Coffee: Health Effects

R Tofalo, University of Teramo, Mosciano Sant'Angelo (TE), Italy
G Renda and R De Caterina, G. d'Annunzio University of Chieti, Chieti, Italy
G Suzzi, University of Teramo, Mosciano Sant'Angelo (TE), Italy

Introduction

Beverages are an important component of our diet. Coffee occupies an important place among beverages, since it holds the second position in consumption after water. On average, people consume 500 billion cups of coffee annually, with a global production of 8 million tons per year. The major consumers are the United States, Brazil, Europe, and Japan.

Coffee (*Coffea* L.) is considered as a valuable and enjoyable beverage, and often, it is consumed due to its stimulatory effects, mainly related to the presence of caffeine (1,3,7-trimethylxanthine): generally, 240 ml of instant coffee contains approximately 100 mg of caffeine. Caffeine content can be, however, influenced by the different technologies used. For instance, green bean dewaxing and wet processing can reduce its content, which remains in the range of 0.65–2.30%.

In addition to caffeine, coffee contains more than a thousand different chemicals, including carbohydrates, lipids, nitrogenous compounds, vitamins, minerals, alkaloids, and phenolic compounds. Some of them, such as trigonelline, nicotinic acid, chlorogenic acid (5-*O*-caffeoylquinic acid, CQA), melanoidins, and diterpenes (cafestol and kahweol), together with caffeine feature relevant nutritional or functional properties.

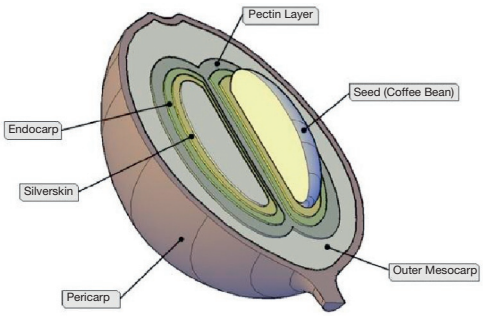
The coffee fruit (also called berry or cherry) is an oval drupe of about 10 mm in size. Coffee beans present an outer skin called pericarp, which is green in unripe and red-violet, deep red, yellow, or orange, depending on the cultivar, in ripe fruits. The pericarp covers the mesocarp (the soft yellowish, fibrous, and sweet pulp), a pectin adhesive layer, which is a highly hydrated layer of mucilage, and the endocarp, called the parchment (Figure 1). Finally, a silverskin covers each hemisphere of the coffee bean (endosperm).

Many factors influence coffee quality, among which the action of microorganisms. Microbial metabolites produced during coffee fermentation can diffuse into the grains and influence the beverage's final quality. There are different kinds of coffee beverages, characterized by different nuances in terms of body, aroma, acidity, and astringency.

Coffee is a complex array of biologically active components that can influence many metabolic processes. The main components are alkaloids (caffeine and trigonelline), phenolic compounds (chlorogenic acids), and diterpenes (cafestol and kahweol) (Table 1).

The main mechanism of action of caffeine is to antagonize adenosine receptors (with its A1 and A2A subtypes); a secondary effect is the inhibition of phosphodiesterases, with the subsequent accumulation of cyclic adenosine monophosphate and an intensification of the effects of catecholamines. Coffee is metabolized in the liver by enzymes known as cytochrome P450 1A2 (CYP1A2). Caffeine effects translate, in most people, in a psychoactive response, which includes increased alertness and attention, through the stimulation of the central nervous system, and in a complex cardiovascular response, mainly consisting of an acute increase in blood pressure. Some benefits related to its consumption include mood enhancement, better exercise performance, and shorter reaction times. Caffeine also produces negative effects, such as sleeplessness, anxiety, restlessness, tension, nervousness, palpitations, tremulousness, and psychomotor agitation. Moreover, the risk of rheumatoid arthritis and osteoporosis increases when coffee is consumed on a regular basis. Some other negative effects can arise strictly related to some special risk groups: for such subjects, a reduced consumption of coffee is recommended (Table 2).

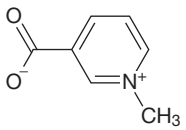
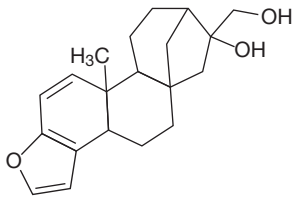
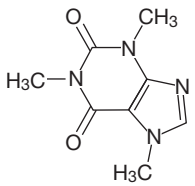
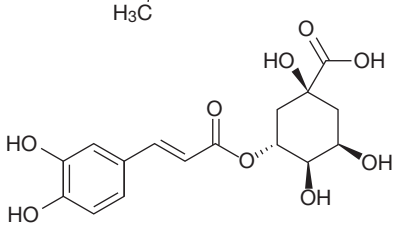
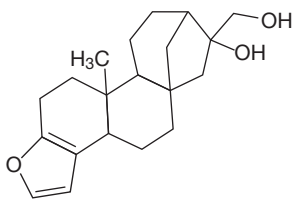
Cafestol and kahweol are also present in coffee. They can increase blood cholesterol and also feature some chemopreventive activity. The way of action of these compounds on lipoprotein metabolism is not completely understood. The only scientific evidence available is that they are absorbed intestinally. The positive association between coffee consumption and serum cholesterol has been observed mainly in Scandinavia and in the United States, where boiled coffee and filtered coffee are very popular. Therefore, the brewing method is probably critical to the cholesterol-raising effect of coffee. Also, French press (cafetière) coffee contains relatively high levels of cafestol and kahweol (6–12 mg/cup).



Kingdom	*Plantae*
Division	*Magnoliophyta*
Class	*magnoliopsida*
Order	*Gentianales*
Family	*Rubiaceae*
Genus	*Coffea*
Species	*Arabica; Canephora*

Figure 1 Coffee fruit structure and botanical classification of coffee plant.

Table 1 Main physiological actions of coffee components

Compound	*Molecular formula*	*Amount (mg/100 ml)*	*Physiological action*
Trigonelline		0.4–1.2 nicotinic acid	Antioxidant and antiinflammatory activities
Kahweol		0–0.1 (filtered coffee) 0.7–10 (boiled coffee)	Increased low density lipoprotein cholesterol and total cholesterol Free radical scavenging
Caffeine		30–54	Central nervous system stimulation Elevation of blood pressure Increased alertness Increased metabolic rate Decreased DNA degradation and reduced hydroxyl radicals Antioxidant properties
Chlorogenic acid (CGA)		35–175 CGA 17–87 caffeic acid	Antiinflammatory and antiangiogenic activities Antioxidant properties
Cafestol		0–0.1 (filtered coffee) 0.5–8 (boiled coffee)	Increased low density lipoprotein cholesterol and total cholesterol Free radical scavenging

Chlorogenic acids and caffeic acids are other important healthy components present in coffee. Chlorogenic acids are a family of esters formed between quinic and *trans*-cinnamic acids, which are an important group of dietary phenols. Caffeoylquinic acid (CQA) is the main compound among chlorogenic acids. The content of chlorogenic acids has been reported to range from 70 to 350 mg, which would provide about 35–175 mg of caffeic acid. These compounds show antioxidant activity *in vitro*. Probably, their action *in vivo* is reduced, because the metabolites deriving from their catabolism have lower antioxidant activity than the parent compounds.

Finally, coffee contains some micronutrients, such as magnesium, potassium, niacin, and vitamin E, which may contribute to the health effects of coffee consumption.

Antioxidant and Antibacterial Properties of Coffee

Lifestyle factors play a key role in human health. Traditional diets rich in bioactive components are associated with a lower risk of different illnesses; for example, the consumption of antioxidants or antioxidant-rich foods induces a lower risk of cancer (colorectal, hepatic, renal, ovarian, pancreatic, esophageal, endometrial, and pharyngeal cancers), as demonstrated by several meta-analyses.

Coffee is known as a dietary source of antioxidants and free radical scavengers, such as caffeine, hydroxycinnamic acids (caffeic, chlorogenic, coumaric, ferulic, and sinapic acids), Maillard reaction products, and melanoidins. Compared to other beverages, coffee stands out for its antioxidant potential; some authors reported levels of phenolic compounds in several beverages,

Table 2 Main groups subjected to caffeine's adverse effects and safe limits

Groups	*Risks*	*Limit (mg day^{-1})*
Women of childbearing age	*Conception*: High intakes of coffee or caffeine ranging from 400 to 800 mg day^{-1} are associated with delays in conception *Pregnancy complications*: Levels of at least 300 mg day^{-1} of caffeine increase the risk of spontaneous abortion. This association could be explained by the relationship between nausea and fetal viability *Fetal growth*: Caffeine intakes ranging from 200 to 400 mg day^{-1} induce a decrease in mean birth weight of about 100 g. Mothers of small for gestational age (SGA) infants had higher caffeine intakes in the third trimester of pregnancy than mothers of non-SGA infants *Lactation*: High maternal caffeine intakes cause irritability and poor sleeping patterns in infants	300
Children	Caffeine doses higher than 3 mg kg^{-1} of body weight can result in some behavioral effects (nervousness, anxiety, and sleep disturbances)	45 for 4–6 years old, 62.5 for 7–9 years old, and 85 for 10–12 years old
Older adults	Higher plasma caffeine concentrations could increase the risk of drug interactions and fracture risk, particularly in the presence of calcium and vitamin D insufficiency	400

drinks, and infusions in concentrations ranging from 0.07 to 4.16 mg l^{-1} in the following order: black tea > instant coffee > coke > red wine > violet carrot juice > apricot nectar > Turkish coffee > white wine. Coffee components exhibit some degree of antioxidant activity, so that coffee has the potential of reducing inflammation by decreasing oxidative stress.

Coffee antioxidant potential is associated with the presence of both natural compounds and substances developed during roasting. The temperature and time of the roasting process can impact on total antioxidant activity. Melanoidins, which are high-molecular-weight nitrogenous and brown-colored compounds, are formed during the roasting process. They show antioxidant, antimicrobial, anticariogenic, anti-inflammatory, antihypertensive, and antiglycative activities. Melanoidins from coffee showed higher antioxidant activity than those isolated from other sources, such as beer. All types of coffee preparations (filter, espresso, and Italian style) show antioxidant capacity, since all are effective free radical scavengers. Decaffeinated coffee has lower antioxidant capacity than regular coffee. The antioxidant capacity is about 6–7% after each 200 ml of coffee consumption, resulting in a reduction of inflammation through the reduction of free radicals and other reactive oxygen species.

Roasted coffee extract also features activity against some microorganisms, such as *Staphylococcus aureus* and *Streptococcus mutans* and several species/strains of Enterobacteriaceae (*Serratia marcescens*, *Enterobacter cloacae*, and *Salmonella enterica*). This activity is related to some coffee characteristic components, such as caffeic acid, trigonelline, caffeine, chlorogenic acid, and protocatechuic acid, all melanoidins with well-known natural antimicrobial activity.

Cardiovascular Effects of Coffee

The effects of coffee on the cardiovascular system are largely debated because the underlying mechanisms are complex and because of the considerable variability in individual responses. Many effects of coffee on the cardiovascular system have been attributed to caffeine, although coffee contains hundreds of chemical substances, many of which, such as polyphenols, are pharmacologically active.

Several epidemiological studies have examined the association between coffee consumption and the risk of coronary heart disease, but the findings have been equivocal. Experimental data from short-term and animal studies have suggested detrimental effects of caffeine on blood pressure, insulin resistance, and arrhythmia and have implicated coffee as a potential cardiovascular risk factor. Moreover, cross-sectional studies have shown an association between coffee and plasma cholesterol concentrations. Additionally, evidence from case–control studies has suggested that coffee consumption is associated with a higher risk of cardiovascular disease.

On the other hand, prospective cohort studies generally have not supported the existence of an association between coffee consumption and a higher risk of cardiovascular diseases, indicating that for most healthy people, moderate coffee consumption is unlikely to adversely affect cardiovascular health. Furthermore, several studies have suggested that also for patients with established coronary heart disease, it is safe to continue their habitual coffee consumption. A randomized clinical trial involving patients with acute ST segment elevation myocardial infarction (MI) has evaluated the effects of an acute ingestion of coffee on the autonomic function and cardiovascular health. Coffee ingestion was associated with an increase in parasympathetic tone, and coffee did not increase cardiac arrhythmia. The authors concluded that coffee ingestion is safe and not associated with adverse cardiovascular outcomes in postmyocardial infarction patients.

The relation between coffee consumption and the risk of arrhythmias has also been investigated. Although early animal studies indicated that coffee appeared to cause arrhythmias in a canine model, more recent studies have suggested that coffee does not increase arrhythmias. Actually, long-term coffee drinking might reduce the risk of abnormal cardiac rhythms, including atrial fibrillation.

Controlled interventional studies have shown that in normal adults, even acute high-dose caffeine did not affect cardiac

rhythm and rate and did not cause clinically significant ventricular or supraventricular arrhythmias. Moreover, prospective cohort studies did not find significant association between coffee consumption and the risk of atrial fibrillation. Mechanisms involved in this potential protection against arrhythmias are still largely unknown, but it has been hypothesized that caffeine attenuates negative effects of endogenous adenosine on cardiac electrical conduction.

The cardiovascular risk factor more extensively studied in relation to coffee is blood pressure: an elevated blood pressure is a risk factor for coronary heart disease, congestive heart failure, stroke, kidney disease, and all-cause mortality, and the relation between blood pressure and subsequent outcomes is direct and progressive throughout the usual range of blood pressure, including the nonhypertensive range. Therefore, even a small change in average blood pressure levels may have a major public health effect. Evidence that caffeine is an antagonist of adenosine receptors suggested the biological plausibility that coffee induces vasoconstriction and elevates systolic and diastolic blood pressure acutely. However, whether coffee consumption has chronic effects on blood pressure and cardiovascular disease is far from obvious and remains controversial. Dietary and other lifestyle factors play an important role in hypertension and blood pressure control: excess intake of salt or alcohol, suboptimal dietary pattern, physical inactivity, and excess body weight are here the most important factors. Coffee drinking might add as another dietary factor causing hypertension, but whether coffee intake per se is associated with detrimental long-term blood pressure changes or increases the risk of hypertension remains debated. A recent meta-analysis of 20 randomized, controlled trials and five cohort studies has shown no clinically important effects of long-term coffee consumption on blood pressure or the risk of hypertension in coffee consumers.

Various confounding factors may have influenced the equivocal results of different studies, including differences in the study design, populations examined (age, sex, usual frequency of coffee drinking, and smoking), types of coffee blend, and types of preparations used. Particularly, the design of epidemiological studies may affect findings about the relation between coffee and blood pressure or cardiovascular risk. Observational (cohort) studies usually have a large sample size and can provide insight into the long-term effects of different doses of coffee on blood pressure and possible changes in the effects by gender, age, race, cardiovascular risk profile, and other characteristics. However, observational evidence does not demonstrate causality, because coffee drinking is part of an individual's lifestyle and is related to many other factors, such as alcohol intake, mental stress, and dietary habits, which may also influence blood pressure.

Randomized clinical trials may provide insight into causality, because both the intervention (e.g., the use of coffee or caffeine in tablets) and the control treatment (e.g., decaffeinated coffee or placebo) are randomly assigned to participating subjects, and any confounder that could distort the relation between coffee and blood pressure should be equally distributed in both groups. The limitation of currently available randomized clinical trials on this subject is however that only fixed doses of coffee or caffeine have been studied, and for a relatively short period of time, the number of participating subjects has been limited; and there have often been problems of poor adherence to the assigned treatments. Furthermore, trials may have suffered from unsuccessful randomization or lack of blinding of the participants and/or investigators, which could introduce bias. Therefore, any conclusion on the cardiovascular effects of coffee has to rely on the overall evidence deriving from multiple sources of information.

The variability observed in the results of coffee studies and meta-analyses may be in part explained by the development of tolerance. For example, tolerance to caffeine-induced pressor effects quickly develops in habitual coffee drinkers, and blood pressure may be increased only temporarily in occasional coffee drinkers, while it is usually not elevated in heavy drinkers. It is possible that the complex set of counterregulatory hormones maintaining blood pressure causes tolerance to the humoral and hemodynamic effects of caffeine. In addition, above a certain level of consumption, caffeine's pressor effect might be counterbalanced by other coffee ingredients, including chlorogenic acid, flavonoids, melanoidins, quinide, magnesium, cafestol, and kahweol. Also, potassium, contained in coffee, may lower blood pressure. This may help explain the observed inverse 'J-shape' relation between habitual coffee drinking and the risk of hypertension, which increased up to three cups per day and then slightly decreased at higher amounts of consumption.

Another reason underlying the heterogeneity of responses to coffee drinking is the interaction between coffee components and the individual genetic constitution (nutrigenetics). For example, the enzyme accounting for approximately 95% of caffeine metabolism (the CYP1A2 isoform) has a wide interindividual variability in activity, resulting in rapid or slow metabolism of caffeine. It has been observed that subjects with slow metabolism have an increased risk of MI. Also, blood pressure responses are variable between subjects, with most subjects experiencing an increase in blood pressure, others showing no change, and some even showing blood pressure reductions. An association between gene variants in the adenosine and adrenergic receptors and blood pressure responses to caffeine has been observed. In principle, the exposure to higher blood pressure values as the result of such nutrigenetic interactions in some genetically predisposed individuals may expose such individuals to a higher coffee-related cardiovascular event. Moreover, it has been observed that genetic variants of adenosine receptors may also explain the interindividual variability in the susceptibility to anxiety and sleep changes induced by caffeine.

Besides blood pressure, other cardiovascular risk factors may be affected by coffee consumption. Some coffee compounds other than caffeine also have insulin-sensitizing and anti-inflammatory effects, and recent evidence from prospective cohort studies has suggested an inverse association between coffee and the risk of type 2 diabetes mellitus. This relationship is consistent across age, obesity, and study location (the United States and Europe), independent of potentially confounding dietary and lifestyle factors. Some proposed mechanisms able to explain this association include effects on insulin sensitivity and/or insulin secretion modulated by different minerals, antioxidants, and phytochemical compounds found in coffee. The role of caffeine in increasing or decreasing the risk of type 2 diabetes mellitus is still poorly understood. Most findings indicated a dose–response relation, with diabetes risk reduction for

higher levels of coffee consumption. Generally, four or more cups of coffee per day have generally been associated with a lower risk of type 2 diabetes mellitus, whereas for lower levels of consumption, results are controversial. Cross-sectional studies have highlighted that high coffee consumption is associated with lower postload plasma glucose concentrations among persons without diabetes and a lower incidence of impaired glucose tolerance and type 2 diabetes mellitus. In short-term metabolic studies, caffeine intake acutely reduces insulin sensitivity, exaggerating the blood glucose response to glucose loads. This action is probably related to the ability of caffeine to exert adenosine receptor antagonism or increase catecholamine levels. Also, decaffeinated coffee consumption has been associated with a reduction of risk of type 2 diabetes mellitus. Caffeinated and decaffeinated coffee consumption has a beneficial effect on insulin sensitivity because both reduce plasma C-peptide concentrations. However, the beneficial effect of decaffeinated coffee on glucose metabolisms requires further study. Chlorogenic acid and quinides are also probably involved in the reduction of risk of type 2 diabetes mellitus because they act on glucose homeostasis in animal models of diabetes. In humans, the components of coffee other than caffeine may exert beneficial effects on glucose metabolism. However, long-term studies on glycemic control are needed.

The previously considered harmful effects of coffee on the lipid profile depend on how the beverage is prepared. In fact, boiled coffee has higher concentrations of cholesterol-increasing compounds, classified as diterpenes, such as cafestol and kahweol. They are extracted from coffee beans by prolonged contact with hot water, while brewed/filtered coffee has a much lower concentration of cafestol and kahweol because of the much shorter contact with hot water and the retention of diterpenes by filter paper. Accordingly, it has been observed that the consumption of boiled coffee dose-dependently increase serum total and low density lipoprotein (LDL) cholesterol concentrations, whereas the consumption of filtered coffee results in very little change in serum cholesterol.

Regarding the association between coffee consumption and the risk of stroke, various findings have led to inconsistent results. Two recent meta-analyses have concluded that moderate coffee consumption has a preventive effect on stroke, and this is probably due to the healthy effect of coffee on the main risk factors for stroke, including hypertension, cardiovascular diseases, and diabetes mellitus. Regarding heart failure, a meta-analysis has indicated that there is a modest inverse association between moderate coffee consumption and the incidence of heart failure. Although potential modifiers of the coffee–heart failure relationship are not known, it is possible that the beneficial effects on blood pressure and other cardiovascular risk factors contribute to positively affect the risk of heart failure. In light of these findings, the current heart failure prevention guidelines have suggested a revision of the warning about coffee consumption, due to the evidence showing that coffee may provide a moderate protection against the incidence of heart failure.

Effects on Cancer

The relationship between coffee and cancer raises great interest, and in fact, more than 500 papers in the last decades have estimated the association between coffee consumption and the occurrence of cancer at 11 organ sites. Some studies found out that coffee consumption is associated with a reduced risk of hepatocellular, kidney, and, to a lesser extent, premenopausal breast and colorectal cancers, while it is unrelated to prostate, pancreas, and ovarian cancers. Since the results obtained are often controversial, in 2007, the World Cancer Research Fund (WCRF) conducted a comprehensive analysis of diet and cancer, using a standardized approach to review the overall evidence. This report showed an inverse relationship between coffee and the risk of pancreatic cancer and kidney cancer. This influence on cancer development appears to be related to the chemical composition of coffee and probably due to compounds able to influence the risk of cancer. For instance, caffeine can both stimulate and suppress tumors, depending on the species and the phase of administration. The consumption of caffeine is inversely related to hepatocellular injury. A population-based case–control study in the United States highlighted that caffeine was associated with a lower prevalence of abnormal alanine aminotransferase activity. Some other compounds, such as cafestol and kahweol, show anticarcinogenic properties, including the induction of phase II enzymes involved in carcinogen detoxification and the reduction of bile acid secretion associated with colon carcinogenesis. Polyphenols and chlorogenic acid are characterized by antioxidant effects. In particular, chlorogenic acid reduces blood glucose levels in rats and increases insulin sensitivity. Chronic hyperinsulinemia and insulin resistance are confirmed markers of high risk for some cancer sites. Moreover, caffeic acid inhibits DNA methylation in human cancer cells: this epigenetic regulation represents an important mechanism, because tumor cells are hypermethylated. In fact, DNA hypermethylation is often associated with the inactivation of genes and pathways involved in the tumorigenic process, including cell cycle regulation, inflammatory and stress response, and apoptosis. In addition, coffee-mediated stimulation of the Nrf2/ARE signaling pathway induces an increase in defense mechanisms against chemical stresses.

The influence of coffee consumption on the main types of cancer is reported in Table 3.

Effects on Neurodegenerative Diseases

Coffee has been shown to reduce the risk of Alzheimer's dementia and other diseases of the central nervous system, including Parkinson's disease.

A trend towards a protective effect of caffeine on Alzheimer's dementia has been frequently reported. Coffee may be the best source of caffeine to protect against Alzheimer's dementia due to a component in coffee that synergizes with caffeine to selectively enhance plasma cytokines. A quantitative review of four studies, despite heterogeneous methodologies and results, indicated that coffee consumption is inversely associated with the risk of Alzheimer's dementia, compared to nonconsumers.

Coffee and caffeine intake have also been associated with a reduced risk of Parkinson's disease, especially in men, in a number of prospective and case–control studies. Caffeine reduces the loss of dopaminergic neurons in animal models,

Table 3 Coffee influence on cancer development

Type of cancers	*Coffee effect*
Breast cancer	Coffee consumption has an inverse association with breast cancer, in particular among premenopausal women. Premenopausal women with a breast cancer 1, early onset (*BRCA*1) or breast cancer 2, early onset (*BRCA*2) gene mutation who habitually drank six or more cups of coffee per day experienced a 70% statistically significant reduction in breast cancer risk
Colorectal cancer	Coffee is a protective factor against colorectal cancer. This action is due to the presence of cafestol and kahweol that regulate the excretion of bile acids and neutral sterols into the colon
Prostate cancer	No association between prostate cancer risk and cumulative lifetime daily coffee consumption, duration of daily drinking, and age when daily drinking was started has been established
Ovarian cancer	No association between coffee and ovarian cancer has been found. However, some studies showed a modest inverse relationship between caffeine intake and ovarian cancer. This effect is probably related to caffeine modulation of estrogen level circulation
Pancreatic cancer	No association between coffee and pancreatic cancer has been found. A reduced risk was apparent among men who drank at least three cups of coffee per day
Liver cancer	Coffee consumption appears to reduce the risk of liver cancer. Probably, coffee polyphenols may maintain a relatively lower iron status and therefore reduce the risk of liver injury
Kidney cancer	Coffee consumption is associated, but not significantly, with a lower risk of kidney cancer. This action is probably due to the fact that caffeine has a diuretic effect by blocking antidiuretic hormone and antioxidant compounds reduce oxidative damage to DNA, proteins, and other molecules. Moreover, coffee consumption may reduce the risk of kidney cancer by improving insulin sensitivity

and its neuroprotective function is attributed to the antagonism on adenosine 2A (A2A) receptors in the brain, which are being increasingly targeted by anti-Parkinson therapies in clinical trials.

Other Effects

Coffee consumption is also associated with various other health effects. For instance, coffee may reduce the risk of depression. Additionally, coffee may improve asthmatic symptoms, probably through caffeine, which is a methylxanthine bronchodilator. Coffee may also enhance physical performance in sustained high-intensity exercise. Coffee may also prevent symptomatic gallstones and its consumption is associated with protection against some infectious and malignant diseases, particularly of the liver.

High levels of caffeine may increase urine output and urinary calcium and magnesium excretion, which have implications for bone health. Caffeinated coffee increases the risk of bone loss and fractures.

Effects on Mortality

Some studies have also investigated the association between coffee consumption and major causes of death, including heart diseases, respiratory diseases, stroke, injuries and accidents, diabetes, and infections. The results of these studies have been variable, and data are lacking to clarify the association between coffee drinking and mortality, to determine whether there is a dose–response relationship, and to assess whether associations are consistent across various subgroups. In a large, prospective cohort study, a dose-dependent inverse association between coffee drinking and total mortality was observed, after adjusting for potential confounders (smoking status in particular). Although the observational nature of the study does not prove a cause/effect relationship, the authors speculated that a plausible mechanism by which coffee consumption might have health benefits is the presence of antioxidant compounds, including polyphenols. The significant inverse associations of coffee consumption with death from all causes provide reassurance with respect to the concern that coffee drinking might adversely affect health.

Conclusions

The currently available overall evidence on cardiovascular effects related to habitual coffee consumption is largely reassuring. Moreover, coffee has a protective effect on cancer and neurodegenerative disease. Therefore, coffee can be included as part of a healthy diet. Many of coffee benefits probably derive from its caffeine content, but other substances may have an important role in health protection, particularly for their antioxidant effect.

It is very difficult to establish the factors responsible for coffee's beneficial or harmful effects. In order to better understand the function of these compounds, they should be isolated and utilized in a controlled experimental situation, using a well-established chemical balance of coffee components and at doses nutritionally achievable. Finally, it is also possible that coffee drinkers differ in other important dietary and sociological aspects from nonconsumers, and coffee use may be a surrogate marker of some other dietary or lifestyle risk factor.

Clinical trials need to verify the relationship between coffee and diseases, controlling coffee type, the original coffee beans, the roasting process, serving sizes, brewing process, and duration over a long period of time, with specific quantitative information (in mg kg^{-1} day^{-1}) on caffeine intake.

See also: Coffee: Analysis and Composition; Coffee: Decaffeination; Coffee: Types and Production; Fermented Foods: Fermented Vegetables and Other Products; Fermented Foods: Use of Starter Cultures; Functional Foods.

Further Reading

Butt MS and Sultan MT (2011) Coffee and its consumption: benefits and risks. *Critical Reviews in Food Science and Nutrition* 51: 363–373.

Costa J, Lunet N, Santos C, Santos J, and Vaz-Carneiro A (2010) Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. *Journal of Alzheimer's Disease* 20: 221–238.

Daglia M, Papetti A, Grisoli P, Aceti C, Spini V, Dacarro C, and Gazzani G (2007) Isolation, identification, and quantification of roasted coffee antibacterial compounds. *Journal of Agricultural and Food Chemistry* 55: 10208–10213.

Dorea JG and da Costa THM (2005) Is coffee a functional food? *British Journal of Nutrition* 93: 773–782.

Frost-Meyer NJ and Logomarsino JV (2012) Impact of coffee components on inflammatory markers: a review. *Journal of Functional Foods* 4: 819–830.

Jee SH, He J, Appel LJ, Whelton PK, Suh I, and Klag MJ (2001) Coffee consumption and serum lipids: a meta-analysis of randomized controlled clinical trials. *American Journal of Epidemiology* 153: 353–362.

Mostofsky E, Rice MS, Levitan EB, and Mittleman MA (2012) Habitual coffee consumption and risk of heart failure: a dose–response meta-analysis. *Circulation: Heart Failure* 5: 401–405.

O'Keefe JH, Bhatti SK, Patil HR, Di Nicolantonio JJ, Lucan SC, and Lavie CJ (2013) Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. *Journal of the American College of Cardiology* 62: 1043–1051.

Panagiotakos DB, Pitsavos C, Chrysohoou C, Kokkinos P, Toutouzas P, and Stefanadis C (2003) The J-shaped effect of coffee consumption on the risk of developing acute coronary syndromes: the CARDIO2000 case–control study. *Journal of Nutrition* 133: 3228–3232.

Rebello SA and van Dam RM (2013) Coffee consumption and cardiovascular health: getting to the heart of the matter. *Current Cardiology Reports* 15: 403.

Renda G, Zimarino M, Antonucci I, et al. (2012) Genetic determinants of blood pressure responses to caffeine drinking. *American Journal of Clinical Nutrition* 95: 241–248.

Santos C, Costa J, Santos J, Vaz-Carneiro A, and Lunet N (2010) Caffeine intake and dementia: systematic review and meta-analysis. *Journal of Alzheimer's Disease* 20: 187–204.

Sofi F, Conti AA, Gori AM, Eliana Luisi ML, Casini A, Abbate R, and Gensini GF (2007) Coffee consumption and risk of coronary heart disease: a meta-analysis. *Nutrition, Metabolism, and Cardiovascular Diseases* 17: 209–223.

Steffen M, Kuhle C, Hensrud D, Erwin PJ, and Murad MH (2012) The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis. *Journal of Hypertension* 30: 2245–2254.