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Review Article

Coffee Drinking and the Human Heart: Cardio-Supportive Effects of Accustomed Coffee-Consumption

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Abstract

Coffee, second only to water, is the most consumed beverage among adults. It is also the primary source of dietary caffeine, having a high antioxidant content. Numerous bioactive compounds are present in coffee. Regular coffee consumption is associated with multiple health benefits, such as reducing the risk of type 2 diabetes mellitus, cancer, neurogenerative disorders, hepatic diseases, and cardiovascular diseases.

Various extensive epidemiological studies have shown that regular coffee consumption reduces mortality risks for all-cause and cardiovascular events. Contrarily, habitual consumption of coffee can lead to tolerance to caffeine and desensitize adenosine receptors responsible for the lack of pressor effects in these individuals.

Coffee's adverse effects are linked to its diterpenes, cafestol, and kahweol, which are in high proportions—especially in unfiltered and boiled coffee—causing an elevation in serum and low-density lipoprotein cholesterol levels and increasing the risk of coronary heart disease. However, in filtered and instant coffee, the diterpenes are significantly less. Diterpenes demonstrate hepatoprotective benefits by exerting an antioxidant effect and decreasing the expression of inflammatory markers.

Coffee, when consumed excessively, can have adverse effects, while the benefits of coffee are not evident at a low consumption. Thus, a moderate 3–4 cups per day are recommended to receive optimal advantages—especially cardio-supportive effects. Furthermore, moderate consumption in people with a history of heart failure does not undermine health.

This review aims to update the reader on recent research regarding the health benefits of chronic coffee intake and its cardio-supportive effects at dietary doses.

Keywords: *Antioxidant; Cancer; Caffeine; Cardiovascular; Neurodegenerative; Nonalcoholic Fatty Liver Disease; Parkinson's Disease; Type 2 Diabetes Mellitus*

Abbreviations

AD: Alzheimer's Disease; ARIC: Atherosclerosis Risk in Communities; BP: Blood Pressure; CGA: Chlorogenic Acid; CHD: Coronary Heart Disease; CHS: Cardiovascular Heart Study; EPIC: European Prospective Investigation of Cancer and Nutrition; FHS: Framingham Heart Study; HF: Heart Failure; NAFLD: Nonalcoholic Fatty Liver Disease; OTA: Ochratoxin A; PD: Parkinson's Disease; T2DM: Type 2 Diabetes Mellitus

Introduction

Coffee is one of the most widely consumed beverages throughout time by numerous cultures around the world. Approximately 9.997 billion kilograms of coffee were consumed in 2020, slightly higher than the preceding year [1]. The history of coffee consumption begins with the discovery of coffee beans in Africa or the Middle East. However, the cultivation of coffee began in Ethiopia and soon was eclipsed by Yemen.

Initially, coffee beans were eaten, evolving into a snack made by grinding and mixing with fatty pastes. By the 10th century, coffee infusions with boiling water became common practice [2]. By the 14th century, the roasting process of coffee was utilized, leading to its rapid expansion in the Arab world, eventually making its way to Spain, North Africa, India, Turkey, and the Balkans [2].

The first recorded use of coffee as medicine was documented by Rhazes in Persia, suggesting that this beverage "'removes skin' and is very good for the stomach" [3]. Ancient Chinese and Japanese medicine practitioners believed that coffee could regulate the liver, purge the gallbladder to prevent the formation of gallstones, and alleviate gastrointestinal discomforts. Coffee was also used to "warm" the blood circulation, open the orifices of the heart, and act as a detoxifier in these traditional medicinal systems [4].

Despite published research suggesting possible health benefits (and risks) of habitual coffee consumption at dietary doses, there are relatively few reliable, evidence-based studies decidedly confirming such suggestions. The current health implications of regular coffee consumption are derived primarily from epidemiological studies with longitudinal or cross-sectional relationships—with a self-reported coffee intake that poses a significant challenge in precisely determining biological significance in the real world [5]. Furthermore, heterogeneity between study designs and population, as well as many unaccounted factors, can confound these findings [6].

Coffee's antioxidant quantity and quality

A study by Moura-Nunes., *et al.* (2009) on 10 subjects—3 men and 7 women aged (25–27)—at the Universidade Federal do Rio de Janeiro, Brazil, reported that the total antioxidant parameter (that traps radicals) and the antioxidant power-reducing ferric ions of plasma were significantly higher ($p < 0.05$) with judicious ingestion of coffee compared to drinking water [7].

Coffee's antioxidant properties are attributed to specific compounds, such as caffeic, ferulic, n-coumaric, chlorogenic acid (CGA), caffeine, and trigonelline (Figure 1). Additionally, compounds—such as melanoidins, phenylalanine, and other heterocyclic compounds—exhibit vigorous antioxidant activities. (However, these antioxidant actions are predominantly detected in roasted coffee [8]). Thus, coffee consumption can prevent or reduce damage to cell components, DNA, lipids, and proteins that otherwise can lead to various degenerative diseases caused primarily by oxidative stress [5]. Figure 1 depicts the specific chemicals found in coffee.

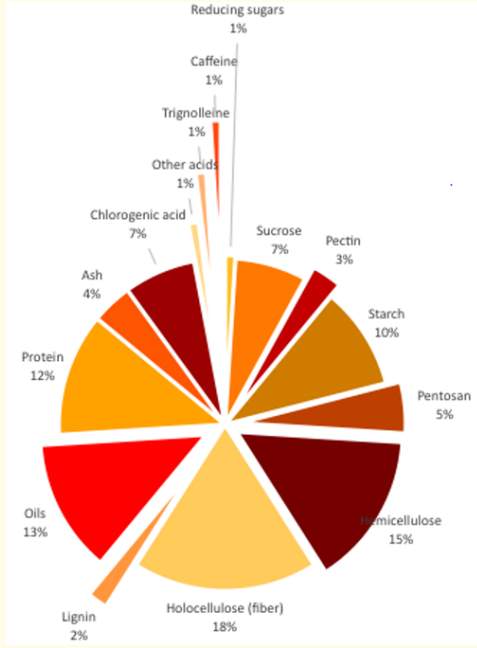

Figure 1: *Chemical composition of coffee.*

Regular coffee consumption is purported to be beneficial in specific disorders and conditions, as follows.

Type 2 diabetes mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a prevalent, chronic condition, requiring investigations for new pharmacological and non-pharmacological approaches to its treatment. Specific studies have shown a strong, positive association between T2DM and coffee consumption [9]. In a systematic review of the literature, 8 studies with 247 subjects were evaluated by Reis., *et al.* (2019) to determine changes in glucose metabolism due to regular coffee consumption [10]. Although coffee intake may hinder the glucose response acutely (hours), improved glucose metabolism, including insulin response under a longer duration (weeks), was reported.

Furthermore, caffeinated coffee and decaffeinated coffee exert a similar protective effect, lowering T2DM risk [10]. van Dam., *et al.* (2002) recruited 17,111 men and women, finding that the risk of developing T2DM was twice as high in those who consumed 2 cups or less of coffee daily versus those who drank 7 cups of coffee daily at a minimum [11].

It is noteworthy that this "Hoorn study" by van Dam., *et al.* (2002) reported that regular coffee drinkers build a tolerance to caffeine and, consequently, to coffee's effects on insulin sensitivity and glucose tolerance [12]. With the paucity of literature evaluating the effects of regular coffee intake for more than 24 hours, it seems premature to be excessively optimistic about the role of coffee in preventing T2DM [13].

Cardiovascular health

Initially, coffee was considered a contributing risk factor for the pathogenesis of various cardiovascular diseases, based on a few dubious studies. However, recent publications have indicated that the content of diterpenes is relatively high in unfiltered and boiled coffee, which can cause a reversible elevation in serum and low-density lipoprotein cholesterol levels. Moreover, the general consumption of boiled and unfiltered coffee has been on the decline. The more common, filtered, and instant coffee contains much fewer diterpenes [5,14].

An acute increase in systolic (5–15 mm Hg) and diastolic (5–10 mm Hg) blood pressure (BP) was observed in both men and women after administering a dose of caffeine equivalent to the average amount ingested by a habitual coffee drinker every day [15]. Adenosine is a potent endogenous neuromodulator structurally similar to the caffeine molecule. Caffeine can occupy the adenosine receptor (A_1 and A_{2a}) to elicit a stimulatory effect by antagonizing the inhibitory effects of adenosine [16]. However, this slight increase in BP occurs in individuals naive to caffeine, whereas habitual coffee drinkers do not show a significant change in their BP levels [17]. Regular coffee drinkers (at 3–6 cups per day) show no BP change [17], and 2–3 cups per day results in tolerance of caffeine molecules [18].

The lack of pressor effects in habitual coffee consumers is due to this reversible tolerance [16]. A single-blind study by Smits., *et al.* (1985) evaluated normotensive individuals consuming 2 cups of regular or decaffeinated coffee. A minor increase in diastolic BP was found in the decaffeinated coffee group versus the regular coffee group, suggesting that the cardiovascular effects of drinking coffee are due, at least in part, to its caffeine content [19].

Coronary heart disease (CHD) generally shows no positive effects with habitual coffee intake. Nevertheless, a landmark meta-analysis of 21 prospective cohort studies from January 1966 to January 2008 concluded that coffee consumption might decrease the long-term risk of CHD with moderate coffee consumption (> 1 cup/day in the US or ≥ 2 cups/day in Europe) with a relative risk of 0.87 ($p = 0.001$) compared to light consumption (< 1 cup/day in the US or ≤ 2 cups/day in Europe) [20].

A multicenter prospective cohort study by Gunter., *et al.* (2017) named the European Prospective Investigation of Cancer and Nutrition (EPIC) enrolled 521,330 men and women from 10 countries with a mean follow-up of 16.4 years showed a lower risk of cardiovascular mortality with regular coffee consumption [21].

A California, USA study by Klatsky., *et al.* (2011) assessed the correlation between coffee drinking and the risk of developing cardiac arrhythmia in 130,054 adults. Long-term follow-up (17.6 months) found an inverse relationship between regular coffee consumption and the risk of hospitalization due to arrhythmia. Furthermore, those participants who consumed at least 4 cups of coffee a day were less

likely to have an arrhythmic episode and atrial fibrillation [14].

The American Heart Association recently presented its analysis of three dietary regimes referred to in the Framingham Heart Study (FHS), the Cardiovascular Heart Study (CHS), and the Atherosclerosis Risk in Communities (ARIC) Study to assess the connection of coffee intake with the episodic risk of heart failure (HF). The study employed the selection of machine learning characteristics to analyze risk factors, reporting that higher coffee consumption (excluding decaffeinated coffee drinks) and caffeine intake were linked to a lower risk of HF in all three epidemiological studies [22].

Larsson., *et al.* (2011), in their meta-analysis of 11 prospective cohort studies, summarized that consuming coffee in moderation may have a weak inverse association with the risk of stroke, while the 1–6 cups of coffee per day is significantly inversely associated with the risk of stroke. Also, 3–4 cups of coffee per day showed the greatest (17%) risk reduction, while heavy coffee consumption of 7 cups per day was not significantly associated with stroke risk [23].

Coffee's effect on the liver and gastrointestinal tract

Several studies have indicated that higher coffee consumption is inversely related to the extent of liver fibrosis in patients with nonalcoholic fatty liver disease (NAFLD) [24]. The hepatoprotective effect of coffee on the progression of NAFLD may depend on its form and preparation methods.

Regular filtered coffee is associated with a lower level of fibrosis in NAFLD than espresso coffee, which may be detrimental [24,25]. The preparation method and the roast profile determine the composition of coffee, as filtered coffee is typically free from cafestol and kahweol but retains the CGA distinct from the espresso variant of coffee [25].

Furthermore, espresso is usually considered to have high sucrose (and contains fructose) added. The severity of hepatic fibrosis in nonalcoholic steatohepatitis is related to the consumption of fructose [24]. The underlying mechanism for the hepatoprotective role of coffee is attributed to 3 out of more than 100 compounds, namely caffeine, diterpenes (cafestol and kahweol), and CGA [26].

Caffeine prevents adhesion and activation of the hepatic stellate cells, triggers ß-oxidation through an autophagy-lysosomal pathway, and inhibits the expression of tissue growth factor by modulating signaling pathways that may limit the progression of fibrosis [27]. Similarly, noncaffeine compounds—like CGA and uridine diphosphate glucuronosyltransferase—may be responsible for limiting lipid accumulation in hepatocytes, reducing inflammation, and boosting insulin sensitivity [28]. Conversely, diterpenes might offer hepatoprotective benefits by exerting an antioxidant effect, decreasing the expression of inflammatory markers.

Zhang., *et al.* (2015) demonstrated a positive correlation between coffee consumption and a significantly lower risk of gallstone disease [29]. An observational study by Iriondo-DeHond., *et al.* (2020) reported an increase in the fecal content of *Bacteroides, Prevotellas, and Porphyromonas* in high coffee consumption, indicating an enhanced metabolic status with routine, high-amount coffee consumption.

Other benefits of coffee intake in the gut mucosa include antioxidant, anti-inflammatory, and antiproliferative effects—and the promotility effect on external muscle layers by fiber effects and direct activation of gastrointestinal smooth muscle cells [30].

Coffee's effect on the brain

Coffee, in general, enhances psychoactive responses and can improve cognitive function, alertness, reaction time, focus, and mood. Caffeine is a central nervous system stimulant that can improve long-term memory [31]. A higher caffeine intake was linked with enhanced cognitive performance and psychomotor abilities in a cross-sectional study conducted by Jarvis (1993) [32]. Coffee consumption in a habitual manner has been strongly correlated with a lower risk of neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD).

In people aged 65 and older, coffee consumption can have a neuroprotective effect against dementia and AD, lowering the risk up to 65%. Furthermore, coffee or caffeine intake can diminish the risk of developing PD [31]. These neuroprotective factors do not have a well-defined mechanism; however, caffeine enhances dopamine, antagonizing adenosine receptors (A_{2a}).

Also, the positive impact on PD could be due to alkaloids, such as caffeine and trigonelline, that can act as monoamine oxidase inhibitors [31,33]. However, a more recent study by Lee., *et al.* (2016) has linked this neuroprotective effect against PD and AD to quercetin [34]. Caffeine intake is also linked to lower risks of depression, suicide, and developing multiple sclerosis [17].

Cancer

Coffee supplies a large portion of daily dietary antioxidants, higher than fruit, vegetables, and tea. Compounds, such as CGA, caffeine, and diterpenes, facilitate enzymatic reactions that stimulate intracellular antioxidant defense as well as detoxify carcinogens, an anticarcinogenic response [8].

A review of meta-analyses on coffee consumption and health outcomes by Poole., *et al.* (2017) found that increased coffee consumption lowered the incidence of cancer by 18% (relative risk = 0.82, 95% confidence interval: 0.74 to 0.89) [35]. This study showed that coffee consumption also reduces the risk of other cancers, such as prostate and endometrial, and is unlikely to cause breast cancer, prostate cancer, or pancreatic cancer.

Study	Study Design and Sample Size	Interventional Coffee Consumers Cups/Day	Comparator Coffee Consumers Cups/Day	Effect in the Intervention Group
van Dam., *et al*. [12]	Investigational Study N=17,111	7	2	50% lower risk of developing type 2 diabetes mellitus
Smits., *et al*. [19]	Single-blind study N=12	2 (Regular)	2 (Decaffeinated)	Diastolic blood pressure was significantly higher in the regular coffee consumer group Absolute Difference = 1.8 ± 25% mmHg ($p < 0.05$)
Wu., *et al*. [20]	Meta-analysis N= 5,599	>1 in the US or ≥2 in Europe	<1 in the US or ≤2 in Europe	Long-term risk of coronary heart diseases reduced with relative risk = 0.87 ($p = 0.001$)
Klatsky., *et al*. [14]	Cohort N=11,679	≥4	0, 1, 1-3	Lower risk of arrythmia with hazard ratio = 0.82 (0.73-0.93) ($p < 0.01$)
Larsson., *et al*. [23]	Meta-analysis N=479,689	2	0	The risk of total stroke is lowered as relative risks = 0.83 (95% CI: 0.74=0.92) ($p < 0.05$)

Table 1: *Summary of habitual coffee consumption and health effects.*

Adverse effects of habitual coffee consumption

A large cohort study by Liu., *et al.* (2017) reported that overconsumption of coffee (> 28 cups per week) by people < 55 years increases the chance of premature death by 50% compared to those 55 years and older. Men who consumed more than 28 cups of coffee per week were more at risk (21%) than their non-consuming counterparts [36]. Caffeine intake has been associated with behavior and mood symptoms, such as anxiety and depression.

Moreover, a higher coffee intake can cause reduced appetite, poor dietary habits, sleep disturbances, and feelings of hopelessness [37]. Chronic users of coffee (caffeine) can build dependence, causing withdrawal upon abstinence. It can also aggravate symptoms of premenstrual syndrome and cause panic disorder [38]. High caffeine intake during pregnancy increases the likelihood of miscarriage by up to 80% at dose 200 mg or more per day, being > 4 cups per day, irrespective of pregnancy-related symptoms [41]. The habitual consumption of caffeinated coffee can increase CYP1A2 enzyme activity and possibly interact with drugs, inhibiting their activity—and the metabolism and elimination of caffeine can lead to toxicity [42].

However, the harmful effects of coffee may be related to various commercial manufacturing, packaging, and storage practices. High levels of ash and heavy metals were found in roasted and milled coffees, indicating the presence of impurities in commercially roasted ground coffees. Metallic contamination may be related to pesticides, fertilizers, and waste pollutants from the steel, mining, and cosmetic industries [39]. Mounting concern for heavy coffee drinkers might be linked to lead consumption, adding to disease burden and potential for congenital disorders [40].

A mycotoxin, typically ochratoxin A (OTA), may be present in coffee due to climatic conditions, handling, and exposure to soil. It is produced by *Aspergillus ochraceus* and *Penicillium verrucosum* that bioaccumulate along the food chain and potentially induces renal toxicity, nephropathy, and immunosuppression [41].

Ideal coffee intake for balanced cardio-supportive effects

Overall, however, most studies generally agree that regular (caffeinated) coffee consumption shows less detrimental effects and more health benefits with an average daily consumption of 3–4 cups per day, limiting the caffeine intake to 400 mg per day for normal healthy adults. These amounts are consistent with a review commissioned by Health Canada. Healthy adults can have 400 mg per day of caffeine without adverse effects, such as toxicity, cardiovascular problems, irregular bone status and calcium balance, behavioral changes, and infertility [42].

Further, in children, caffeine intake should be limited to ≤ 300 mg per day [42]. Additional evidence indicates that more than 4 cups per day can increase inflammatory markers and impair thrombosis and fibrinolysis in hypertensive smokers. When coffee is consumed > 9 cups per day, the odds of having premature ventricular complexes are doubled, especially in subjects already prone to cardiac diseases.

A Swedish epidemiological study by Ribeiro., *et al.* (2020) demonstrated an odds ratio of 1.11 for having heart failure in those who consumed coffee at 5 cups per day compared to non-consumers [43]. Furthermore, the researchers concluded that coffee consumption is safe in patients with a history of myocardial infarction without cardiovascular events and all-cause mortality [44]. However, patients prone to CHD must avoid boiled, filtered, and caffeinated coffee as the active compounds therein can contribute to CHD risk [42–44].

Conclusion

Coffee—and the culture surrounding coffee consumption—is an integral and inextricable part of modern society, as habitual coffee consumption is a lifestyle choice for many and its impact on health with regular intake is of particular interest. However, many studies describe protective and harmful effects (resulting in uncertainty), study design flaws, and random errors.

Moreover, there are upwards of 1000 constituents in coffee, of which many are unidentified but could have detrimental effects, while others might possess protective properties. Unless more research studies provide firm evidence regarding the therapeutic effects of regular coffee consumption, coffee's inclusion in prescribed treatment for the prevention of specific conditions, disorders, or diseases remains tentative.

In general, coffee in moderation (3–4 cups per day) can be included in a heart-healthy lifestyle, although the brew selection must be assessed based on individual health status and risk factors. Moderate coffee consumption has shown cardio-supportive effects by reducing the risks of heart failure, coronary heart disease, atrial fibrillation, and arrhythmia.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Global coffee consumption (2021). https://www.statista.com/statistics/292595/global-coffee-consumption/

2. Fredholm BB. "Notes on the history of caffeine use". *Handbook of Experimental Pharmacology* (2011): 1-9. https://www.researchgate.net/publication/46394171_Notes_on_the_History_of_Caffeine_Use

3. Hajar R. "The Air of History (Part IV): Great Muslim Physicians Al Rhazes". *Gulf Heart Association. Address. Gulf Heart Association 14* (2013): 93-95. https://pubmed.ncbi.nlm.nih.gov/23983918/

4. Namba T and Matsuse T. "[A historical study of coffee in Japanese and Asian countries: focusing the medicinal uses in Asian traditional medicines]". *Yakushigaku Zasshi* 37 (2002): 65-75. https://pubmed.ncbi.nlm.nih.gov/12412599/

5. Ludwig IA., *et al*. "Coffee: biochemistry and potential impact on health". *Food and Function* 5 (2014): 1695-1717. https://pubmed.ncbi.nlm.nih.gov/24671262/

6. Pourshahidi LK., *et al*. "A Comprehensive Overview of the Risks and Benefits of Coffee Consumption". *Comprehensive Reviews in Food Science and Food Safety* 15 (2016): 671-684. https://www.researchgate.net/publication/301308535_A_Comprehensive_Overview_of_the_Risks_and_Benefits_of_Coffee_Consumption_Coffee_consumption_and_human_health

7. Moura-Nunes N., *et al*. "The increase in human plasma antioxidant capacity after acute coffee intake is not associated with endogenous non-enzymatic antioxidant components". *International Journal of Food Sciences and Nutrition* 60 (2009): 173-181. https://www.researchgate.net/publication/26808476_The_increase_in_human_plasma_antioxidant_capacity_after_acute_coffee_intake_is_not_associated_with_endogenous_non-enzymatic_antioxidant_components

8. Yashin A., *et al*. "Antioxidant and Antiradical Activity of Coffee". *Antioxidants* 2 (2013): 230-245. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4665516/

9. Carlström M and Larsson SC. "Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis". *Nutrition Reviews* 76 (2018): 395-417. https://pubmed.ncbi.nlm.nih.gov/29590460/

10. Reis H., *et al*. "PD-L1 Expression in Urothelial Carcinoma With Predominant or Pure Variant Histology: Concordance Among 3 Commonly Used and Commercially Available Antibodies". *The American Journal of Surgical Pathology* 43 (2019): 920-927. https://pubmed.ncbi.nlm.nih.gov/31135485/

11. Van Dam RM and Feskens EJ. "Coffee consumption and risk of type 2 diabetes mellitus". *The Lancet* 360 (2002): 1477-1478. https://pubmed.ncbi.nlm.nih.gov/12433517/

12. Van Dam RM., *et al*. "Coffee consumption and incidence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes: the Hoorn Study". *Diabetologia* 47 (2004): 2152-2159. https://pubmed.ncbi.nlm.nih.gov/15662556/

13. Teas, Cocoa and Coffee: Plant Secondary Metabolites and Health (2021). https://www.wiley.com/en-us/Teas%2C+Cocoa+and+Coffee%3A+Plant+Secondary+Metabolites+and+Health-p-9781444334418

14. Klatsky AL., *et al*. "Coffee, caffeine, and risk of hospitalization for arrhythmias". *The Permanente Journal* 15 (2011): 19-25. https://pubmed.ncbi.nlm.nih.gov/22058665/

15. James JE. "Is habitual caffeine use a preventable cardiovascular risk factor?" *The Lancet* 349 (1997): 279-281. https://pubmed.ncbi.nlm.nih.gov/9014929/

16. James JE. "Critical review of dietary caffeine and blood pressure: a relationship that should be taken more seriously". *Psychosomatic Medicine* 66 (2004): 63-71. https://pubmed.ncbi.nlm.nih.gov/14747639/

17. O'Keefe JH., *et al*. "Coffee for Cardioprotection and Longevity". *Progress in Cardiovascular Diseases* 61 (2018): 38-42. https://pubmed.ncbi.nlm.nih.gov/29474816/

18. Surma S and Oparil S. "Coffee and Arterial Hypertension". *Current Hypertension Reports* 23 (2021): 38. https://pubmed.ncbi.nlm.nih.gov/34370111/

19. Smits P., *et al*. "The cardiovascular effects of regular and decaffeinated coffee". *British Journal of Clinical Pharmacology* 19 (1985): 852-854. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1463879/

20. Wu J., *et al*. "Coffee consumption and risk of coronary heart diseases: a meta-analysis of 21 prospective cohort studies". *International Journal of Cardiology* 137 (2009): 216-225. https://pubmed.ncbi.nlm.nih.gov/18707777/

21. Gunter MJ., *et al*. "Coffee Drinking and Mortality in 10 European Countries: A Multinational Cohort Study". *Annals of Internal Medicine* 167 (2017): 236-247. https://pubmed.ncbi.nlm.nih.gov/28693038/

22. Stevens LM., *et al*. "Association Between Coffee Intake and Incident Heart Failure Risk". *Circulation: Heart Failure American Heart Association* 14 (2021): e006799. https://pubmed.ncbi.nlm.nih.gov/33557575/

23. Larsson SC and Orsini N. "Coffee Consumption and Risk of Stroke: A Dose-Response Meta-Analysis of Prospective Studies". *American Journal of Epidemiology* 174 (2011): 993-1001. https://pubmed.ncbi.nlm.nih.gov/21920945/

24. Anty R., *et al*. "Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery". *The Journal of Hepatology* 57 (2012): 1090-1096. https://pubmed.ncbi.nlm.nih.gov/22820478/

25. Saab S., *et al*. "Impact of coffee on liver diseases: a systematic review". *Liver international: official journal of the International Association for the Study of the Liver* 34 (2014): 495-504. https://pubmed.ncbi.nlm.nih.gov/24102757/

26. Zhou A and Hyppönen E. "Long-term coffee consumption, caffeine metabolism genetics, and risk of cardiovascular disease: a prospective analysis of up to 347,077 individuals and 8368 cases". *The American Journal of Clinical Nutrition* 109 (2019): 509-516. https://pubmed.ncbi.nlm.nih.gov/30838377/

27. Temple JL., *et al*. "The Safety of Ingested Caffeine: A Comprehensive Review". *Frontiers in Psychiatry* 8 (2017): 80. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5445139/

28. Wijarnpreecha K., *et al*. "Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis". *European Journal of Gastroenterology and Hepatology* 29 (2017): e8-12. https://pubmed.ncbi.nlm.nih.gov/27824642/

29. Zhang Y-P., *et al*. "Systematic review with meta-analysis: coffee consumption and the risk of gallstone disease". *Alimentary Pharmacology and Therapeutics* 42 (2015): 637-648. https://pubmed.ncbi.nlm.nih.gov/26198295/

30. Iriondo-DeHond A., *et al*. "Effects of Coffee and Its Components on the Gastrointestinal Tract and the Brain-Gut Axis". *Nutrients* 13 (2020): E88. https://pubmed.ncbi.nlm.nih.gov/33383958/

31. Lire Wachamo H. "Review on Health Benefit and Risk of Coffee Consumption". *Medicinal and Aromatic Plants* (2017). https://www.longdom.org/open-access/review-on-health-benefit-and-risk-of-coffee-consumption-2155-9821-1000301.pdf

32. Jarvis MJ. "Does caffeine intake enhance absolute levels of cognitive performance?" *Psychopharmacology* 110 (1993): 45-52. https://pubmed.ncbi.nlm.nih.gov/7870897/

33. Mathew B., *et al*. "Emerging therapeutic potentials of dual-acting MAO and AChE inhibitors in Alzheimer's and Parkinson's diseases". *Archiv der Pharmazie* 352 (2019): e1900177. https://pubmed.ncbi.nlm.nih.gov/31478569/

34. Lee M., *et al*. "Quercetin, not caffeine, is a major neuroprotective component in coffee". *Neurobiol Aging* 46 (2016): 113-123. https://www.researchgate.net/publication/304814728_Quercetin_not_caffeine_is_a_major_neuroprotective_component_in_coffee

35. Poole R., *et al*. "Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes". *British Medical Journal* 359 (2017): j5024. https://www.bmj.com/content/359/bmj.j5024

36. Liu J., *et al*. "Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality". *Mayo Clinic Proceedings* 88 (2013): 1066-1074. https://pubmed.ncbi.nlm.nih.gov/23953850/

37. Bertasi RAO., *et al*. "Caffeine Intake and Mental Health in College Students". *Cureus* 13 (2020): e14313. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8099008/

38. Clementz GL and Dailey JW. "Psychotropic effects of caffeine". *American Family Physician* 37 (1988): 167-172. https://pubmed.ncbi.nlm.nih.gov/3284301/

39. Pigozzi MT., *et al*. "Quality of Commercial Coffees: Heavy Metal and Ash Contents". *Journal of Food Quality Hindawi* (2018): e5908463. https://www.hindawi.com/journals/jfq/2018/5908463/

40. Nędzarek A., *et al*. "Concentrations of heavy metals (Mn, Co, Ni, Cr, Ag, Pb) in coffee". *Acta Biochimica Polonica* (2013): 60. https://pubmed.ncbi.nlm.nih.gov/24340307/

41. Toschi TG., *et al*. "Coffee silverskin: characterization, possible uses, and safety aspects". *Journal of Agricultural and Food Chemistry* 62 (2014): 10836-10844. https://pubs.acs.org/doi/10.1021/jf503200z

42. Nawrot P., *et al*. "Effects of caffeine on human health". *Food Additives and Contaminants* 20 (2003): 1-30. https://pubmed.ncbi.nlm.nih.gov/12519715/

43. Ribeiro EM., et al. "Safety of coffee consumption after myocardial infarction: A systematic review andmeta-analysis". *Nutrition, Metabolism and Cardiovascular Diseases* 30 (2020): 2146-2158. https://pubmed.ncbi.nlm.nih.gov/33158718/

44. Cornelis MC and El-Sohemy A. "Coffee, caffeine, and coronary heart disease". *Current Opinion in Clinical Nutrition and Metabolic Care* 10 (2007): 745-751. https://pubmed.ncbi.nlm.nih.gov/17218826/

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