

Current Opinion in Clinical Nutrition and Metabolic Care

CHRONIC INFLAMMATORY LIVER DISEASES AND COFFEE INTAKE

--Manuscript Draft--

Manuscript Number:	MCO220504R1
Full Title:	CHRONIC INFLAMMATORY LIVER DISEASES AND COFFEE INTAKE
Article Type:	Review Article
Corresponding Author:	Lidia Santarpia Naples, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
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First Author Secondary Information:	
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Order of Authors Secondary Information:	

Editorial Manager MS Check Form, Current Opinion

MS Number	MCO220504 Santarpia
Corresponding Author name (# of authors?)	Lidia Santarpia
No. of Authors	3
Review title	CHRONIC INFLAMMATORY LIVER DISEASES AND COFFEE INTAKE
Section	Nutrition and the Gastrointestinal Tract
Author address on MS?	Y
Author email on MS?	Y

Structured abstract	Y
Key words	Y
Introduction	Y
Headings in text	Y
Conclusion	Y
Key points	Y

Word count: abstract	137
Word count: text	1371

Bullets/annotations	Y
Refs. in sequence?	Y

Conflicts of Interest	Y
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	Identify	Permissions
Colour figures	N/A	N/A
Half tones	N/A	N/A
Line drawings	N/A	N/A
Tables	N/A	
Figures/Tables cited in text?	N/A	
Figure legends and titles?	N/A	

Colour online? (Y/N, charge or free)	N/A
Colour in print? (Y/N, charge or free)	N/A

Supplementary Digital Content	N/A
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Comments for **copyeditor**:

Editorial Manager MS Check Form, Current Opinion

Cited in text?	N/A
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Comments for **copyeditor**:

1 **CHRONIC INFLAMMATORY LIVER DISEASES AND COFFEE INTAKE**

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19 **ABSTRACT**

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

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

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

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

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

32

33 **Keywords:** coffee, caffeine, liver diseases, cancer

34

35

36 **INTRODUCTION**

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

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

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

50 **WHAT IS COFFEE?**

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

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

63

64 **CHRONIC INFLAMMATORY LIVER DISEASES**

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

81 **COFFEE PROTECTIVE EFFECTS**

82 a) Suggested mechanisms

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

87 suppression. In rats, liver steatosis, experimentally induced by a high fat diet (HFD), is
88 characterized by increased serum bilirubin, ALT, AST, and Hyper TG. Increased oxidative stress is
89 attenuated by caffeine due to reduced hepatic fatty acid synthesis and to acetyl CoA carboxylase
90 activity associated with increased activity of peroxisome proliferation-activated receptor alpha
91 (PPAR-alpha) and of carnitine-palmitoyl-transferase 1 (CPT1). [12] During fatty acid synthesis,
92 concurrent caffeine administration reduces lipogenesis and stimulates lipid beta-oxidation after
93 consumption of a high-fat diet. Furthermore, PPAR-alpha stimulation activates the lipoprotein
94 lipase, which reduces fat accumulation but also has anti-inflammatory and antioxidative effects.
95 [13] These experimental findings support a previous epidemiological observation carried out on a
96 multi-ethnic US population of 125,580 liver disease-free individuals, showing the protective action
97 of regular coffee against liver cirrhosis, especially alcohol-induced liver cirrhosis. [3] Another
98 beneficial effect of caffeine is specifically that it is anti-fibrotic and prevents hepatic stellate cell
99 (HSC) adhesion and activation. In fact, after their activation due to hepatocyte damage, HSCs
100 differentiate into myofibroblast-like cells and secrete extracellular matrix leading to hepatic fibrosis.
101 [14] In alcoholic liver fibrosis (ALF), ethanol oxidation produces a highly reactive acetaldehyde
102 compound, which stimulates type 1 collagen, which activates hepatic stellate cells. Caffeine may
103 inhibit this process by inhibiting the cAMP/PKA/CREB protein expression signal pathway through
104 adenosine A2A receptors in HSCs. The beneficial effects of other non-caffeine chemical
105 components of coffee beans come indirectly from the observation that decaffeinated coffee exerts
106 similar effects, although to a lesser degree, to caffeinated coffee. Diterpenes (i.e., cafestol, kahweol)
107 may have an antioxidant action through stimulation of glutathione-S-transferases (GSTs) and
108 nuclear factor erythroid 2-related factor 2 (Nrf-2). [1] Furthermore, melanoidins, brown-coloured
109 compounds present in coffee, confer significant protection against oxidative noxae in human
110 HepG2 cells by reducing TNF-alpha and tissue transglutaminase and by transforming growth factor
111 beta expression in the liver. [3, 15, 16] Other, still not identified, coffee components, besides
112 caffeine and diterpenes, may have a protective action on progression to hepatic liver cirrhosis by

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

115 b) Some experimental, epidemiological and clinical evidence

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

128 **CONCLUSIONS**

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

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

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

148

149 **KEY POINTS**

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

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

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

156

157 **Acknowledgements:** none

158 **Financial support and sponsorship:** none

159 **Conflict of interest:** none

160

161 **References**

162 1. ****Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee**
163 **consumption and health: umbrella review of meta-analyses of multiple health outcomes.**

- 164 BMJ. 2017 Nov 22; 359: j5024. *An umbrella comprehensive review which takes into*
165 *account other previous reviews*
- 166 2. *Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee,
167 including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a
168 systematic review and dose-response meta-analysis. *BMJ Open*. 2017 May 9; 7(5):
169 e013739. *The study considers both caffeinated and decaffeinated coffee allowing an indirect*
170 *evidence of the potential benefic role of other coffee components besides caffeine*
- 171 3. **Marventano S, Salomone F, Godos J, Pluchinotta F, Del Rio D, Mistretta A, Grosso G.
172 Coffee and tea consumption in relation with non-alcoholic fatty liver and metabolic
173 syndrome: A systematic review and meta-analysis of observational studies. *Clin Nutr*. 2016
174 Dec;35(6):1269-1281. ** *A key study supporting the relation between NAFLD and the*
175 *Metabolic Syndrome*
- 176 4. Salomone F, Galvano F, Li Volti G. Molecular Bases Underlying the Hepatoprotective
177 Effects of Coffee. *Nutrients*. 2017 Jan 23; 9(1).
- 178 5. Kamiyama M, Moon JK, Jang HW, Shibamoto T. Role of degradation products of
179 chlorogenic acid in the antioxidant activity of roasted coffee. *J Agric Food Chem*. 2015 Feb
180 25;63(7):1996-2005.
- 181 6. ** Zelber-Sagi S, Salomone F, Webb M, Lotan R, Yeshua H, Halpern Z, et al. Coffee
182 consumption and non-alcoholic fatty liver onset: a prospective study in the general
183 population. *Transl Res* 2015; 165: 428-36. *This cross-sectional/prospective study utilized*
184 *several diagnostic criteria to demonstrate that coffee intake may exert beneficial effects on*
185 *liver fibrosis progression.*
- 186 7. **Birerdinc A, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients
187 with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2012; 35:76-82. *A large*
188 *USA case-control study showing that caffeine intake was independently associated with a*
189 *lower risk for NAFLD.*

- 190 8. * Malloy J W, Calcagno C J, Williams C D, Jones F J, Torres D M, Harrison S A,
191 Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic
192 steatohepatitis, and degree of hepatic fibrosis, *Hepatology* 2012, 55, 429-36. *The study*
193 *reports an inverse correlation between caffeine intake and fibrosis among NASH patients.*
- 194 9. * Catalano D, Martines GF, Tonzuso A, Pirri C, Trovato FM, Trovato GM. Protective role
195 of coffee in non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci* 2010; 55: 3200-6. *The*
196 *study showed that more coffee drinking was inversely associated with bright liver score.*
- 197 10. **Helal MG, Ayoub SE, Elkashefand WF, Ibrahim TM. Caffeine affects HFD-induced
198 hepatic steatosis by multifactorial intervention. *Hum Exp Toxicol.* 2018 Sep;37(9):983-990.
199 *The study discusses the evolution from liver steatosis up to hepatocellular carcinoma*
- 200 11. Dickson JC, Liese AD, Lorenzo C, Haffner SM, Watkins SM, Hamren SJ, Stiles JK,
201 Wagenknecht LE, Hanley AJ. Associations of coffee consumption with markers of liver
202 injury in the insulin resistance atherosclerosis study. *BMC Gastroenterol.* 2015 Jul 28;15:88.
- 203 12. Klatsky AL, Morton C, Udaltsova N, Friedman GD. Coffee, cirrhosis, and transaminase
204 enzymes. *Arch Intern Med.* 2006 Jun 12; 166 (11):1190-5.
- 205 13. Montagner A, Polizzi A, Fouché E, Ducheix S, Lippi Y, Lasserre F, Barquissau V, Régnier
206 M, Lukowicz C, Benhamed F, Iroz A, Bertrand-Michel J, Al Saati T, Cano P, Mselli-Lakhal
207 L, Mithieux G, Rajas F, Lagarrigue S, Pineau T, Loiseau N, Postic C, Langin D, Wahli W,
208 Guillou H. Liver PPAR α is crucial for whole-body fatty acid homeostasis and is protective
209 against NAFLD. *Gut.* 2016 Jul;65(7):1202-14.
- 210 14. *Shim SG, Jun DW, Kim EK, Saeed WK, Lee KN, Lee HL, Lee OY, Choi HS, Yoon BC.
211 Caffeine attenuates liver fibrosis via defective adhesion of hepatic stellate cells in cirrhotic
212 model. *J Gastroenterol Hepatol.* 2013 Dec;28(12):1877-84 *The study shows, at cellular*
213 *level, the caffeine protective action against the evolution of liver fibrosis to cirrhosis and*
214 *liver carcinoma*

- 215 15. *Vitaglione P, Morisco F, Mazzone G, Amoruso DC, Ribocco MT, Romano A, Fogliano V,
216 Caporaso N, D'Argenio G. Coffee reduces liver damage in a rat model of steatohepatitis: the
217 underlying mechanisms and the role of polyphenols and melanoidins. *Hepatology*. 2010
218 Nov;52(5):1652-61. *For the first time in an experimental model, beneficial effects for*
219 *minor components of coffee on liver function are shown.*
- 220 16. Chen S, Teoh NC, Chitturi S, Farrell GC. Coffee and non-alcoholic fatty liver disease:
221 brewing evidence for hepatoprotection? *J Gastroenterol Hepatol*. 2014 Mar;29(3):435-41.
- 222 17. *Guertin KA, Freedman ND, Loftfield E, Stolzenberg-Solomon RZ, Graubard BI, Sinha R.
223 A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP
224 Diet and Health Study. *Br J Cancer*. 2015 Sep 29;113(7):1081-5. *Suggests a relation*
225 *between gut microbioma and coffee action*
- 226 18. Xiao Q, Sinha R, Graubard BI, Freedman ND. Inverse associations of total and
227 decaffeinated coffee with liver enzyme levels in National Health and Nutrition Examination
228 Survey 1999-2010. *Hepatology*. 2014 Dec;60(6):2091-8.
- 229 19. * Catalano D, Martines GF, Tonzuso A, Pirri C, Trovato FM, Trovato GM. Protective role
230 of coffee in non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci* 2010; 55: 3200-6. *The*
231 *study showed that more coffee drinking was inversely associated with bright liver score.*
232