Coffee Consumption to Reduce Liver Fibrosis

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ABSTRACT

As one of the most popular drink consumed daily, coffee is known to be good for health. One of the main substance found in coffee is caffeine. Several previous studies explained that caffeine found in coffee could act as hepatoprotective agents, and recently an antifibrotic agent. Since liver fibrosis is a fatal condition that could lead to liver cirrhosis and hepatocellular carcinoma, a lot of studies were trying to find any alternatives to reduce fibrosis, one of them is coffee. Several studies have reported that coffee was significantly, able to reduce fibrosis process because of its caffeine which is found in coffee. Recently, some studies also reported that a non-caffeinated coffee also showed an antifibrotic effect. It is believed that several substances beside caffeine found in coffee were also played an important role in reduce liver fibrosis. By its cellular mechanism, coffee would be a new alternatives way to reduce liver fibrosis, and of course other chronic liver disease.

Keywords*: coffee, consumption, caffeine, liver fibrosis*

ABSTRAK

Sebagai salah satu minuman yang paling populer dikonsumsi sehari-hari, kopi diketahui baik untuk kesehatan. Salah satu zat utama yang ditemukan dalam kopi adalah kafein. Beberapa penelitian yang pernah dilakukan menjelaskan bahwa kafein yang ditemukan dalam kopi bisa bertindak sebagai agen hepatoprotektif, dan baru-baru ini diketahui sebagai agen antifibrosis. Karena fibrosis hati merupakan kondisi fatal yang dapat menyebabkan sirosis hati dan karsinoma hepatoseluler, banyak studi mencoba mencari alternatif untuk mengurangi fibrosis, salah satunya adalah kopi. Beberapa penelitian menunjukkan bahwa kopi secara signifikan, mampu mengurangi proses fibrosis karena kafein yang ditemukan dalam kopi. Baru-baru ini, beberapa penelitian juga menunjukkan bahwa kopi non-kafein juga menunjukkan efek antifibrotis. Diyakini bahwa beberapa zat samping kafein yang ditemukan dalam kopi juga berperan penting dalam mengurangi fibrosis hati. Dengan mekanisme selular, kopi akan menjadi alternatif baru untuk mengurangi fibrosis hati, dan penyakit hati kronis lainnya.

Kata kunci*: kopi, konsumsi, kafein, fibrosis hati*

INTRODUCTION

Coffee is a popular drink with combination of carbohydrate, fat, vitamin, alkaloid, nitrogen, phenolic compound, and lot of other substances. Besides its delicious taste and aroma, caffeine found in coffee also plays an important role to make this drink popular.[1] Caffeine contained in a cup of coffee was believed that it has an association with lower chronic liver disease

risk. In the two last study conducted by The National Health and Nutrition Examination Survey (NHANES) I and III, its was reported that high coffee consumption (more than two cups per day) were strongly associated with lower risk in increase transaminase enzyme and chronic liver disease.[2]

Chronic liver disease, such as cirrhosis and hepatocellular carcinoma, were a highly morbidity and mortality disease. Patient with those end stage liver disease have a higher risk of liver failure, even 80% among them could lead to hepatocellular carcinoma. Hepatocellular carcinoma ranked as the fifth most cancer found worldwide, account for 600,000 death every year. This situation should get a higher attention.[3] One of the most common cause of chronic liver disease is hepatitis B and C virus, alcoholism, and non-alcoholic steatohepatitis (NASH). Chronic liver disease could lead to liver fibrosis, defined as accumulation of extracellular matrix protein. This accumulation will interfere hepatic tissue structure by producing fibrotic tissue, lead to a regeneration nodule in all liver tissue (cirrhosis).[1] This fibrotic process were associated with transforming growth factor- β1 (TGF-β1) production, so that many recent study were aimed to know its signaling pathway, in order to find any alternatives to inhibit liver fibrosis process.[1,3]

Recent study by Gressner et al showed that caffeine could inhibit CTGF expression on hepatic cell by inducing proteasomal degeneration of SMAD 2 (TGF-β1 mediator), inhibit SMAD 1 and 3 phosphorilation, and up-regulating peroxisome proliferator-activated receptor γ (PPAR γ) . Therefore, long period of caffeine consumption were an interesting alternative way that expected as antifibrotic for chronic liver disease, both in human and animal.[1] Beside that, a study by Modi et al showed that a frequent coffee consumption could reduce liver fibrosis process in chronic hepatitis C patients, while non- caffeinated coffee and caffeinated coffee did not show any significant differences. This lead into a question that wether any other compound in coffee were associated with lower chronic liver fibrosis.[2]

COFFEE AND ITS COMPONENT

Coffee consists of various compound with good antifibrotic potential.[4] Based on its concentration and physiological effect, there are three main components of coffee:[5]

- Caffeine
  Caffeine (1,3,7-trimethylxanthine) is a purin alkaloid with antagonist effect on adenosine subtype A_1 and A_{2A} receptor. Some physiological effect of caffeine are central nervous system stimulant, raise blood pressure, increase metabolic process, and diuretic. Caffeine were widely distributed in serum and metabolized by liver, mostly in CYP1A2 (90%).[6] In general, instant coffee consists of less caffeine than brewed coffee, but it can be consumed more frequent. Caffeine found in robusta coffe were two times higher than Arabica coffee. A cup of coffee with standard size assumed to have 100 mg caffeine, a 240 mL (8 oz) instant coffe assumed to have 72-130 mg coffee, while espresso were contained 58-76 mg caffeine per servings (40 mL).[6,7] While no recommendation on coffee yet, food and drug administration (FDA) proposed that daily consumption of 400 mg coffee were considered safe and cause a lower side effect risk for adult, while pregnant women were limited to < 300 mg coffee daily.[8] A large amount of coffee consumption could lead to anxiety, headache, nausea, and emotional instability. Immediate stop in coffee consumption could lead to a mild side effect.[9]
- Diterpene alkaloid (cafestol and kahweol)
  This compound were found in coffee bean oil and known to increase serum cholesterol level. Diterpene were a product of coffee bean brewing, but often filtered by coffee filter paper. Scandinavian, Turkish, and French coffee often have a high diterpene alkaloid (6-12 mg/cup) rather than filtered coffee, percolated coffee, and instant coffee (0.2–0.6 mg/cup). While diterpene was found higher, a cup of espresso only consist of 4 mg diterpene because of its small servings. Study in ileostomy patient showed a 70% diterpene found in unfiltered coffee were absorbed in gut. Diterpene consumption in French coffee were believed to increase cholesterol ester transfer protein (CETP) activity continously, so that it could increase low density lipoprotein (LDL) cholesterol production. Cholesterol ester transfer protein (CETP) brought ester cholesterol from high density lipoprotein (HDL) into other lipoprotein, LDL and very low density lipoprotein (VLDL).[6]
- Chlorogenic acid and other polyphenol
  Chlorogenic acid is ester compound build of quinic acid and trans-cinnamic acid, commonly found as caffeoylquinic acid (known as chlorogenic acid). Coffee is primary source of chlorogenic and cafeic acid. In 200 mL of coffee, about 70-350 mg chlorogenic acid and 35-175 mg of cafeic acid were founded. About 33% of chlorogenic acid and 95%

of cafeic acid were absorbed by gut. Although both acids were known to have antioxidant activity in vitro, it is not clear how significant the impact of its antioxidant effect.[6] Recent study showed that hepatoprotective effect were found in filtered coffee because of its less cafestol and kahweol substance, although it consists more chlorogenic acid than espresso. In USA, filtered coffee were the most consumed, while in Europe, espresso were more popular. It is not clear the amount of coffee should be consumed to gain its hepatoprotective effect. Some epidemiological study showed that coffee consumption less than three cups per day could reduce chronic liver disease risk and severity.[4]

COFFEE AND ITS EFFECT ON CHRONIC LIVER DISEASE

Several study reported that the effect of coffee to transaminase enzyme, viral hepatitis, NAFLD, cirrhosis, and hepatocellular carcinoma. Coffee consumption were highly associated with serum gamma glutamyltransferase (GGT), ALT, and AST improvement in high risk liver disease patients. Beside that, it also reduce cirrhosis, risk, mortality, and hepatocellular carcinoma incidence among chronic liver disease. In hepatitis C patients, coffee also increase antiviral response against virus. Coffee consumption also reduce severity rate of steatohepatitis in NAFLD patients.[4] Other studies showed coffee role in chronic liver disease can be seen in table 1.

COFFEE AND ITS MECHANISM TO INHIBIT LIVER FIBROSIS PROCESS

Liver parenchym was built by epithelial cell (hepatocyte), endothelial cell, and non-parenchymal cell (hepatic stellate and kupffer cell). Hepatic sinusoid was a microvascular unit of liver that marginized by endothelial cell, shown as the existence of pores which separate hepatocytes in subendothelial space of Disse, consist of hepatic stellate cell. Subendothelial space contained matrix such as low density basal membrane that functioned as metabolic barrier that balance hepatocyte and blood vessel. In normal liver

Table 1. Studies about coffee effect on chronic liver disease[10]

Study & Year	Population	Diagnosis	Result
Klatsky et al (1992)	128.934 subject	High risk of alcoholic cirrhosis	Daily coffee consumption of > 4 cups were having 0.2 risk of alcoholic cirrhosis compared to those that not consumed coffee
Ruhl et al (2005)	5.994 subject	NHANES III	SGPT reduce in concominant with more coffee consumption; consumption > 2 cups per day compared to non coffee cumsumer; OR 0.56 for increase SGPT level
Ruhl et al (2005)	9.849 subject	NHANES I: Continous epidemiological study	Coffee consumption > 2 cups per day vs < 1 cups per day were javing < ½ times risk (OR 0.43) to progress to chronic liver disease
Bravi et al (2007)	1.551 subject	Meta analysis of case-control studies of hepatocellular carcinoma in Europe/Japan	Hepatocelullar carcinoma risk were foundr lower as 41% in coffee consumer than coffee non-consumer
Larsson et al (2007)	2.260 case 239.146 control	Meta analysis from 9 hepatocelullar carcinoma studies	Consumption of 2 cups of coffee everyday were associated with lower risk of hepatoceular carcinoma about 43%
Freedman et al (2009)	766 subject	Hepatitis C patient in HALT-C trial	RR from disease progressivity were contrary to coffee consumption (1.1 for < 1 cup per day; 0.73 for 1-3 cup per day; and 0.47 for > 3 cups per day) if compared to non-coffee consumer subect
Modi et al (2010)	177 subject	Hepatitis C patient	Coffee consumption of 2.25 cups per day were associated with lower liver fibrosis risk (OR 0.33)
Leung WW et al (2011)	234 subject	Chronic Hepatitis B Carier	Moderate coffee consumption were associated with lower risk of hepatoceullar carcinoma (OR 0.54)
Johnson et al (2011)	63.257 subject	Healthy adult in China	Coffee consumption of ≥ 3 cups per day were associated with lower hepatocellular carcinoma risk (OR 0.56)
Constentin et al (2011)	238 subject	Hepatitis C patients in therapy	Caffeine consumption of > 408 mg daily were in contrary to tissue activity (OR 0.32)
Yamashita et al (2012)	2.554 men 763 women	Healthy worker in Japan	Coffee consumption were associated with higher adiponectin and lower leptin
Matsuura et al (2012)	3.284 subject	Healthy adult in Japan	Coffee consumption ≥ 4 cupr daily were associated with lower metabolic syndrome (OR 0.79)
Gutierrez-Grobe et al (2012)	73 subject 57 control	NAFLD patient dan control group	Caffeine consumption in several dosage range were in contrary with steatosis grade severity
Freedman et al (2012)	229.119 men 173.141 women	NIH and AARP diet study	Coffee consumption were in contrary to overall mortality specifically
Molloy et al (2012)	306 subject	NAFLD patients	Coffee consumption were associated with fibrosis risk in NASH patients
Anty et al (2012)	195 subject	Patients with severe obesity	Routine coffee consumption, but not espresso, were associated with lower risk of liver fibrosis in severe obesity patients

tissue, extracellular matrix were a dynamic substrate balancing synthesis and degradation process in the tissue. In chronic liver disease, extraceullar matrix synthesis were higher than its degradation process, so that fibrotic septum were thickening progresively with crossreaction among its collagen. Extracellular matrix composition change was also induced fibrogenesis.[11]

Liver fibrosis was a reparation process that is reversible, marked with accumulation of extracellular matrix in conjunction with hepatocyte damage. This liver structure could be improved and reverse to its normal form in acute damage settings. But, if it is a chornic damage, liver parenchym will be replaced by scar tissue. It will begin cirrhosis process as a consequence of progressive fibrosis, known to have a fatal prognosis with high mortality rate. This is a slowly continuous process, could range between 20-40 years, and implicated by various genetics and environmental factors. Liver fibrosis affect both quality and quantity of liver extracellular matrix. The most important extracellular matrix are collagen, proteoglycans, laminin, fibronectin, protein matrixcelullar, and several growth factors and matrix metalloproteinase (MMPs). Therefore, extracellular matrix could regulate cellular activity and availability of growth factors. As an example, decorin and biglycan were two main component of extracellular matrix that bond to transforming growth factor-β (TGF-β); fibronectin and laminin that bond to tumor necrosis factor-α (TNF-α); and collagen that bond to platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), and interleukin-2 (IL-2). Increase expression of those growth factors could inhibit apoptosis and proteolytic process in liver disease. Interaction among extracellular matrix and other substance were a two-way interaction. After liver damaged, extracellular matrix will modulate activity and proliferation of stellate hepatic cell, angiogenesis, growth factors, and MMPs. Extracelullar matrix also express a signal for polarization, adhesion, migration, proliferation, defence, and cell differentiation. Interaction between extracellular matrix with cell were regulated by specific membrane adhesion receptor.[11]

Stellate hepatic cell were a mesencymal cell found in Disse subendohtelial space, located betfween endothelial sinusoidal and hepatocyte. If liver were damaged, stellate hepatic cell will activated and induce proliferation of proinflammatory, profibrogenic, and promitogenic cytokines. This activated cell will increase migration and deposition of extraacelullar matrix. The most important growth factors in stellate cell activation and collagen synthesis were PDGF and TGF-β. PDGF was upregulated during stellate cell activation and associated with inflammation and fibrosis degree. On the other hand, TGF-β, especially TGF-β1, was produced by monocyte and macrophages and played an important role in liver fibrosis process. After immediate activation, TGF-β1 will transduce signal by its receptor to SMAD protein that will increase target gene expression.[11] TGF-β have a role in every stage of chronic liver disease, from the mild liver damage at the beginning of the process until progression into cirrhosis and hepatocellular carcinoma. Nowadays, a lot of study were conducted to explore TGF-β signaling pathway in order to found any alternative to inhibit chornic liver disease progression.[3]

It also known that hepatocyte produce connective tissue growth factors (CTGF) in liver damage condition. CTGF was a TGF-β modulator that can increase its profibrogenic activity. The use of small interfering RNA (siRNA) to inhibit CTGF could reduce liver fibrosis process. Therefore, CTGF were considered as one of the target therapy in liver fibrosis. Cyclic adenosine monophosphate (cAMP) was known as one of the CTGF inhibitors, while caffeine and

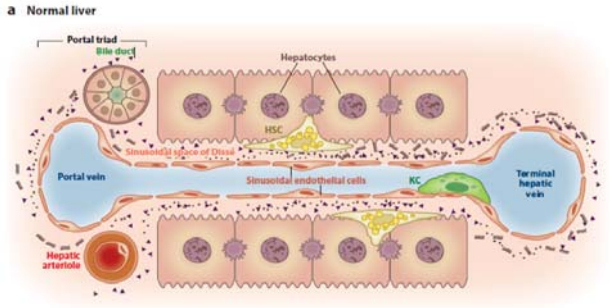

Figure 1. Normal liver. Disse space separate sinusoid and hepatocytes. If liver damaged, stellate hepatic cell will be activated and produce extracellular matrix in larga amount so that septum will be thickening porgresively.[11]

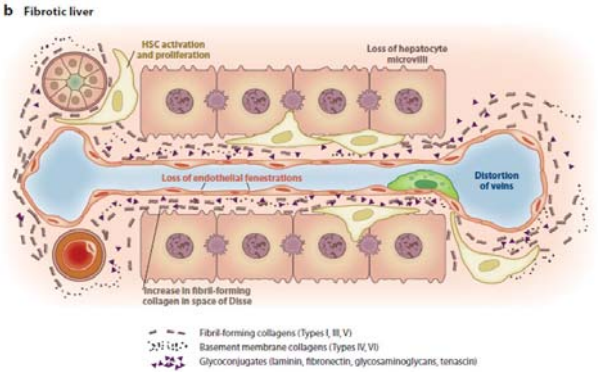

Figure 2. Fibrotic liver. Accumulation of extraceullar matrix in Disse space will impair metabolic balance between portal vein and hepatocyte, causing a portal hypertension.[11]

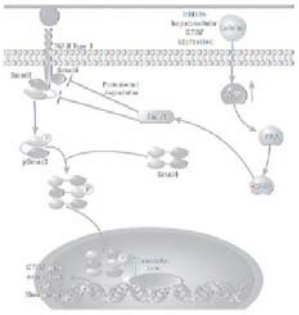

Figure 3. Role of TGF-β in liver damage stages. It is known that TGF-β have various effect in each stage, so that a need of targeted cell therapy in TGF-β signaling pathway is crucial.

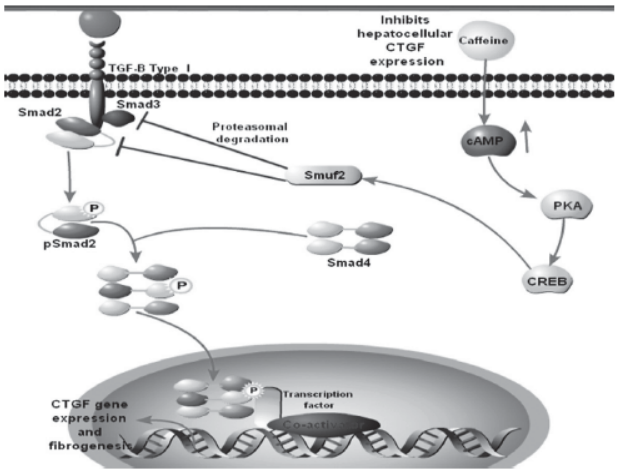

Figure 4. TGF-β induce CTGF expression in hepatocyte and fibrogenesis process

other methylxantine were known to increase cAMP intracelullarly by inhibit phospodiesterase activity. Based on those condition, it is proved that coffee, especially caffeine, could prevent liver fibrosis and cirrhosis.[1]

A study by Gressner et al showed that caffeine could inhibit CTGF expression in hepatocyte by induce SMAD 2 proteasomal degradation (TGF-β signal mediators), inhibit phosphorilation of SMAD 1 and 3, and regulate peroxisome proliferator-activated receptor γ (PPARγ) expression on its receptor.[12] Other study by Arauz et al evaluated antifibrotic effect of coffee in liver damage model by giving TAA (thioacetamide) in male Wistar rats. In 8-weeks therapy, coffee consumption were proved to inhibit liver tissue damage caused by TAA.[5] Caffeine could prevent hepatic enzyme production, and also inhibit TGF-β, CTGF, and its mRNA expression. Beside that, caffeine also reduce stellate hepatic cell activation by blocking α-SMA expression. Zymograph assay showed that caffeine were affect MMP 2 and 9 activity.[13] Otherwise, it is still unknown yet about daily coffee amount that could reach those effect, because of various type and servings method.[13] Furtado et al also evaluated effect of coffee or caffeine in liver tissue damage induced by TAA continuously. The result showed that conventional coffee consumption and 0.1% caffeine will give a better effect compared to instant coffee on liver tissue damage. Dosage used in that research (3-4 cups of coffee per day) were nearly the same with previous study about hepatoprotective effect of coffee on chronic liver disease, such as fibrosis, cirrhosis, and hepatocellular carcinoma. This is expected as coffee is an non-selective antagonist adenosine A receptors that regulate endogenous tissue repair and inflammation.[14]

Histologically, inflammation and periportal fibrosis degree were found to be more severe in TAA groups than control groups. Caffeine showed an ability to reduce its severity, as found a lower inflammation and fibrosis in groups given caffeine therapy.[15] Conventional coffee or caffeine were found reduce collagen level and collagen 1 mRNA expression. Instant coffee and caffeine were also proved to reduce preneoplastic lesions. This findings proved antifibrotic effect of coffee, especially in conventional and 0.1% caffeine coffee, while anticarcinogenic effect of coffee primarily found in instant and 0.1% caffeine coffee. This difference were believed as presence of chemoprotective component that differ between various coffee types.[16]

Shim et al investigate direct effect of caffeine in stellate hepatic cell and assess whether caffeine could reduce intrahepatic fibrosis in liver cirrhosis model. In this study, migration and proliferation of stellate hepatic cell were evaluated by various caffeine concentration (0.1 mmol, 1 mmol, 5 mmol, and 10 mmol), and procollagen type 1c and α-SMA measured using western blot. The result showed that caffeine were played an important tole in inhibiting adhesion and activation process of stellate hepatic cell by reduce procollagen type 1c and α-SMA.[16] In this study also showed that F-actin expression and FAK (focal ashesion kinase) were reduce because of caffeine consumption in several periods. F-actin regulate migration, adhesion, and morphological adaptation of stellate hepatic cell, while FAK regulate growth factor stimulation of extracellular matrix.

CONCLUSION

Based on previous study above, it has been proved that coffee, especially caffeine as its main

component, were reduce fibrosis in liver tissue by several mechanism. Although it is known that coffee have a hepatoprotective effect, it is still unclear the amoun of coffee which can give those effect. Several epidemiological study reported that daily consumption coffee of ± 2 cups could give hepatoprotective nd antifibrotic effect. Besides, it also affected by coffee type, composition, and coffee making method. There were several other compound that believed to play a role in inhibit liver fibrosis. It is known by the antifibrotic effect that found in non-caffeinated coffee. Therefore, a further evaluation were needed to investigate the effect of non-caffeinated coffee.

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