 33). With regards to tea consumption, studies have found no statistically significant association between tea intake and risk of cirrhosis (33, 34), death from cirrhosis (36), chronic liver disease (32), HCC (58), or death due to HCC (56, 64, 80). Most studies

Table 6. Proposed antifibrotic and cancer preventive mechanisms of action of coffee

Compound	Mechanism†	Principal site of action	Effect/Properties
Caffeine	Decrease TGF − B	Hepatocyte	Antifibrotic
	Inhibit FAK and actin synthesis	Hepatic Stellate Cell	Antifibrotic
	Increase HSC apoptosis and intracellular F-actin and cAMP expression	Hepatic Stellate Cell	Antifibrotic
	Inhibit procollagen type 1C and alpha-SMA Expression	Hepatic Stellate Cell	Antifibrotic
	Stimulate ARE-regulated signaling	Hepatocyte	Cancer prevention
Cafestol and Kahweol	Inhibit phase I activating enzyme expression and activity	Hepatocyte	Cancer prevention
	Induce phase II detoxifying enzymes (i.e.- glutathione S−transferase)	Hepatocyte	Cancer prevention
	Stimulate ARE-regulated signaling	Hepatocyte	Cancer prevention
	Induction of GCS	Hepatocyte	Cancer prevention

TGF-B, Transforming growth factor-beta; FAK, Focal adhesion kinase; HSC, Hepatic stellate cell; Alpha-SMA, alpha-smooth muscle actin; ARE, Antioxidant-responsive element; GCS, Gamma-glutamylcysteine synthetase.
†Mechanisms of action may not be exclusive of the compound.
References: 70–78.

did not specify which type of tea participants consumed. However, Inoue *et al.* studied green tea and Kurozawa *et al.* studied green, black, and oolong tea (60, 64).

Coffee preparation methods include filtered, unfiltered, and espresso, and can also vary in its roast profile (medium vs. dark). Differences in preparation method (filtered, unfiltered, espresso) as well as type of roast play a role in the composition of coffee. Filtered coffee does not contain cafestol and kahweol; however, filtration of coffee better preserves chlorogenic acids than the barista method of espresso preparation (50). The various degrees of roast refer to the internal bean temperatures found during roasting. Darker roasts have had higher roasting temperatures. Caffeine content also varies between types of coffee [generic brewed coffee (95–200 mg per 8 oz), espresso (40–75 mg per 1 oz), generic instant coffee (27–173 per 8 oz)].

There are numerous limitations when interpreting the studies regarding the health benefits of coffee. Many of the larger studies, including those by Freedman *et al.*, Modi *et al.*, Hu *et al.*, and Molloy *et al.*, did not necessarily account for differences in socioeconomic status or other dietary factors (31, 42, 49, 61). Although one would argue that perhaps patients who had greater coffee intake were likely healthier, Freedman *et al.* found that coffee drinkers tended to have poorer overall health ($P = 0.29$) and vitality scores ($P = 0.018$) compared to non-coffee drinkers. In addition, participants who drank coffee may have had higher cigarette use and alcohol consumption (42). Also, many studies collected data on coffee intake at only one time point, thus, the coffee intake noted may not have accurately reflected participants' intake over time (30, 34, 36–38). If it is assumed that caffeine is indeed responsible for the hepatoprotective effects of coffee, then another potential limitation is the variation of caffeine content of coffee within and among coffee shops (80). Furthermore, many studies failed to define coffee cup size (24, 30, 33, 36). Although it is clear that coffee intake has hepatoprotective effects, the lack of standardization of coffee cup size amongst various studies leads to ambiguity regarding how much coffee intake is necessary for these effects.

Our study is limited in that it is based mostly upon observational studies with inherent biases, including recall bias in retrospective studies, as well as selection bias and unmeasurable confounding factors amongst all non-randomized controlled studies (81). Cross-sectional studies, such as NHANES III, are limited in that they cannot establish a temporal association between coffee intake and study findings (30, 81).

Numerous epidemiological studies suggest that consumption of approximately 3 or more cups of coffee daily will reduce the risk for and severity of hepatotoxicity due to a variety of underlying pathologic processes. While the aforementioned studies provide compelling evidence to suggest that coffee is useful as an alternative medicine in the treatment of the most common types of liver disease, blinded randomized controlled trials must be performed to provide evidence for causation, and to eliminate confounding variables and various types of bias inherent in cross-sectional, cohort, and case-control studies. Additional animal and cell culture studies are also warranted to further elucidate the biochemical basis for the potential beneficial effects of coffee in liver disease patients.

Acknowledgments

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