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CHRONIC INFLAMMATORY LIVER DISEASES AND COFFEE INTAKE

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CHRONIC INFLAMMATORY LIVER DISEASES AND COFFEE INTAKE

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ABSTRACT

Purpose of the review: The healthy protective effects of coffee against several metabolic diseases and some types of cancer. In this short review, the possible preventive and/or therapeutic actions of coffee on liver function is focused.

Recent findings: The protective mechanisms of coffee are various and due to several components with anti-inflammatory and antioxidant properties besides caffeine.

As a matter of the fact, polyphenols in decaffeinated coffee have a similar effect on liver fibrosis and on serum levels of liver enzymes as those in caffeinated coffee.

Furthermore, diterpenes may exert a detoxifying action and antioxidant activity, with benefits on liver fibrosis, cirrhosis and cancer.

Summary A regular coffee consumption may have preventive healthy effects, especially if consumed without added sugars. Certainly, coffee consumption should not be prohibited in individuals with chronic inflammatory liver diseases, including hepatocellular carcinoma.

Keywords: coffee, caffeine, liver diseases, cancer

INTRODUCTION

Recent literature offers a series of comprehensive reviews on the health effects of coffee in beverage form as evaluated for the presence or absence of caffeine (caffeinated or decaffeinated, respectively), other specific minor chemical components, the type of seed utilized (Arabica versus Robusta variety), and the method of preparation (instant, espresso, boiled, filtered, etc). [1-3]

The overall impression is that coffee has a healthy protective action against neurodegenerative, liver, cardiovascular, and metabolic diseases and some types of cancer when it is consumed, in the absence of specific contraindications or intolerance and according to individual sensibility, at the reasonable dose of 1-3 (2-4) cups of caffeinated coffee per day, corresponding to 100-400 mg caffeine per day. [1,2]

In this short review, we will focus on the possible preventive and/or therapeutic actions of caffeine (but also of coffee in beverage form as a whole) on liver function in chronic inflammatory liver diseases such as steatosis, steatohepatitis, cirrhosis, and cancer and on its role in limiting progression of these types of diseases.

WHAT IS COFFEE?

Coffee is the most frequently consumed beverage worldwide; it is prepared from the seeds of a plant, of the family Rubiaceae and genus Coffea and includes a number of different species. Coffee is mainly produced from the coffee seeds of the Arabica and Robusta varieties. Besides caffeine (an alkaloid of the methylxanthine family), coffee contains many other specific compounds, representing a rich source of phenols, polyphenols, flavonoids, non-flavonoids, melanoidins, etc., most of which have anti-inflammatory and antioxidant properties. [4] Chlorogenic acids (CGAs) in particular belong to the conjugated hydroxycinnamate family of non-flavonoid phenols; CGAs are the most abundant antioxidant in coffee. A percentage of CGAs and flavonoids is degraded by roasting temperatures of 230 °C, but alternative antioxidant compounds are formed, thus maintaining an overall strong active antioxidant property. [5] For these elementary reasons, coffee

is completely different from other diffusely marketed, non-natural, caffeine-rich soft drinks (with or without added sugars).

CHRONIC INFLAMMATORY LIVER DISEASES

Liver steatosis (either non-alcoholic fatty liver disease (NAFLD), which is often associated with metabolic syndrome, or alcoholic fatty liver disease (AFLD)) pathogenesis is metabolically characterized by alteration of hepatic synthesis and of metabolism of fatty acids (FAs) and triglycerides (TGs). Marventano *et al.* in particular support the concept that NAFLD and metabolic syndrome are interrelated, as they share common pathogenic determinants such as insulin resistance and oxidative stress. [3,6,7] In their review the authors discuss a study by Malloy *et al*. showing an inverse correlation of prevalence and severity of biopsy-proven fibrosis of NAFLD and coffee caffeine consumption but not of prevalence and severity of fibrosis and total caffeine intake. [8-9] The presence of these metabolic alterations in predisposed individuals or in others with related diseases such as type 2 diabetes predisposes the liver to the aggressive action of inflammatory cytokines with increased oxidative stress, leading to steatohepatitis and cirrhosis or even to hepatocellular carcinoma, the most frequent type of liver cancer. [10, 11] Reactive oxygen species (ROS) generation in fact stimulates TNF-alpha production, and TNF-alpha action may impair cellular function, potentially resulting in hepatic fibrogenesis and necrosis through increased nitric oxide production. In conclusion, oxidative stress seems to be the most important factor in different pathways leading to fibrogenesis and consequently to NASH.

COFFEE PROTECTIVE EFFECTS

a) Suggested mechanisms

The protective mechanisms of coffee are various and due to several components of coffee besides caffeine. Coffee appears to exert this protective action independently of the type of noxa (e.g. alcohol, virus, diabetes, and metabolic syndrome). [11] Caffeine exerts its protective effects on liver function by beta oxidative stimulation of lipolysis, lipogenesis and oxidative stress

suppression. In rats, liver steatosis, experimentally induced by a high fat diet (HFD), is characterized by increased serum bilirubin, ALT, AST, and Hyper TG. Increased oxidative stress is attenuated by caffeine due to reduced hepatic fatty acid synthesis and to acetyl CoA carboxylase activity associated with increased activity of peroxisome proliferation-activated receptor alpha (PPAR-alpha) and of carnitine-palmitoyl-transferase 1 (CPT1). [12] During fatty acid synthesis, concurrent caffeine administration reduces lipogenesis and stimulates lipid beta-oxidation after consumption of a high-fat diet. Furthermore, PPAR-alpha stimulation activates the lipoprotein lipase, which reduces fat accumulation but also has anti-inflammatory and antioxidative effects. [13] These experimental findings support a previous epidemiological observation carried out on a multi-ethnic US population of 125,580 liver disease-free individuals, showing the protective action of regular coffee against liver cirrhosis, especially alcohol-induced liver cirrhosis. [3] Another beneficial effect of caffeine is specifically that it is anti-fibrotic and prevents hepatic stellate cell (HSC) adhesion and activation. In fact, after their activation due to hepatocyte damage, HSCs differentiate into myofibroblast-like cells and secrete extracellular matrix leading to hepatic fibrosis. [14] In alcoholic liver fibrosis (ALF), ethanol oxidation produces a highly reactive acetaldehyde compound, which stimulates type 1 collagen, which activates hepatic stellate cells. Caffeine may inhibit this process by inhibiting the cAMP/PKA/CREB protein expression signal pathway through adenosine A2A receptors in HSCs. The beneficial effects of other non-caffeine chemical components of coffee beans come indirectly from the observation that decaffeinated coffee exerts similar effects, although to a lesser degree, to caffeinated coffee. Diterpenes (i.e., cafestol, kahweol) may have an antioxidant action through stimulation of glutathione-5-transferases (GSTs) and nuclear factor erythroid 2-related factor 2 (Nrf-2). [1] Furthermore, melanoidins, brown-coloured compounds present in coffee, confer significant protection against oxidative noxae in human HepG2 cells by reducing TNF-alpha and tissue transglutaminase and by transforming growth factor beta expression in the liver. [3, 15, 16] Other, still not identified, coffee components, besides caffeine and diterpenes, may have a protective action on progression to hepatic liver cirrhosis by

upregulating glucuronidation processes. Finally, individual genotype and gut microbiota may affect the bioavailability and selection of the type of absorbed metabolites.[17]

b) Some experimental, epidemiological and clinical evidence

Poole *et al.* in their recent meta-analysis confirm previous findings and add that in habitual coffee consumers, there is also present a significant dose-response relation for coffee consumption and low risk of several types of cancer, including prostate, endometrial, melanoma and liver cancers; in addition, a low risk of NAFLD, liver fibrosis and cirrhosis was reported. [1] A significantly lower risk of gallstone disease has also been observed in coffee consumers than in non-consumers. [13] A part of the direct positive effect of caffeine on liver fibrosis is due to polyphenols, as indirectly shown by the observation that polyphenols in decaffeinated coffee have a similar, but to a lesser degree, effect on serum levels of liver enzymes as those in caffeinated coffee. [18] Furthermore, Vitaglione *et al.* observed, in an experimental model of rats fed a high-fat diet, that coffee polyphenols decrease oxidative stress, insulin resistance and liver fibrosis. [15] Diterpenes may exert their preventive action against liver fibrosis, cirrhosis and liver cancer through a detoxifying effect in which intracellular antioxidant activity is stimulated. [4]

CONCLUSIONS

Coffee is a natural, complex drink with a consumer base that is widely found throughout the world and is not confused with other still popular caffeine-rich soft drinks. Regular coffee consumption has, generally speaking, a beneficial health effect, although its consumption has some contraindications (increased gastric acid secretion, anxiety, insomnia, palpitation) and some individuals may be intolerant, as may happen for many natural substances. Coffee, as a whole and through many of its specific components, appears to be beneficial more as a preventive agent than as a therapeutic agent; consequently, data are limited to suggest its use as a therapeutic agent in liver fibrosis, cirrhosis, and hepato-cellular carcinoma. However, coffee is not contraindicated in these clinical conditions, particularly if assumed without added sugars. Although experimental data confirm these effects, we cannot exclude, as already suggested, that coffee is also a surrogate

marker of social wellness, high income and education, which positively and directly affect human health. Other factors biasing the results may include the possible relation between the method of preparation and consumption and the degree of effectiveness. In fact, it is difficult to determine if seed variety, brand, and brewing method may influence coffee's efficacy in protecting liver function and in performing the described beneficial effects on other organs and processes. In our opinion, regular consumption, 2 – 4 cups per day, without added sugars, particularly sucrose and fructose, is important.

A positive, conclusive suggestion may be that coffee consumption is not prohibited in individuals with chronic inflammatory liver diseases, including hepatocellular carcinoma.

KEY POINTS

Coffee exerts detoxifying and antioxidant effects with benefits on liver fibrosis, cirrhosis and cancer.

Coffee healthy protective effects have been described also against several metabolic diseases and some types of cancer.

Besides caffeine, other coffee components (polyphenols, diterpenes) have anti-inflammatory and antioxidant properties.

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