Coffee as Modulator of Liver Injury: Fact and Fiction

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Coffee is one of the most popular beverages consumed in the United States. A report by the National Coffee Association in 2010 noted that 56% of people older than 18 years drink coffee daily.¹ A number of studies have demonstrated the health benefits of coffee on not only chronic health conditions such as diabetes, Parkinson's disease, and dementia, but also on improved survival.^{2,3} The health benefits of coffee have also been described for a number of liver diseases. The purpose of this article is to briefly discuss the epidemiological and biological evidence of the beneficial effect of coffee on liver disease progression.

Epidemiological Evidence of the Effect of Coffee on Liver Disease

Coffee consumption is associated with a decreased risk for hepatic fibrosis and development of cirrhosis in patients with nonalcoholic fatty liver disease, hepatitis C virus (HCV), and alcoholic liver disease. Lower levels of markers of liver injury such as gamma-glutamyl transferase and alanine transaminase are described with coffee intake.² Nevertheless, there are a number of unanswered questions such as whether the benefits of coffee consumption extend to all causes of liver disease. The single study assessing the impact of coffee consumption in patients with hepatitis B failed to find a beneficial impact, but the use of alcohol in the participants may have mitigated the potential beneficial effect of coffee.⁴

Although epidemiological studies favor two to three cups of coffee per day for the hepatoprotective effect because the effect of coffee appears to occur in a dose-dependent manner, there is also a lack of standardized coffee preparations and uncertainty regarding the duration of coffee consumption to yield benefit.⁵⁻⁷

Current understanding of the hepatoprotective effect of coffee has primarily been focused on the potential role of caffeine. The result of a recent cross-sectional study on close to 1000 patients with HCV-related liver disease showed that caffeine intake independent of the source of caffeine was beneficial.⁸ The study reported that modest intake of caffeine (~100 mg/day) leads to approximately a one-third reduction in the odds of advanced fibrosis.⁸ The study noted that although all sources of caffeine reduced the odds of advanced fibrosis, the benefit was greatest in coffee.⁸ The benefit of caffeine from other sources is still under study because rat models using caffeine from tea has been inconsistent in showing a benefit.⁹

Coffee in Prevention of Liver Cancer

The results of several systematic reviews and meta-analyses suggest that the consumption of coffee was associated with decreased risk for development of hepatocellular carcinoma (HCC).^{3,5,6,10} For instance, the results of one meta-analysis demonstrated that an increment of 1 cup of coffee per day was associated with a relative risk (RR) of 0.8 (95% confidence interval, 0.77-0.84) for development of HCC.¹⁰ The benefit of coffee appears to be dose dependent, with more consumption of coffee leading to a greater benefit.¹⁰ The anticarcinogenic effect of coffee on the liver is not fully described, but important mediators of this effect include two chemicals in particular, cafestol and kahweol.⁶ Studies have shown that these chemicals, known as diterpenes, have various effects including an inhibition of activity of carcinogenic cytochrome P450s.¹¹ The inverse relationship of coffee consumption and HCC has led some

Abbreviations: α -SMA, alpha-smooth muscle actin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HSC, hepatic stellate cell; ROS, reactive oxygen species; TGF- β , transforming growth factor- β .

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TABLE 1 Potential Beneficial Effects of Coffee Consumption on Liver Disease

	HSC Activation	Reactive Oxygen Species	Carcinogenesis
Possible hepatoprotective mechanisms of coffee	Modulates inflammatory cytokines and decreases TGF- β and α -SMA levels	Provides exogenous antioxidants (phenolic acids) Upregulation of glucuronidation-mediated antioxidant activity	Inhibits carcinogenic cytochrome P450s Increases expression of antioxidant proteins
Outcome	Decreased activation and transformation of HSCs to myofibroblasts	Decreasing consumption of endogenous antioxidants and decreased hepatic injury	Decreased risk of carcinogenic transformation of cells

to advocate for coffee consumption in those at risk for development of HCC.⁷

Biological Evidence of the Effect of Coffee on Liver Disease

Several mechanisms have been described for the protective effect of coffee consumption on liver disease. The progression of liver disease into fibrosis is in part mediated by the activation of hepatic stellate cells (HSCs) through liver injury.¹² Liver injury directly leads to activation of quiescent HSCs that further differentiate into collagen-secreting myofibroblasts that promote the formation of fibrotic scars, eventually leading to liver cirrhosis.¹² An array of signaling factors are involved in activating HSCs including transforming growth factor- β (TGF- β) that promotes HSC differentiation and deposition of collagen, as well as inducing hepatocyte expression of connective tissue growth factor.^{12,13} Multiple studies have shown an inhibitory effect of caffeine on TGF- β ,¹³ as well as a decreased expression of alpha-smooth muscle actin (α -SMA), a commonly used marker for the presence of activated HSCs.¹⁴ These suggest that the overall effect of caffeine converges on decreasing the activation of HSCs, leading to decreased deposition of collagen and fibrosis (Table 1).

The generation of reactive oxygen species (ROS) is another important component in the pathogenesis of liver fibrosis.¹⁵ ROS can also be generated by Kupffer cells, liver macrophages known to secrete inflammatory cytokines, which are activated by hepatic injury and hepatocyte cell death.¹² Coffee contains many antioxidants in the form of phenolic acids that are known to be able to scavenge free radicals, thereby preventing hepatic injury by the ROS.^{13,16} The results of animals studies demonstrated decreased levels of malondialdehyde, a marker of lipid peroxidation in the liver that prevents consumption of endogenous mechanisms

for scavenging free radicals, by cirrhotic rodents treated with coffee.^{13,17,18}

Risks of Coffee Consumption

Most studies suggest the health benefits of coffee are lost in unfiltered coffee.¹⁸ Unfiltered coffee may even be detrimental to liver health, indicating the importance of mechanisms other than that of just caffeine affecting the liver.¹⁸ For example, unfiltered Turkish coffee led to elevated transaminases and an increase in liver lipid peroxidation levels in rats with carbon tetrachloride-induced cirrhosis.¹⁸

Coffee is not without adverse effects; for instance, coffee may increase in blood pressure and heart rate.¹⁹ Regular consumption of caffeinated drinks can lead to patient dependence, and abrupt discontinuation can then lead to withdrawal symptoms such as difficulty focusing, headache, and fatigue.²⁰ In addition, consumption of boiled coffee, unlike filtered coffee, has been reported to increase total cholesterol and low-density lipoprotein in a dose-dependent manner.²¹

Conclusions

Coffee is a well-tolerated beverage with potentially significant benefits in patients affected by a variety of causes of liver disease. It is readily available and generally safe. However, not all coffee formulations may be equally helpful and not all causes of liver diseases will be improved. Several mechanisms have been described to explain the role of coffee in improving liver disease health, but the exact advantageous substance or substances have yet to be completely described and further study is required.

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