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Daily coffee: safeguard against liver injury?

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ABSTRACT:

A growing body of epidemiological and experimental evidence suggests that coffee may exhibit protective effects on the liver, and thus prevent or reduce the risk of liver damage. The aim of this research was to identify and review original investigations, which characterize the association between coffee consumption and serum alanine aminotransferase (ALT), a common marker of liver injury. A literature search was conducted via an electronic search of the PubMed database between years 1993 and 2015. Twelve observational studies were identified, eleven of which demonstrated a significant inverse association between coffee intake and serum ALT. In contrast, three experimental studies from one week to 6 months in duration report a rise in serum ALT with coffee consumption. In summary, many current research findings appear to support that consistent and/or high coffee consumption is associated with a decreased risk of elevated serum ALT. Additional experimental research is warranted to further explore possible contributors of the underlying mechanism of protection, which is poorly understood.

INTRODUCTION:

Coffee is an exceedingly popular beverage around the world, frequently consumed for the   stimulating effects of its caffeine content on the central nervous system.[1] Knowledge of the effects of habitual coffee consumption on human physiology and health is thus of marked significance. Numerous studies suggest that coffee may be involved in a mechanism of hepatoprotection. For instance, coffee intake is demonstrated to be associated with decreased risk and prevention of non-alcoholic fatty liver disease, [2] alcoholic cirrhosis,[3] hepatocellular carcinoma,[4,5] and liver fibrosis.[5] The primary drivers underlying such protective outcomes are unknown due to the complex composition of coffee, which contains over 1,000 different compounds.[1,5] Several observational studies report an inverse relation between coffee consumption and liver enzymes, including serum alanine aminotransferase (ALT). Serum ALT levels are presently used as a marker for early detection of liver disease.[6] ALT is primarily found in the cytosol of hepatocytes, and released upon injury or death of the cells.[6,7] Prior to extensive fibrotic progression, ALT is typically elevated in chronic hepatocyte injury.[6] Relationships between coffee intake and serum ALT are described in a broad range of study populations. The review will summarize and discuss the findings of such studies.

METHODS:

Research articles investigating the interactions between coffee consumption and serum ALT levels were identified via an electronic search of the PubMed database. The following combinations of terms were used as part of the literature search strategy: 'coffee

and ALT'; 'coffee and serum aminotransferases'; 'coffee and transaminase enzymes.' The inclusion criteria for this review consisted of the following: 1) primary research article; 2) quantitative measures of coffee consumption in cups, grams, or milliliters; 3) and its relation to serum ALT levels (U/L) as the outcome variable; 4) statistical analysis including multivariate analyses for cross-sectional studies; 5) conducted in humans. Data on coffee consumption, serum ALT levels, methods, study population, study size, and study type was collected from eligible studies.

The preliminary search identified 63 articles, which were assessed for eligibility. Articles were excluded from the final analysis based on the following: conducted in mice or rats, conducted in cells, lacked direct measurement of ALT as an outcome variable, lacked appropriate statistical analysis, lacked coffee exposure as the independent variable, lacked quantitative measurement of coffee exposure, or was not a primary research article. Fifteen were included in the final analysis (See figure 1).
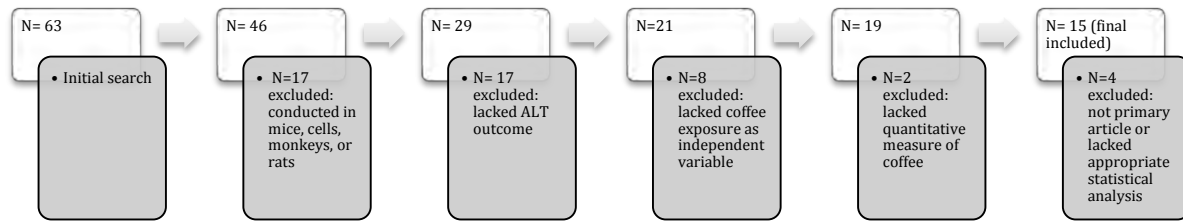

Fig.1 Search strategy.

RESULTS:

Eight cross-sectional studies[3,8–13], four cohort studies[14–17], and three randomized controlled studies[18–20] examining the relationship between coffee and serum ALT levels were identified; these studies were published from years 1993-2015. Seven cross-sectional studies demonstrated a statistically significant inverse relation between coffee intake and risk of elevated serum ALT, while one reports a non-significant relationship. Four cohort studies also observed a significant inverse relation between coffee and serum ALT. In contrast, three randomized controlled studies ranging from three weeks to six months in duration reported an increase in serum ALT levels with coffee intake.

Cross-sectional studies:

The following cross-sectional studies were conducted via survey or interview arrangements. Klatsky *et. al.* demonstrated a lower risk of elevated serum ALT levels with increased coffee consumption in a large population of Northern California residents (OR $_{\geq 4 \text{ cups vs. none}}$ [95% CI]: 0.6[0.6-0.7]).[3] Similarly, Ruhl and Everhart observed a decreased risk of elevated serum ALT with higher coffee intake (OR $_{\geq 2 \text{ cups vs. none}}$ [95% CI]: 0.56[0.31-

Year	Author	N & Age	Study Population	Study Type	Methods	Coffee Exposure	Outcome: ALT Upper limit	Results: OR (95% CI) & P values
2014	Xiao et. Al	N: 27,793 Age: ≥ 20 years	Nationally representative U.S. population	Cross sectional: data from the NHANES (1999 – 2010)	Interviews: 24-hour dietary recall	Caffeinated coffee: none, <1, 1 - <2, 2- <3, and ≥ 3 cups/day (one cup = 10oz. or 285.5ml) Decaffeinated coffee: 2 highest categories combined.	M: >47 U/L W: >30 U/L	Caffeinated coffee: (P = 0.0002) >3 cups/day: 0.75 (0.63, 0.89) 2-<3 cups/day: 0.91 (0.77,1.06) 1-<2 cups/day: 0.92 (0.81, 1.04) <1 cup/day: 0.97 (0.85, 1.11) 0 cups/day: reference Decaffeinated coffee: (P = 0.002) >2 cups/day: 0.62 (0.41, 0.94) 1-<2 cups/day: 0.74 (0.52, 1.04) <1 cup/day: 0.82 (0.62, 1.06) 0 cups/day: reference
2005	Ruhl & Everhart	N: 5994 Age: ≥20 years	U.S. population at high risk for liver injury	Cross sectional: data from NHANES III conducted (1988-1994)	Survey	< 1, 1-2, >2 cups/day	> 43 U/L	(P=0.034) >2 cups/day: 0.56 (0.31, 1.0) 1-2 cups/day: 0.83(0.49, 1.4) <1 cup/day: 1.4 (0.84, 1.24) 0 cups/day: 1 (reference)
2001	Honjo et. Al	N: 7313 Age range: 48-59 years	Apparently healthy individuals (male officials of the Self-defense forces of Japan)	Cross-sectional	Questionnaire: 4-week referent period.	<1, 1-2, 3-4, and ≥5 cups/day	> 40 U/L	≥5 cups/day: 0.61 (0.42 0.88) 3-4 cups/day: 0.69 (0.53 0.90) 1-2 cups/day: (0.62, 1.03) 0 cups: 1 (reference) N= 415 with elevated ALT: Not significant N= 6898 without elevated ALT: P trend = 0.0001
2006	Klatsky et. Al	N: 125,580	General population (specifically without liver disease)	Cross sectional: data from Northern California comprehensive health care program from 1978 1985	Questionnaire: past year intake	<1, 1-3, ≥4 cups/day	M: >52 U/L W: >31 U/L	<1 cup: 1.0 (0.9-1.1) 1-3 cups: 0.8 (0.8 -0.9) ≥4 cups/day: 0.6(0.6-0.7); P<0.001
2015	Dickson et. Al	N: 1005	Multi-ethnic and non-diabetic individuals from four U.S. geographic areas: San Antonio TX, San Luis Valley CO, Oakland and Los Angeles CA	Cross sectional: data from the Insulin Resistance Atherosclerosis Study (IRAS)	Food frequency questionnaire: eight 24hr recalls on randomly selected days over a 1-year period. Caffeinated vs. decaffeinated coffee assessed individually.	Frequency: 9-category scale ranging from none or < 1/ month, >6 times/day. Quantity: small, medium, or large. Integration: weighted intake frequency by a factor of 0.5, 1 or 1.5 for reported portion size of small, medium or large, respectively.	Fasting serum ALT; (no specific upper limit)	Caffeinated: (β = −0.07, p = 0.0177) Not significant for decaffeinated coffee.

2010	Ikeda et. Al	N: 12,020 Age: 49 - 76years	Healthy Japanese Individuals	Cross-sectional: data from the Kyushu University Fukuoka Cohort study	Questionnaire: weekly or daily intake	null consumption, and < 1, 1–3, or ≥ 4 cups per day	M: > 40U/L W:>30U/L	<u>Men: (P trend = 0.0003)</u> ≥4 cups/day: 0.66 (0.46, 0.95) 1- 3 cups/day: 0.59 (0.45, 0.77) <1 cups/day: 0.83 (0.63, 1.09) 0 cups/day: 1 (reference) <u>Women: (P trend= 0.12)</u> ≥4 cups/day: 0.70 (0.48, 1.00) 1- 3 cups/day: 0.85 (0.67, 1.08) <1 cups/day: 0.81 (0.62, 1.05) 0 cups/day 1 (reference) <u>Serum ALT levels</u>: Men: p<0.0001 Women: p=0.0003 Subjects **with normal ALT**: Men: p<0.0001 Women: p= 0.03 Subjects **with an elevated ALT**: not significant
1998	Tanaka et. al	N:12,687 Age: 40- 69 years	General population of Nagano, Japan	Cross sectional; data from Chubu Institute of Public Health Medicine	Questionnaire	Cups/day	>40 U/L	<u>ALT serum concentrations</u>: Men: P=0.003 Women: Not significant
1997	Meltzer & Everhart	N:2999 Age range: 20-74 years	Mexican American population of the southwestern U.S.	Cross sectional; data from the Hispanic Health and Nutrition Examination Survey (HHANES)	Survey	rarely,7-14, or ≥15 cups/week.	> 43 U/L	Non-significant association
1993	Casiglia et. al	N: 2240 Age: >65 years	General population of Italy	Retrospective cohort study: 7 year follow-up	Not specified	Class 1: <3 cups/day Class 2: ≥3cups/day	>55 U/L	≥ 3cups/day vs. <3cups/day: Regression coefficient= - 1.331, p=0.0001
2014	Patrizia Carrieri et. Al	N: 990 (1684 Visits) Median [IQR] age: 45 [42–48] years	HIV-HCV co-infected individual in France	Retrospective cohort: median (IQR) duration of follow-up: 40 [34-49] months.	Questionnaire during the follow-up period (October 2006 - June 2008); Visits scheduled every 6 months for cirrhotic patients and every year for non-cirrhotic patients. Coffee consumption: 6 months prior to the visit.	never, occasionally, 1, 2, or > 2 cups/day (1 cup = 150–200 ml). Elevated consumption: ≥ 3 cups of coffee/day at a given visit.	>2.5 times the upper normal limit (65 U/L)	≥3 cups of coffee/day: 0.65 (0.44–0.97) P=0.04
2013	Sasaki et. Al	N:376	Individuals with chronic HCV infection	Hospital based prospective cohort 12 month duration of follow-up	Questionnaire at time of recruitment: follow-up surveys for 12 months at 1-3 month intervals. Separate analysis: baseline normal vs. elevated serum ALT levels	Frequency of consumption: daily, weekly, monthly, or no consumption Brewing method: filtered/unfiltered/decaffeinated	>45 U/L	<u>Normal baseline ALT (N=229): 12 months</u> OR of maintaining normal ALT levels (≥1 cup/day coffee intake): Caffeinated: 2.74 (1.0, 7.54) P trend= 0.037. Decaffeinated: 0.26 (0.06-1.15) P trend=0.076 <u>Baseline elevated serum ALT levels (N=147):12 months</u> OR of ALT reduction (≥1 cup/day): Reductions ≥10U/L: N=61 1.80 (0.64, 5.05); P trend = 0.215 Reductions ≥20U/L: N=39 3.79 (1.07,13.47); P trend = 0.034 Reductions ≥30U/L: N=39 21.68 (1.69, 278.63); P trend = 0.010 Decaffeinated coffee: not significant

1.0]) in U.S. individuals who are at risk for liver injury.[9] Xiao *et. al* and Dickson *et. al* also showed a decreased risk of elevated serum ALT with increasing coffee intake in nationally representative U.S. populations (OR $_{>3cups\ vs.\ none}$ [95% CI]: 0.75[0.63-0.89] and p=0.017, respectively). [8,11] In addition, the caffeine component of coffee was analyzed separately in these investigations. Xiao *et. al* reported that both caffeinated and decaffeinated coffee are related to a lower risk of elevated serum ALT levels (p trend =0.0002 & 0.002, respectively). Dickson *et. al* observed an inverse relation between caffeinated coffee and serum ALT levels, but demonstrated no significant associations of decaffeinated coffee with serum ALT.[11]

Honjo *et. al* and Ikeda *et. al* investigated the relation between coffee and serum ALT in large Japanese populations; Honjo *et. al* includes only men in their study.[10,12] Analyses within these studies include three categories of participants: 1) all participants; 2) participants with an elevated ALT; and 3) participants without an elevated ALT. For all participants, Honjo *et. al* observed a decreased risk of elevated ALT with increasing levels of coffee intake (OR $_{\geq5\ cups\ vs.\ none}$ [95% CI]: 0.61[0.42-0.88]).[10] For participants without an elevated ALT, an inverse association of serum ALT with coffee consumption was found (p = 0.0001).[10] For participants with an elevated serum ALT, there was no trend towards an inverse relationship between coffee consumption and ALT levels.[10] Ikeda *et. al* showed an inverse association between coffee consumption and elevated serum ALT for men in the 'all participants' group but reports no statistically significant relation for women.[12] This study also reported progressively lower serum ALT activity with increasing coffee intake among both sexes (M: p<0.001 & F: p =0.0003), and for participants with a normal ALT (M: p<0.001 & F: p=0.03)[12]. Tanaka *et. al* also found a difference among genders, reporting an inverse association between coffee and serum ALT levels for men (p=0.003), but not for women.[21] Participants with an elevated serum ALT demonstrated no inverse association of coffee with serum ALT levels.[12] Finally, Meltzer and Everhart observe no significant relation between coffee consumption and serum ALT in a Mexican American population.[13]

Cohort studies:

In a forty-month retrospective study, Patrizia Carrieri *et. al* examined coffee's association with ALT in an HIV-HCV co-infected population. They reported a reduced risk of elevated ALT levels with higher coffee consumption (OR $_{\geq3cups\ vs.\ none}$ [95% CI]: 0.65[0.44-0.97]).[14] Casiglia et. al also conducted a retrospective cohort study with a longer follow up time of seven years.[17] They also found an inverse relation between coffee consumption and serum ALT levels (p=0.0001).[17]

In a twelve-month prospective cohort study, Sasaki *et. al* analyzed the effects of coffee on serum ALT levels in individuals with chronic HCV infection.[15] They concluded that study participants with a normal baseline ALT are more likely to maintain normal serum ALT levels with daily coffee intake (OR $_{\geq1cup\ vs.\ none}$ [95% CI]: 2.74[1.0-7.54]).[15] Decaffeinated coffee drinkers showed an opposite effect with decreased ORs of maintaining normal ALT levels during follow-up (OR $_{\geq1cup\ vs.\ none}$ [95% CI]: 0.26[0.06-1.15]) [15] Also, study participants with baseline-elevated serum ALT were more likely to show

reductions in serum levels of ALT with daily coffee consumption (OR for ALT reductions ≥20 U/L ₌₁cup vs. none [95% CI]: 3.79[1.07-13.74]).[15] Another prospective cohort study of a Japanese population by Nakanashi *et. al* also reported an inverse association between coffee consumption and the incidence of elevated serum ALT (p = 0.019 for ALT ≥40 U/L).[16]

Randomized controlled studies:

Urgert *et. al* conducted a randomized controlled study, which enrolled healthy individuals (N=14). The experimental group consumed a coffee beverage containing 8 grams of fine ground, unfiltered coffee for 21 days, while the control group did not consume coffee.[19] Those consuming coffee grounds showed a mean increase in serum ALT levels (18 U/L) in comparison to the control group (p=0.02).[19] As a follow up study, Urgert et. al conducted another randomized controlled study in which healthy individuals consumed 5-6 cups/day of unfiltered or filtered coffee for six months. The results of this investigation showed a plasma ALT rise at 24 weeks in those consuming unfiltered coffee (p=0.007). The results for filtered coffee were not statistically analyzed, but appear to have caused no change or a decrease in serum ALT at 24 weeks.[20] A recent randomized controlled study by Onuegbu *et. al* investigated the effects of coffee on serum ALT levels in healthy Nigerian individuals (N=30). Participants of the study consumed a coffee beverage containing 2 grams of coffee daily for 30 days. In comparison to baseline values of ALT for each subject prior to coffee consumption, ALT levels rose significantly (p<0.001).[18]

DISCUSSION

Analysis of the epidemiological data of observational studies collectively reveals a strong association between coffee consumption and serum ALT levels. In summary, eleven observation studies report an inverse association between coffee intake and elevated serum ALT and/or serum ALT levels, while one observes no significant association. Three randomized controlled studies support an entirely opposite effect between coffee and serum ALT levels.

Interestingly, there are variances amidst findings of decaffeinated vs. caffeinated coffee's association with serum ALT levels. One cross-sectional analysis revealed a lower risk of elevated serum ALT with both caffeinated and decaffeinated coffee;[8] while another demonstrated no significant relation particularly with decaffeinated coffee. Further, a follow-up cohort study reported that decaffeinated coffee is associated with a decreased likelihood of maintaining normal ALT levels or reducing serum ALT levels over time.[12] These conclusions suggest that although caffeine may be a participant in the protective interaction between coffee and liver injury, as described by several studies,[5,8,9] it is likely that there are other components of coffee that contribute to the overall mechanism of defense. In addition this point, a slightly opposing hypothesis may be that caffeine is the significant player in hepatoprotection, and necessary to some extent in order for coffee's protective effects to be manifest in the liver.[5]

Polyphenols are also a proposed contributor to coffee's hepatoprotective mechanism.[5,8,14] Carrieri *et. al* evaluates the effects of chocolate consumption on serum ALT levels, as coffee and chocolate contain a similar class of polyphenols[14]. Parallel to the outcomes of coffee intake, this study reported an inverse relation between chocolate and elevated ALT.[14] The conclusions here substantiate the possibility that polyphenols are entwined in the mechanisms of coffee's protection against liver inflammation.[8,14] Nonetheless, it is important to note that in addition polyphenols, chocolate also contains small amounts of caffeine,[1] which may have influenced this outcome.

Another significant observation is the result of coffee intake on serum ALT in subjects with elevated baseline ALT levels, and thus some degree of liver damage. Two observational studies separately analyze elevated ALT baseline groups, and show no significant relation between coffee and a decreased risk of elevated serum ALT.[10,12] These findings may suggest that coffee elicits a more effective defensive mechanism in earlier stages of liver injury. This notion is also supported by observations that coffee is hepatoprotective in populations that are at risk for liver injury, and are thus in the premature or initial stages of liver inflammation.[9,14,15] Seemingly contrary to these suggestions, a 12-month prospective cohort study finds that subjects with elevated baseline ALT levels are more likely to have reduction in ALT levels with daily coffee intake.[15] The findings here imply that coffee may be involved in amelioration of liver inflammation over longer periods of time. Gender differences also appear to affect the outcome of coffee intake and serum ALT levels.[12] Weaker associations are evident among women, with two observational study reporting an absence of a statistically significant association between coffee consumption and elevated or serum ALT levels in women.[12]

Notably, randomized controlled studies reported an opposite effect, in which coffee raises the serum ALT levels.[18,19] Upon coffee consumption for about one month, study subjects demonstrated a significant rise in serum ALT levels compared to their baseline levels or to the control group.[18] In the study by Onuegbu *et. al*, the participants consumed a coffee beverage containing only 2 grams of coffee grounds. This may have been an inappropriate experimental dose, as most coffee beverages are prepared with approximately 8 grams or more of coffee grounds per cup.[19] Additionally, unfiltered coffee was used in the first experimental study by Urgert *et. al.* Unfiltered coffee contains the diterpenes cafestol and kahweol in oil droplets, which have been shown to elevate serum ALT and may have contributed to the observed rise in serum ALT.[19] However, the effects of the oil droplets in coffee may not be the driving cause of this ALT elevation, as participants of the observational studies who did not exhibit such elevations may have also consumed unfiltered coffee. Finally, in the six-month experimental study by Urgert et. al, both filtered and unfiltered coffee were considered. There was a plasma ALT rise at the 24-week mark for unfiltered coffee; the results for filtered coffee were not statistically analyzed, but there appears to be a slight decrease in serum ALT at the 24-week mark. These experimental studies may be indicative of the acute effects of coffee on the liver. It may be that long-term, habitual coffee consumption is related to protective effects, while short-term consumption is associated with mildly detrimental outcomes.

CONCLUSION

Ultimately, a strong association between coffee intake and a lower risk of elevated serum ALT levels is supported by observational investigations. Limitations of observational studies include an ill-defined dosage of coffee, inaccuracies associated with self-administered surveys or interviews, and bias in retrospective analysis. Randomized controlled studies demonstrated opposing outcomes, reporting a rise in ALT with coffee consumption. It appears that this may be due to the differences in short-term vs. long-term effects of coffee, experimental study designs, or the diterpene content of unfiltered coffee. If future research is conducted involving serum liver enzymes and coffee intake, current areas of discrepancy should be addressed, including the implications of caffeinated vs. decaffeinated coffee, differences amongst gender response to coffee and liver protection, coffee's effect on individuals presenting with baseline liver inflammation, short-term vs. long term effects of coffee intake, and possible contributors to coffee's hepatoprotective effect.

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2000	Nakanishi et. Al	N: 1221 Age range: 35-56 years	Healthy (specifically no history of liver disease) male Japanese office workers	Prospective cohort study	Interviews; Mean observation period: 3.7 years (SD ±0.2 years); Mean number of ALT measurements: 4.8	None, 1-2 cups/day, and ≥ 3 cups/day	Stratified as: ≥40 U/L, ≥50 U/L, ≥60 U/L	Inverse association: ALT ≥40 IU/L (p=0.019), ≥50 IU/L (p=0.002), ≥60 IU/L (p=0.007).
2011	Onuegbu et. Al	N: 30 Mean age: 23.6 years SD ± 2.0 years	Healthy Nigerian individuals	Randomized controlled study	Study participants consumed brewed coffee daily x 30days	2g/day x30days	ALT (U/L) 30 days after coffee consumption	Compared to baseline: increased plasma ALT (p<0.001)
1995	Urgert et. Al	Study 1: N=14 Study 2: N=15	Healthy individuals mostly lean, young, and nonsmoking who consumed no or only moderate amounts of coffee and alcohol	Study 1: randomized controlled parallel to study the effect of fine grounds Study 2: crossover to study particle size (fine or coarse grounds)	Coffee brews were prepared with the following types of grounds: coarse, fine, very fine, or powdery grounds. Study 1: Participants consumed fine coffee grounds x 21 days Study 2: Participants were randomly assigned two groups, and either consumed fine or coarse grounds x11 days	Study 1: 8g/day x21 days Study 2: 6.6g fine grounds or 7.1g course grounds x11days	53.5 U/L	Study 1: Consuming coffee grounds (n=7): mean rise of 18 U/L ALT (95% CI 4-32 U/L) in comparison to the control group (n=7).(P = 0.02). Study 2: Fine grounds consumption: 29 U/L ALT Coarse grounds consumption: 21 U/L (P value for the difference = 0.02)
1996	Urgert et. Al	N: 46 Age: 19-69 years	Healthy	Randomized controlled study	Trial from October 1994 – July 1995: 4 week run in period, 24 weeks of treatment, and 12 week follow up. Subjects brewed coffee at home according to provided instructions	Group 1: cafetiere coffee; 5-6 cups/day x6 months Group 2: filtered coffee; 5-6 cups/day x 6months	54 U/L	Group 1: Plasma ALT rise at 24 weeks: 9U/L (95% CI 3-15U/L, P=0.007) Group 2: Not analyzed; appears to be no marked trend/evolution