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Multiple Beneficial effects Associated with Coffee Consumption on Human Liver

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Abstract

Coffee is widely consumed beverage in the world. Incidence of chronic liver disease decreases with intake of coffee.The main objective of this study is to elucidate the hepatoprotective as well as chemo protective effect of coffee consumption in relation to previous published data. Prospective cohort studies based on relationship between coffee intake and ultimate effects on liver cancer have drawn various conclusions. Coffee's beneficial effects in various disease states have been demonstrated in variety of studies. Studies have provided data regarding effects of coffee in hot as well as in cold state. Level of blood cholesterol, following filtration, is affected by the coffee components. Among the components of coffee, caffeine played the significant role in reducing the level of ALT in coffee consumers as compared with non-coffee consumers. Coffee intake is associated with cardiovascular events and hypertension risks. However, intake of coffee has been found to be inversely related to the level of serum enzymes like gamma-glutamyltransferase, and alanine aminotransferase when studies relating to coffee effect on liver were performed in different countries. Moreover, the data based on epidemiological analysis, clearly suggested that liver cirrhosis had inverse relationship with coffee consumption; however, the results obtained were not sufficient to demonstrate that coffee may have hepatoprotective effect in liver injury. There is emerging evidence revealing that consumption of coffee has been associated with reduction of risks of various types of cancers. The emerging data on coffee consumption has revealed that it has beneficial effects in colorectal, pancreatic, and pharyngeal as well as in liver cancer. A systematic review was performed regarding association of coffee consumption and effect of coffee intake on liver diseases like hepatocellular carcinoma (HCC), viral hepatitis, cirrhosis and nonalcoholic fatty liver disease (NAFLD). Coffee consumption, in dose dependent manner, was found to improve the level of serum gamma-glutamyltransferase, alanine aminotransferase and aspartate aminotransferase in individuals which were found to be at risk of liver diseases. Anticancer effect of coffee on liver is achieved by induction as well as inhibition of specific enzymes. The patients with history of chronic liver disease who consume coffee, were reported to be at a reduced risk of liver to be cirrhotic, and a decreased mortality rate was observed in cirrhosis patients, as well as a decreased rate of development of Hepatocellular carcinoma was observed. In individuals with history of chronic hepatitis C, coffee intake was found to be associated with enhanced virologic reaction to antiviral drug therapy. Furthermore, coffee intake was reported to be inversely associated with the severeness of steatohepatitis in individuals with non-alcoholic fatty liver disorder. Therefore, in patients with chronic liver disease, coffee consumption on daily basis should be persuaded.

Keywords: Liver; Coffee; Effect of coffee

Introduction

Liver is considered to be an important organ of the human body. It is second largest organ of the body after skin. It mainly performs the functions of digestion, metabolism, and storage of nutrients. Liver is located at upper right quadrant of human body. Nutrients have to pass through liver after absorption into blood stream. Liver metabolizes amino acids derived from food sources. Liver performs urea production as well as alcohol metabolism. Liver detoxifies chemicals, toxins and drugs after administration. Ultimately liver nullifies effect of various toxins. These functions make the liver a vital organ. Liver product is bile and many other hormones that are involved in metabolism of food. Liver synthesizes proteins like albumin and also involved in glycogen synthesis.

Food may have diverse effect on liver. Liver is involved in digestion of food by secreting bile and other hormones which break down food components into simpler ones so they can be absorbed into blood. Beverages affect the liver functioning in various ways. Liver has definite level of microsomal enzymes responsible for metabolism. Level of enzymes may be raised in different diseases. Inflammation of liver may result in high level of alanine amino transferase (ALT) and alanine aspartate transferase (AST). Liver diseases can be due to viral attack as in case of hepatitis. Liver cirrhosis can be cause of viral attack on hepatocytes leading to hepatitis and various ingredients may have carcinogenic effects on liver.

Daily use beverages affect the liver activity. Among them coffee is taken as most common among working personnel. It is widely consumed beverage among people for at least 1200 years. Its use is favored because of unique flavor and aroma [1].

Coffee

Coffee is considered to be second most popular beverage consumed, after water for many centuries. Coffee confers health benefits in couple of diseases. Coffee has CNS stimulating properties and enhances alertness therefore it is used as beneficial drink. Coffee is a blend of

different ingredients like lipids, carbohydrates, alkaloids, vitamins, phenolic compounds and nitrogenous compounds [1]. Coffee contains large amounts of compounds with antioxidant, anti-inflammatory, and anticarcinogenic properties. Like other chemicals, coffee is also metabolized by liver. Current data support that coffee intake may have healthy and beneficial effect in number of medical ailments. Long-term coffee drinkers may be at a decrease risk for type II diabetes [2], symptomatic disease of gallstone, Parkinsonism [3], cardiovascular events [4,5] and stroke etc.Once coffee was supposed to be associated with an increased risk of cardiovascular disorders as well high blood pressure. Recently, studies were performed which were mainly based on prospective and meta-analyses demonstrate a favorable and beneficial effect of coffee on liver [6]. Coffee consumption was reported to be associated with reduced risks of development type 2 diabetes mellitus [7], metabolic disorders [8]. Intake of coffee defends the body against gestational diabetes [9]. The data available in literature reports that coffee consumption has favourable effects in various disease states. The results of previous studies have provided evidence that coffee is eventually a beneficial beverage in hepatic disorders. Although excess coffee consumption may provide valuable effects but in moderate intake it reduces the risk of neurodegenerative disorders such as Parkinson's Disease as well as Alzheimer's disease [10,11]. This phenomenon is clearly indicates dose dependent effect of coffee. Significantly, current meta-analysis performed covering almost 17 prospective analyses suggested that coffee consumption in light to moderate range was associated with diminution in all-cause mortality rate [12]. Coffee may have risk potential as well as beneficial effects on liver. Coffee affects liver enzymes level in various ways. Coffee consists of various antioxidants like, chlorogenic acid that have beneficial inhibitory carcinogenic effect on liver [13]. A number of researchers are focusing their attentions to determine the correlation between the coffee consumption and liver problems.

Role of Caffeine

Coffee has caffeine as major component that has inverse relationship with liver injury. Caffeine (1,3,7-trimethylxanthine) (Figure 1) is a purine and belongs to chemical class of alkaloids that occurs innately in coffee beans. Of the liver microsomal enzymes, human CYP1A2 is responsible for caffeine biotransformation, particularly in catalysis of N-demethylation reactions [14-16].

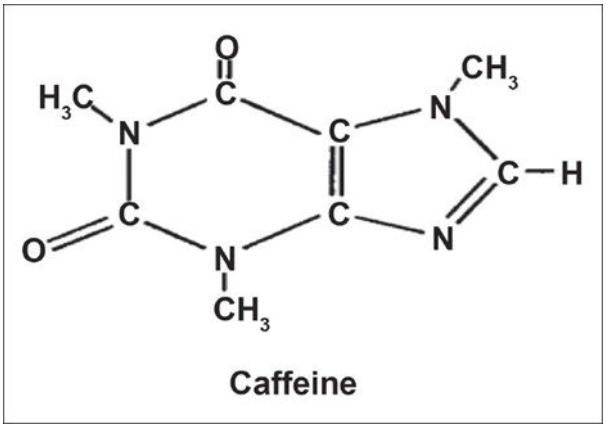

Figure 1: Caffeine (1,3,7-trimethylxanthine).

Caffeine has most significant role in hepatic functions. The study data regarding caffeine metabolism has provided evidence that if there is liver injury then caffeine metabolism is inhibited then ultimate increase in serum caffeine level. The individual with liver injury usually consume less coffee owing to the adverse effects of caffeine. However, the inverse correlation between inverse serum ALT functioning and coffee intake was not changed in individuals with normal or abnormal liver activity [17]. Work of Ruhl and Everhart [17] has reported that the relationship between caffeine intake and reduced serum ALT levels was of prime importance than that for coffee. Sharp and Benowitz [18] have
suggested that caffeine administration and serum level of caffeine were related to decreased levels of GGT however, studies performed in animals have provided data that caffeine has been effective in inhibiting chemical induced carcinogenesis [19]. Liver enzymes level may be affected by coffee components. Although caffeine is of utmost importance and major component of coffee but it is not reported to be responsible for hepatoprotective effect of coffee on liver. Coffee components can invoke enzymes release or synthesis. Coffee consumption has also been reported to be associated with a reduced occurrence of chronic liver disease. In an animal study, levels of caffeine which were extracted from coffee beans, found to be inversely related to liver damage [20]. This delineates the relationship between caffeine level and serum gamma-glutamyltranserase. A human population based study was performed in United States (US) which concluded that greater the rate of coffee consumption, more commonly caffeine, the lower will be the level of alanine aminotransferase (ALT). The enzyme ALT is prominent marker of liver damage [17]. The beneficial effect of coffee and caffeine were regular among subgroups which were reported to be at risk of liver failure and retained in analysis that was limited to individuals with no defective liver activity [17].

Effects of Coffee in Boiled State and Filtered State

Not all kinds of coffee have favorable effects in liver disease. A specific type of coffee exerts its effect in different ways. A number of studies suggest that hepatoprotective effect regarding coffee consumption may be associated with filtration. Filtration is a procedure that eradicates impurities from a formulation. Filtered coffee is found to have possible beneficial effect on liver. While potentially deleterious effect may be seen with unfiltered coffee [21,22]. It has been postulated that this distinguished effect achieved is attributable to the presence of cafestol and kahweol. These are diterpenes of caffeine and are liberated from the coffee beans when they are in ground state. These diterpenes were removed by paper filters [22,23]. Therefore these diterpenes were eventually responsible for beneficial response of coffee. Coffee lipids also produced alterations in liver enzymes alanine aminotransferase (ALT or SGPT) and gamma-glutamyltransferase (GGT). Not only diterpenes but lipids present in coffee composition were prone to be responsible for lowering the level of liver enzymes. These conclusions prompted the researchers to study whether long term use of coffee can affect the liver biochemistry.

Effects of coffee vary according to boiled or cold state. Experiments have shown that coffee in-boiled state elicit the serum cholesterol level [24-28], as compared with drip filtered coffee [29] or does not affect [25-27,30-32]. Experimentally, it is reported that boiled coffee that has been filtered before consumption does not affect the cholesterol level

[33,34]. This indicates that the components involved in cholesterol level enhancement are retained by the paper.

Carcinoma and Coffee

The hepatoprotective effect of coffee consumption is considered to be emerging evidence. Coffee exerts possible beneficial effects in a variety of liver diseases ranging from abnormal elevation of liver enzymes to hepatocellular carcinoma [35]. Hepatic carcinoma may develop due to several reasons. Several studies have supported the postulation that coffee consumption may result in reduced danger of liver carcinoma [36]. Recent data has shown that coffee exerts beneficial effect in liver carcinoma. Recent reports have provided the evidence of reducing incidences of hepatocellular carcinoma by coffee drinking. Coffee contains various components that are involved in carcinogenic detoxification e.g. cafestol, kehweol etc. These components work by blocking the enzymes involved in carcinogenesis [37,38]. Different case-control studies performed on coffee and hepatocellular carcinoma demonstrated that coffee had beneficial effect on liver in dose dependent pattern.

Anticancereous effect of coffee is achieved by blocking as well as by inducing different enzymes. Induction of glutathione-S-transferase and inhibition of N-acetyltransferase results in anticarcinogenic effect of coffee components (Figure 2) (cafestol, kahweol and diterpenes) [39]. Coffee has advantage that it reduces risk of liver injury and cirrhosis [40-44] that is actually a most significant step in the exercise of hepatocarcinogenesis. Recently, three large, case-control studies of hospital base, have added further weight to the proposition of a hepato-protective effect associated with coffee [45]. Ohfuji et al. performed experiments to study relationship between coffee consumption and Hepatitis C virus-related Hepatocellular carcinoma. He concluded from his study that risk of carcinoma decreases in dose dependent fashion. Intake of at least one cup coffee per day results in significant decrease in hepatocellular carcinoma in coffee drinkers as compared with those who do not drink coffee. This study suggests that impact of coffee intake is observed in coffee drinkers while, non-drinkers show different behavior towards the hepatocellular carcinoma. Another researcher, Montella et al. also conducted study on coffee-hepatocellular carcinoma relationship [46]. He demonstrated his findings of a case control study based on hospital, regarding the relationship of coffee association with hepatocellular carcinoma. This study also suggested the favorable results of coffee when taken in surplus amount. Intake of coffee in sufficient amount provided beneficial results in liver cancer. He found that consumption of 28 cups of coffee per week had significant effect than the persons drinking less than 14 cups. He concluded that coffee has dose dependent effect. A study conducted on wide scale including more than 12000 health examinees in Japan [47], Tanka et al. suggested that excess coffee consumption had a significant role in decreasing GGT activity in males.

Figure 2: Mechanism of anticarcinogenic effect of coffee.

The Mechanism of Coffee's Hepatoprotective Effect

The data available for coffee effect on liver, suggest that various mechanisms are involved in this phenomenon. Although there is no sufficient published data regarding the relationship between caffeine consumption and chronic viral hepatitis, currently numerous studies provided more evidence regarding anticancereous effect of coffee components. The components of coffee can control Keap1/Nrf2/ ARE signaling pathways involved in protection against carcinoma [48,49]. Keap1 is a protein i.e. cysteine-rich. Of this protein about 27 cysteine residues found in Keap1 are reported to be responsible for a sensory role in identifying the agents causing oxidation as well as xenobiotics involved in carcinogenesis [50]. This pathway is attributed to play a role in preventing carcinogenesis. Despite number evidences supporting the hepato-protective effect of coffee, the mechanism behind this response is yet to be explained. Coffee is a complex 'mixture' of a vast number of chemicals, some of which may be liable for its reported beneficial effects on the liver. Coffee intake is very common worldwide and it may possibly have favourable effects on liver. However, coffee consumption plays significant role in decreasing level of liver enzymes. Coffee intakeis reported to be associated with reduced level of liver enzymes like gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [51]. Coffee consumption has also suggested to be related to lower severeness of liver problems and lower speed of liver disease progression [17,52,53]. Epidemiological data obtained from studies have strongly suggested that consumption of coffee is defensive against hepatocellular carcinoma (HCC) as well as chronic liver disease (CLD) [18,54-59]. There are hundreds of compounds in coffee, namely caffeine, diterpenes, potassium, niacin,magnesium, antioxidants, chlorogenic acids and tocopherols [60]. The coffee constituent which is mostly studied in regard to liver function and health are caffeine, diterpenes (cafestol and kahweol) as well as chlorogenic acids [61]. It has the familiar response of elevating blood concentration of the liver enzyme i.e. glutamyltransferase (GGT) that is widely assumed to be a indicator of alcohol use, while it is recoded that other factors also are related to serum levels of GGT [21,62,63]. The work of Cavin et al. [64] has provided evidence that coffee components namely kehweol and cafestol play a significant role as compared with other components.

The study conducted in animal models as well as in cell culture models, concluded that cafestol and kehweol were reported to decrease the incidence of toxicity associated with different types of carcinogenic substances. Moreover, cafestol and kehweol have been reported not only to enhance phase II enzyme functioning but also enhance liver glutathione levels [64-66]. The amount of these components is different in normal coffee as compared with filtered coffee, unlikely; the resulting hepatoprotrctive response achieved is because of these components. The concentration of these components decreases in filtered coffee as compared with unfiltered coffee. An inverse relationship between serum level of GGT and coffee consumption has been reported in the study conducted by Arnesen et al. [67] in Norway. The studies based on prospective hypothesis were conducted in Northern California [68], reported an inverse coffee-cirrhosis association for the very first time. The study reported that drinking of Coffee, instead of tea, was inversely associated with risk of alcoholic cirrhosis in individuals drinking four or more than four cups of coffee per day were at one fifth the risk of those who did not consume coffee. These findings were later supported by case-control studies conducted in regard to morbidity associated with liver cirrhosis as end point.

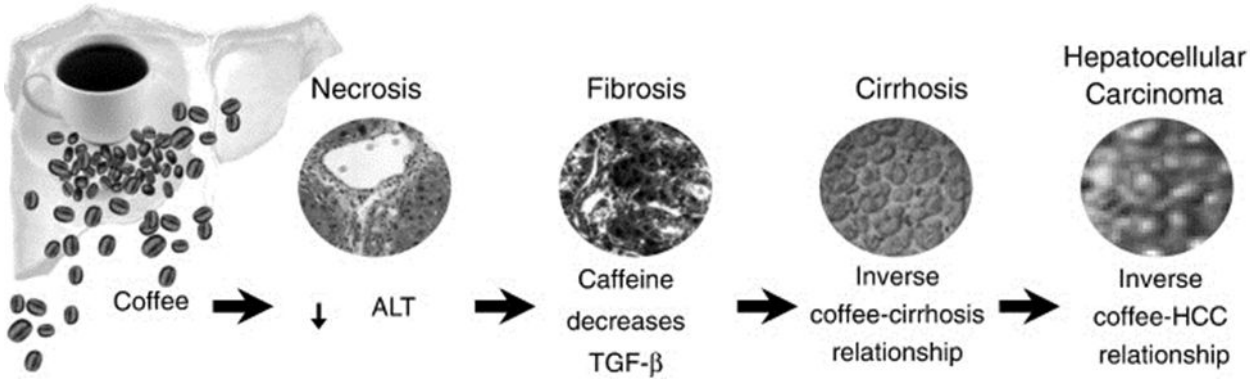

Figure 3: Coffee effect on liver.

In 1980s, Arnesen [63] was the first researcher to suggest an inverse relationship between coffee consumption and serum gamma-glutamyltransferase (GGT) level in the Tromso Heart Study. Eventually, a sequence of cross-sectional studies as well longitudinal studies provided same outcomes. Tanaka et al. [47] carried out a cross-sectional review on large scale of 12,687 physically fit Japanese volunteers, while precluding the ones having pre-existing liver problem or aberrant level of liver enzymes. This group also exhibited that there has been an inverse relationship between coffee consumption and serum GGT concentration. A number of investigators have reported that the inverse correlation which has been delineated between coffee intake and liver disorders may not be related to coffee effect only. The given data providing the evidence of well-documented impairment of coffee component; caffeine biotransformation by liver enzymes in individuals with cirrhosis [69], the relationship may demonstrate a diminution in coffee intake in patients with impaired liver in order to restrict caffeine unwanted effects [44,47,70]. However, the outcomes provided by these studies do not explain this elucidation [44,47]. The histologically beneficial effect of coffee was first represented by Modi *et al* He analyzed the relationship between intake of caffeine on daily basis and severeness of hepatic fibrosis amongst the patients with chronic liver diseases [18]. The authors suggest that daily intake of two or more cups of coffee were related to reduce rates of hepatic fibrosis (Figure 3). A preventive role of coffee consumption in non-alcoholic fatty liver disorder (NAFLD) is contentious. A few studies have reported that, in patients with NAFLD, coffee intake may be preventive against liver steatosis and fibrosis [71]. The studies based on ultrasound data have provided evidence that coffee intake is inversely related to the degree of liver steatosis. Likewise, the studies utilizing serum markers of fibrosis and histology have demonstrated coffee consumption inversely related to fibrosis in patients with NAFLD [53,72,73]. Molloy et al. also reported a relation between coffee intake and histopathology of liver [53]. They suggest that higher the coffee intake in persons with steatosis in comparison to those individuals with non-alcoholic steatohepatitis (NASH), providing evidence of preventive response against inflammation. Moreover, the coffee consumption, in patients with history of NASH, was related to a remarkable diminution in danger of advanced fibrosis [53]. The protective effect of coffee has been suggested by many studies. While, currently a prospective study provided the data suggesting no beneficial effect of coffee intake on developing liver steatosis [72]. Furthermore, a study based on a community of 1223 individuals has reported no correlation between coffee use and found no association between coffee intake and the universality of fatty liver disease [74].

Conclusion

A plenty of data is available in literature substantiating the beneficial effects related to coffee consumption on liver function. Various evidences have supported the beneficial effects associated with coffee intake on biochemistry of abnormal liver. The reported useful effects of coffee in liver abnormality i.e. cirrhosis may lead to improved life style as well reduced risk of cirrhosis related mortality. Coffee components have been found to be beneficial in cirrhosis and carcinoma of hepatocytes. Various components of coffee are reported to play pivotal role in liver cancer. Serum levels of liver enzymes were found to reduce in persons drinking more cups of coffee than in normal persons. Greater the intake of coffee, lower will be the level of liver enzymes observed. There are a number of evidences which support the useful effects of coffee beverages on liver activity and different liver diseases. Epidemiological data obtained robustly suggest that intake of almost 3 cups of coffee per day decreases the severeness of liver injury associated with a variety of causative agents. A number of logical and mechanistic data demonstrate that there is evidence based molecular analysis to accept eventually that coffee is useful for the liver. Various ingredients of coffee have been found to be related to such a beneficial

effect, including caffeine, kahweol, cafestol, and antioxidants obtained from beans of coffee, but there is no significant data is available for any such ingredient. The component that exerts the hepatoprotective effects of coffee on cirrhotic liver is not evident yet. Indeed, work of different researchers have suggested that caffeine intake and resulting serum level of caffeine was related to reduced levels of GGT and, however, the studies conducted in animals, caffeine has inhibited hepatic carcinogenesis induced by chemicals. Though, there are a significant number of studies that do not validate this hypothesis. The studies performed in relation to coffee consumption and effects of coffee on liver, also suggested that serum cholesterol level is also affected by hot or cold state of coffee. Boiled and filtered coffee affects the liver biochemistry in different ways. The recent studies have suggested the potentially deleterious effects of coffee when use in unfiltered form. The use of coffee in non-alcoholic fatty liver disease is still controversial. Drinking coffee in liver fibrosis and steatosis has favorable effects in dose dependent manner that drinking 2 to 3 cups of coffee may relieve the individual. By taking into account other beverages that also contain caffeine in their composition like cola or green tea, the studies have not provided any remarkable data regarding their correlation with liver enzymes. No data is available for their hepatoprotective effect. Comprehensively, there is evidence based data suggesting to some extent that intake of moderate amount of coffee may grant some beneficial effects on human beings. Although the dose required for achieving the beneficial effects could not be elucidated. The mechanism that is involved in hepatoprotective effect of coffee is unclear yet and future prospects may be considered. Concisely, the results obtained from studies and data reporting association with coffee liver interaction might be interesting, but their significance remains open for discussion in clinical settings for further experiments. In future clinical trials in this domain may be expected.

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