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MINIREVIEWS

Coffee: The magical bean for liver diseases

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Abstract

Coffee has long been recognized as having hepatoprotective properties, however, the extent of any beneficial effect is still being elucidated. Coffee appears to reduce risk of hepatocellular carcinoma, reduce advancement of fibrotic disease in a variety of chronic liver diseases, and perhaps reduce ability of hepatitis C virus to replicate. This review aims to catalog the evidence for coffee as universally beneficial across a spectrum of chronic liver diseases, as well as spotlight opportunities for future investigation into coffee and liver disease.

Key words: Coffee; Hepatocellular carcinoma; Liver; Hepatitis; Fatty liver

Core tip: Coffee is one of the most popular beverages consumed in the United States, with about 75% of the population reporting consuming it. Coffee has also long been associated with hepatoprotective effects, the extent of which there appears to be an ever growing body of benefits as well as a wide variety of etiologies of chronic liver disease it may positively affect. This article reviews recent available literature and summarizes the potential positive or preventive effects of coffee on liver malignancy as well as chronic liver disease secondary to alcohol, viral hepatitis, and fatty infiltration. These studies collectively suggest a simple lifestyle modification patients may be able to incorporate to enhance their own health.

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INTRODUCTION

With 1.4 billion kilograms of coffee consumed yearly

in the United States alone, coupled with 74.7% of the population being coffee drinkers some may call drinking coffee the national pastime[1,2]. Beyond the taste and stimulating effects, coffee has been associated with improved outcomes with chronic liver disease, hepatocellular cancer (HCC), cirrhosis, colorectal cancer, esophageal cancer, breast cancer, prostate cancer, pancreatic cancer, ovarian cancer, kidney cancer, hepatitis B virus (HBV), hepatitis C virus (HCV), and non-alcoholic fatty liver disease (NAFLD). A recent 2015 meta-analysis of 16 case-control and cohort studies of Western populations demonstrated significantly reduced incidence of cirrhosis amongst coffee drinkers when compared to those who did drink the beverage[3]. As coffee continues to grow in popularity, with daily consumption of coffee-based beverages increasing from 19% to 41% in the 25-39 years old age group from 2008, the documented benefits of increased coffee intake have also grown[4,5]. Furthermore, coffee is generally considered to have a wide safety profile, with the American Food and Drug Administration noting caffeine as a substance generally recognized as safe, not known to be a health hazard[6]. Many countries' health agencies set no upper limit for daily caffeine intake; in 2006 Health Canada did set an upper limit of 450 mg per day as safe[6]. Over 30 million Americans have chronic liver disease and about 31000 deaths have been attributed to it yearly[7]. Studies evaluating coffee's potential hepatoprotective effect on liver disease are important as they may represent a simple lifestyle modification patients can incorporate to enhance their own health.

COFFEE AND AN ASSOCIATION WITH DECREASED LIVER ENZYMES

In numerous studies, it has been noted that coffee consumption has been associated with decreased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP). One of the first studies to document consumption of coffee with relatively decreased GGT was in 1985 in the Tromsø Heart Study[8]. That same year, another study noted an inverse relationship between coffee consumption and AST and ALT levels amongst both Korean and Japanese immigrants[9]. These studies began an investigation into elucidating a more direct relationship between coffee and possible hepatoprotective properties. The Tromsø study looked at multiple beverages, notably including green tea. Since 1985 multiple other studies have been performed with similar findings when testing specifically for the possible effect of coffee consumption on liver disease.

One such study, performed in 1993, tested an Italian population of 2240 with findings indicating not only a decrease in GGT but also ALT and ALP in drinkers of three or more cups of coffee daily when compared to groups that drinking less than this amount[10]. Another Japanese study in 1998 of 12687 participants with no history of liver disease or abnormal serum aminotransferases indicated significantly decreased levels of GGT, ALT, and AST in men; however, this finding was unable to replicate in women greater than 50 years of age in the study. Another noteworthy aspect of this study was the lack of similar effect on green tea, suggesting a specific role for coffee in liver disease.

A later 2000 Japanese study of 1353 men demonstrated lower GGT levels in coffee drinkers[11]. A follow-up study by this same group noted lower AST and ALT in Japanese men aged 35-56 years of age[12], noting a decrease in these liver enzymes over a 4 year period with increased coffee consumption. A 1998 amongst Japanese men and women, excluding those with a history of chronically elevated liver enzymes or chronic liver disease, evaluated GGT levels amongst subgroups of alcohol drinkers, body mass index (BMI), and cigarette smoking, and green tea consumption[13]. While coffee consumption was not associated with significantly decreased GGT activity in male non-alcohol drinkers, the response was noted to be significant in male alcohol consumers. Results published in 2014 from the National Health and Nutrition Examination Survey utilized self-reported dietary logs, demonstrating individuals drinking > 3 cups of coffee daily demonstrated significantly lower levels of AST, ALT, ALP and GGT[14]. A 2001 Japanese study evaluated AST and ALT levels amongst 7313 men, excluding former alcohol drinkers or a history of a chronic liver disease, examining for a dose related response by subgrouping men amongst self-reported drinking of < 1, 1-2, 3-4, or > 5 cups of coffee daily[15]. Transaminases were significantly lower in groups reporting increased coffee usage. Of note, men reporting ongoing alcohol use with concurrent coffee consumption exhibited a relatively reduced rise in AST compared to non-coffee drinking alcohol users. A 2010 study in Japan evaluated levels of AST, ALT, and GGT amongst various subgroups of men and women with high BMI, low BMI, and high and low alcohol consumption. Transaminases were noted to be lower amongst men and women with higher coffee consumption, the relationship appearing to be stronger in those with higher alcohol consumption and lower BMI[16].

While studies had been performed previously testing for coffee consumption and its association with liver enzyme levels, one study evaluated effect of coffee in patients with risk factors for chronic liver disease: consumption of greater than two alcoholic beverages daily, positive serum HBV antigen, positive serum HCV antibody, transferrin saturation > 50%, elevated BMI, and uncontrolled diabetics[17]. This study demonstrated relatively reduced levels of ALT amongst these higher

risk groups.

COFFEE AND LIKELY PROTECTIVE EFFECTS AGAINST DEVELOPMENT OF FIBROSIS

Given the above information the association between coffee and relative reduction of liver enzymes appears clear, however, the benefits of coffee appear to extend further. In a 2015 population-based prospective cohort study demonstrated coffee intake with reduced mortality from chronic liver disease[18]. In fact, as little as 1 cup of coffee consumed daily resulted in 15% reduction in risk of death from chronic liver disease; 4 cups daily was associated with 71% reduction, suggesting a dose-dependent response. This study appears to reaffirm findings of an earlier 2005 study noting that consumers of coffee and tea exhibited significantly decreased risk of chronic liver diseases[19]. The study followed 9849 participants for a median of 19 years and a decreased risk of hospitalization or death with a chronic liver disease; a dose-dependent response was seen again in this group, with consumption of 2 or more cups of coffee doubling the relatively reduced risk of complications than those drinking 1 cup. A 2003 Norwegian study found similar findings, noting progressively improved mortality with increasing coffee consumption, though the effect appears to negligible beyond drinking 4 cups of coffee daily[20]. In addition to less frequent complications of liver disease, there is evidence demonstrating coffee has an association with reduced fibrosis. A 2010 study evaluated effect of coffee intake over a six month period in a group of 177 patients with variable degrees of liver fibrosis[12]. In this study, intake of at least 2 cups of coffee daily was associated with the less advanced observed fibrotic disease. A 2011 study echoes these findings, noting that advanced fibrosis in a population of chronic HCV patients was not only seen significantly less frequently in coffee drinkers but that the frequency decreased with increasing reported coffee intake, again suggesting a dose-dependent response[21]. A 2014 Brazilian study reinforces this impression, evaluating 136 patients with biopsy, ultrasound, or endoscopic evidence of fibrotic disease, finding that individuals drinking higher amounts of coffee demonstrated a significantly lower frequency of advanced fibrosis on liver biopsy[22]. A 2015 study of 910 chronic HCV male patients evaluated the association of daily intake of various caffeinated beverages, including coffee, finding a higher percentage of coffee drinking amongst patients without advanced fibrosis than those with demonstrated fibrotic disease[23]. A recent meta-analysis of multiple cohort studies and case-control studies independently demonstrated a significantly reduced risk of cirrhosis with consumption of at least 2 cups of coffee daily[24].

Coffee clearly correlates with reduced frequency of fibrosis, but is coffee itself responsible for these effects, or can its probable protection against fibrosis be seen utilizing any caffeinated beverage? Other studies referenced above seem to suggest hepatoprotection is unique to coffee amongst caffeinated beverages, however, a 2001 study attempted to answer this question head-on[25]. This group noted that caffeine intake from other beverages did not show significant odds ratio along with no evidence of significant trends over the amount of intake whereas with coffee intake there was an inverse association with cirrhosis and coffee consumption with just one cup of coffee daily[15]. A 2012 study found a similar association of reduced observation of advanced in coffee drinkers but not in espresso[26].

There is always a concern when findings of a beverage are correlated with health benefits that there may be confounding factors in play. In a case-control study performed in Italy, it was confirmed that the inverse relationship between coffee consumption and cirrhosis across strata of tobacco use, alcohol consumption, age, and sex. A consistent inverse relationship was still noted in moderate alcohol drinking indicating the relationship between coffee consumption and cirrhosis is not restricted to alcohol-related cirrhosis[27].

The variety of different liver diseases, as well as a variety of ethnicities, involved in the aforementioned studies, suggests a possibly universal effect of coffee on this disease spectrum, however, further studies have been done in populations with more homogenous liver pathology. As one can glean from the above information, chronic viral hepatitis etiologies appear to be most heavily represented population in liver disease literature related to coffee.

COFFEE AND EVIDENCE OF HEPATOPROTECTION IN PATIENTS WITH VIRAL HEPATITIS

In the United States, the most predisposing factors to hepatocellular cancer are alcohol abuse, HBV, and HCV. The aforementioned case-control study in Italy determined that the inverse relationship exists between coffee consumption and cirrhosis across varying degrees of alcohol consumption it is documented that hepato-cellular carcinoma risk is also decreased with the intake of coffee[27].

A similar Italian case-control study performed a few years later also demonstrated a substantial decrease in hepatocellular carcinoma risk in drinkers of coffee of 3 or more cups of coffee daily, going on to note a decreased risk of hepatocellular carcinoma regardless of etiology of chronic liver disease[28]. A large prospective study of 776 participants with advanced HCV-related liver disease was also exhibited lower rates of disease progression with regular coffee consumption. This prospective study noted that drinkers of 3 or more cups

of coffee per day had 53% lower risk of liver disease progression than non-coffee drinkers with advanced HCV-related liver disease[29]. A 2014 study evaluated levels of AST and ALT levels in HCV-HIV co-infected patients, with those self-reporting higher levels of coffee (> 3 cups/d) demonstrating lower levels of liver enzymes[30]. A 2013 cohort study amongst 229 HCV patients with normal baseline ALT levels found that 189 retained normal ALT levels one year after being followed; daily coffee drinks were three times more likely to maintain their baseline ALT level than non-coffee drinkers[31]. Another 2013 study evaluated 40 HCV patients, splitting them into two groups; one drank 4 cups of coffee/day, the other drank no coffee. HCV viral loads were significantly higher in the non coffee drinking group, as well as oxidative damage *via* telomere length and measured 8-hydroxydeoxyguanosine levels[32]. Studies demonstrating a dose-dependent response in patients specific for HCV mediated disease are lacking, however, the previously presented data suggests direction for future studies. A common thread one may note amongst these and aforementioned studies is a large number of studies of HCV infected population. One 2011 cross-sectional study of Asian populations with HBV did not demonstrate any correlation between caffeine drinking and liver fibrosis using elastography as a tool for evaluating severity of disease[33]. While this evidence does not demonstrate that coffee intake in this population may not be associated with decreased risk of HCC, it does suggest that coffee's protective mechanism may be unrelated to prevention of fibrosis.

Beyond demonstrating an association with decreased fibrotic disease, studies are beginning to emerge suggesting a more specific hepatoprotective role for coffee in patients with HCV. A 2015 study utilizing human hepatoma cell line infected with HCV demonstrated significantly decreased HCV viral load in lines introduced to caffeic acid, an organic acid found in coffee, compared to control lines infected with HCV[34]. Another study done in 2015 yielded similar results, with caffeine inhibiting HCV replication a hepatic cell line infected with the virus[35].

COFFEE, METABOLIC SYNDROME, AND NAFLD

While alcohol has been noted to be hepatotoxic, it has long been observed not all alcohol abusers develop cirrhosis. Development and progression of fibrosis appear to involve multiple factors at play in the disease process. Metabolic syndrome appears to be linked to increased risk of fibrosis, though the relationship has not been fully described at this juncture. Research involving coffee and liver disease appears to demonstrate a close relationship between these disease states. In a mortality follow-up study of 51036 individuals, it was noted that coffee drinking had an inverse association with cirrhosis risk in the setting of four or more cups of coffee consumed daily[20]. A fair question, again, concerns whether coffee is a confounding variable; are individuals consuming this much coffee are generally avoiding other foods and beverages which would predispose one to liver disease? Two 2008 Japanese studies appear to reinforce this belief, noting that metabolic syndrome appears to be associated with increased risk of HCC, whilst coffee drinkers appear to be less likely to have metabolic syndrome[36,37]. Given that metabolic syndrome appears to be a risk factor HCC, perhaps due to steatosis, this would imply an indirect benefit of coffee. It is worth noting the second study was done in exclusively HCV patients, suggesting again that coffee is hepatoprotective against a large spectrum of liver disease[37]. Studies have also indicated an association between coffee consumption and NAFLD and liver fibrosis. An inverse relationship between NAFLD patients and fibrosis was noted in a 2011 cross-sectional study[38]. Another two studies was performed using bright liver score as a method to gauge the advancement of NAFLD, noting again an inverse relationship between progression of fibrosis and coffee consumption[39,40]. A 2003 study noted relatively decreased fibrosis in obese women drinking coffee compared to those that did not[25]. The mechanism of possible hepatoprotection in NAFLD is unclear. One 2015 cross-sectional study of a random German patients demonstrated expected correlations between NAFLD and obesity, however, saw no significant difference in either levels of ALT nor sonographic evidence of NAFLD when comparing coffee drinkers *vs* those who did not drink coffee, though is unable to comment on coffee's effect on rate of disease[41]. An earlier noted meta-analysis, it should be stated, did note its protective effect in coffee drinkers significant for HCV and alcoholic liver disease populations, though not in NAFLD[6]. While the NAFLD population is not heavily represented in this study, one must consider the possibility that coffee's potential protective effect on NAFLD may be due to disease modifying effects on metabolic syndrome. Taken together, however, these studies suggest evidence for a positive influence of coffee consumption on NAFLD.

COFFEE AND DECREASED RISK OF HEPATOCELLULAR CARCINOMA

There have been numerous studies performed which have indicated the association between coffee consumption and risk of HCC. We have previously presented information suggesting protective effects of coffee in patients with viral hepatitis, a known risk factor for HCC. Further studies demonstrate broad support for the hypothesis that coffee protects again HCC in general. An earlier referenced population-based prospective cohort study performed involving > 215000 men and women found that when compared with non-coffee drinkers that consumption of 2-3 cups per day had 38% reduction in

Table 1 Summary of findings from studies evaluating coffee consumption and reduced risk of hepatocellular cancer

Studies	Year	Study type	Summary
Setiawan *et al*[18]	2015	Prospective cohort	2-3 cups/d noted to have 38% HCC reduction risk 4 cups/d noted to have 41% risk reduction
Yu *et al*[45]	2013	Prospective cohort	Significantly decreased risk of HCC noted among coffee drinkers
Bravi *et al*[44]	2013	Meta-analysis (14 studies)	40% HCC risk reduction with 1-3 cups coffee/day
Bravi *et al*[43]	2007	Meta-analysis (10 studies)	Inverse association noted between coffee consumption and HCC
Larsson *et al*[42]	2007	Meta-analysis (9 studies)	43% HCC risk reduction
Gelatti *et al*[28]	2005	Case control	Inverse relationship noted between coffee and HCC

HCC: Hepatocellular cancer.

risk for HCC and with 4 cups per day found to have 41% reduction in HCC[18]. Yet another hospital-based case control study found that regardless of the etiology of HCC, there was an inverse relationship of observed HCC with coffee consumption[28]. According to a meta-analysis done involving relevant studies from 1966 to 2007 indicated a 43% reduced risk of liver cancer with the consumption of two cups of coffee[42]. Yet another meta-analysis performed involving ten studies with 2260 HCC cases and six case-control studies from southern Europe and Japan with 1551 cases and four cohort studies from Japan accounting for 709 cases also confirmed an association with decreased risk of liver cancer and coffee consumption[43]. A 2013 meta-analysis of studies through 1966 to 2012 found 14 studies demonstrating a pooled reduced risk of HCC by 40%, suggesting strong evidence that coffee consumption is associated with decreased risk of HCC, though the necessary minimum appears to be anywhere from 1 cups daily to 3 cups[44]. Another 2013 study of Western populations who recorded their consumption of coffee for 24 years, stratifying for age, BMI, as well as smoking and alcohol use with a decreased risk of HCC demonstrated amongst this group of people[45]. These studies together (Table 1) suggest a universally decreased risk of HCC amongst people of all ethnicities with potentially a variety of different risk factors to develop HCC.

COFFEE AND EVIDENCE OF DECREASED RISK OF OTHER GI TRACT MALIGNANCIES

As though the already stated benefits of coffee consumption were not enough there has been emerging data of other malignancies that may also be affected by coffee consumption. In a hospital based case-control study conducted in Italy and Switzerland, it was noted that with greater than three cups of coffee consumed daily was associated with an odds ratio of 0.6 when compared to drinkers of one or less cups of coffee daily in relation to pharyngeal cancer. The same study also noted an odds ratio of 0.6 for esophageal cancer; indicating a decreased risk of pharyngeal and esophageal cancer with greater than three cups of coffee[46]. One case-control study performed earlier indicated an inverse relationship with coffee consumption and colon cancer along with rectal cancer. However, the same study was unable to find a significant association with cancers of the mouth, stomach, or pancreas[47]. Ultimately; coffee consumption appears to have an association with decreased risk of colon, rectal, esophageal, and pharyngeal cancer.

DISCUSSION

With coffee growing in popularity its documented health benefits are also growing. With the benefits of coffee consumption ranging from liver enzyme laboratory test improvement to improved mortality from cirrhosis, HCC, as well as other malignancies, and chronic liver diseases secondary to HBV, HCV and NAFLD.

In summary, the etiology of coffee's apparent beneficial effects have been greatly debated. One hypothesis involves the observation that coffee consumption is associated with better lifestyle choices, confounding the positive effects that had been associated with coffee consumption. One previously discussed cohort study argues against this hypothesis, demonstrating subjects that were prone to increased coffee consumption actually had higher median consumption of cigarettes, lower education levels, and higher median intake of alcohol than those with decreased coffee consumption[16].

An additional question regarding coffee consumption's benefits relates to the attribution of the caffeine content than the coffee itself. In a study involving inpatient cirrhotics, it was noted that caffeine intake from beverages other than coffee did not show significant odds ratio at least in relation to liver cirrhosis[15] Multiple studies referenced above demonstrate beneficial effects related to coffee that are generally not reproducible when testing against other caffeinated beverages. Regardless, as a biologic mechanism has not been proposed, the link is still unclear.

A few hypotheses exist to possibly demonstrate a physiologic basis of coffee's beneficial effects. One hypothesis is that coffee activates enzymes that detoxify the liver *via* activation of uridine 5'-diphospho-glucuronosyltransferases[48]. A 2002 study demonstrates increased expression of such enzymes in mice fed coffee specific compounds known as diterpenes, kahweol and cafestol,

conferring protection against toxins associated with colon cancer[48]. A 2007 study demonstrated that kahweol and cafestole administered to hepatocytes subsequently treated with carbon tetrachloride significantly prevented markers of liver injury as compared to control *via* measured ALT and AST levels, reduced glutathione content and lipid peroxidation[49]. Another hypothesis suggests the anti-oxidant properties of polyphenols present in coffee mediate its hepatoprotective effects[25,50]. As for the mechanism with which coffee prevents worsening of hepatic fibrosis, one thought involves caffeine decreasing transforming growth factor-β (TGF-β), a mediator of fibrogenesis[51]. Hepatic stellate cells are induced by TGF-β for differentiation to myofibroblasts, synthesizing connective tissue involved in fibrogenesis. A study in rat hepatocytes demonstrated caffeine inhibited TGF-β signaling by upregulating peroxisome proliferator activated receptor γ (PPAR-γ)[52]. As noted above, not all studies reviewed suggest a modifying effect of fibrogenesis as the protective etiology conferred in what appears to be a generally positive outcome effect on chronic liver disease, however, further studies appear warranted to evaluate for any possible delayed onset of fibrosis amongst coffee drinkers *vs* non coffee drinkers in comparable populations at risk for cirrhosis. In addition, the studies demonstrating the potential effects of caffeic acid on HCV replication suggest a possible mechanism for the apparent positive affects of coffee in this population. Further studies need to be done to verify these and others noted above, such as coffee potentially preventing HCV replication. Regardless, with the wealth of evidence suggesting a positive disease modifying effect of coffee on chronic liver diseases in a multitude of patient populations, there is clearly a strong basis with which to move forward with studies evaluating the potential causative agent. To conclude, while the reason why coffee is good for you is not yet completely clear, these studies should encourage the vast number of patients with chronic liver disease to enjoy the beverage as many others already do.

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