

The Effects of Coffee Consumption on Cardiovascular Heart Diseases and Other Diseases

Kahve Tüketiminin Kardiyovasküler Kalp Hastalıkları ve Diğer Hastalıklar Üzerine Etkileri

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ABSTRACT

Coffee is the most consumed drink in daily life after tea and water. Coffee has become an indispensable part of our sociocultural life. Most people start their day with coffee and finish with this. Coffee can be called superfood because it has many bioactive components, minerals and vitamins that affect human health. Therefore, coffee has attracted the attention of many researchers with its rich bioactive components and then studies about the effects of coffee on animal and human health have been realized. In this review, we aimed to investigate the effects of coffee on health, especially cardiovascular disease (CVD) and cardiovascular risk factors.

Keywords: Antioxidant, Bioactive Components, Cardiovascular Diseases, Coffee, Health

ÖZET

Kahve, çay ve sudan sonra günlük yaşamda en çok tüketilen içeceklerdir. Kahve, sosyokültürel yaşamımızın vazgeçilmez bir parçası haline gelmiştir. Çoğu insan güne kahve ile başlar ve kahveyle bitirir. Kahve süper besin olarak isimlendirilebilir çünkü insan sağlığını etkileyen birçok biyoaktif bileşeni, mineralleri ve vitaminleri vardır. Böylece kahve, zengin biyoaktif bileşenleri ile birçok araştırmacının dikkatini çekmiş ve ardından kahvenin hayvan ve insan sağlığı üzerindeki etkileri ile ilgili çalışmalar yapılmıştır. Bu derlemede kahvenin sağlığa, özellikle kardiyovasküler hastalıklar (CVD) ve kardiyovasküler risk faktörleri üzerine etkilerini irdelemeyi planladık.

Anahtar Kelimeler: Antioksidan, Biyoaktif Bileşenler, Kardiyovasküler Hastalıklar, Kahve, Sağlık

INTRODUCTION

Coffee is one of the most consumed drink on worldwide and it has taken important place in populations since at least 1200 years (Bonita et al., 2007). Countries where coffee is consumed mostly are Finland, Norway and Denmark respectively (ICO, 2016). It is estimated that coffee consumption will increase as nontraditionally in Africa, Asia, and Oceania in many years and it is predicted that the request for coffee marketing will expand by 2.5% in North America and by 1% in Europe (ICO, 2018).

Coffee belongs to Rubiaceae family and it has two main type forms (*Coffea arabica* L. and *Coffea canephora*) that have originated from Ethiopia and in tropical Africa (ICO, 2016). The coffee is

generally prepared by hot water and ground coffee but it can be consumed in different forms. It is drunk as espresso in Italy that is prepared by extracting finely ground powder with high-pressure hot water. In today, the coffee can be cooked by the coffee machine that hot water is forced up through the coffee to the top of the machine (Martini et al., 2016).

The coffee and bioactive components

Coffee is a complex mixture of chemical structures and it is the main source of caffeine (Figure 1). Also, it contains many different chemicals such as carbohydrates, lipids, nitrogenous compounds, vitamins, minerals, alkaloids and phenolic components (Spiller, 1984).

The polyphenols are represented by chlorogenic acid and its components such as caffeine, caffeic acid, trigonelline, chlorogenic acid and diterpenes that have effects on human health (Frost-Meyer et al., 2012).

Caffeine: Caffeine (1,3,7-trimethylxanthine) is a purine alkaloid (Louarn et al., 2001). There is between 84 mg and 112 mg caffeine in a cup of coffee (Gilbert et al., 1976). Caffeine is an antagonist of phosphodiesterases and adenosine receptors (Boswell-Smith et al., 2009; Holtzman et al., 1991). It affects the central nervous system by increasing dopamine, nor adrenaline and glutamate (Ferré et al., 1997). It may increase heartbeat, systolic and diastolic blood pressure and it may reduce cerebral and coronary blood flow (Namdar et al., 1990; Namdar et al., 2009). Mitani et al. have observed that caffeine might suppress lipid accumulation in adipocytes by inhibiting the secretion of inflammatory cytokines (Mitani et al., 2017).

Caffeic acid: Caffeic acid is one of the metabolites of chlorogenic acid (Sato et al., 2011). Caffeic acid has anti-inflammatory, anticarcinogenic, and enzyme-inhibiting properties (Chung et al., 2004). It has been shown that there is a negative linear relationship between the serum caffeic acid levels and colon cancer risk. Also, it has been observed that caffeic acid might inhibit IL-8 production in colon cells (Shin et al., 2015).

Chlorogenic acid: Chlorogenic acids have quinic acid and trans-cinnamic acids components (Upadhyay and Mohan Rao, 2013). The major source of chlorogenic acid is coffee that is intaken by diet and the amount of chlorogenic acid depends on daily coffee consumption (Mohan Rao et al., 2012). It is uncertain that it prevents or induces DNA damage. Some researchers claim that it has protective effects against free radical induced DNA oxidation in human colon HT29 and liver HepG2 cancer cell lines. On the other hand, some other researchers observed that the increased concentration of chlorogenic acid triggered DNA damage (Glei et al., 2006).

Kahweol: Kahweol is a coffee-specific diterpene that is found in Arabic coffee beans oil and its concentration in coffee changes in between the ranges 0.1 to 7 mg/mL (Gross et al., 1997; Arab, 2010). It may increase serum cholesterol levels on

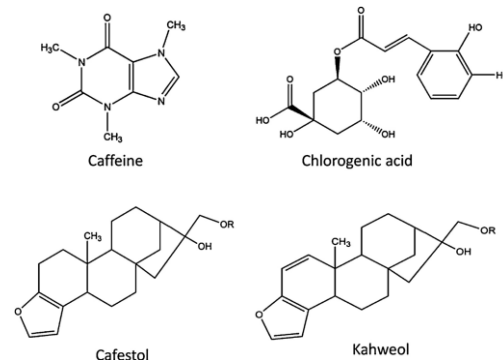


Figure 1. The chemical structures of bioactive components of coffee (Bae et al., 2014)

animals and human (DeRoos et al., 1999). However, it may have protective properties against carcinogens (Huber et al., 1997).

Hypertension: The effects of consumption coffee consumption is transient on hypertension is transient. It has been observed that the coffee increases acute blood pressure rarely and the coffee's blood pressure effects are not important on chronic coffee consumers (Mesas et al., 2011). When coffee is consumed regularly, the tolerance develops against its hemodynamic and humoral effects (Robertson et al., 1981). In a study, it has been demonstrated that 6 cups of coffee consumption daily were not associated with increased risk of hypertension (Robertson et al., 2005).

Type 2 Diabetes Mellitus (T2DM): The coffee consumption may reduce the risk of T2DM according to results of cohort studies (Carlsson et al., 2004). There are two hypotheses that for reduction of the risk of diabetes due to coffee consumption may reduce the risk of diabetes. One of them is that the chlorogenic acid component of coffee may inhibit glucose-6-phosphatase system and it may be competitive inhibitor of glucose-6-phosphate translocase (Arion et al., 1997). Other hypothesis is inhibition of intestinal glucose absorption by chlorogenic acid and other phenolic components of coffee (Welsch et al., 1989). In a prospective study, the risk of T2DM was %50 lower in adults consuming at least 7 cup of coffee daily compared to less coffee consumers (<2 cups of coffee) (VanDam et al., 2002).

Insulin Sensitivity: In a recent study, the researchers have observed that 5 cups of coffee

consumption reduced insulin resistance and it increased tissue adiponectin tissue levels (Wedick et al., 2011).

Hyperlipidemia: Coffee contains cholesterol increasing components such as diterpenes, cafestol and kahweol but the concentrations of these compounds depend on method of how coffee is preparationed (Urgert et al., 1997). In a study, the volunteers were divided into three groups. The first 2 groups consumed 4 to 6 cups of boiled or filtered coffee daily and the other group was placebo. After 9 weeks, there was significant rise in total serum cholesterol levels in volunteers consuming boiled coffee and there was no significant rise serum LDL levels in this group. There was no significant difference in serum lipid levels between other groups (Grobbee et al., 1989). In another study, there was no evidence about the filter coffee increasing serum lipid levels increase due to filter coffee consumption (Lopez-Garcia et al., 2006).

Homocysteine: It has been demonstrated that coffee consumption may increase plasma total homocysteine levels in man as dose-dependently in researchs (Husemoen et al., 2004). In a study, the homocysteine levels were found higher in participants consuming one liter of unfiltered coffee daily compared to those consuming one liter of filtered coffee (Urgert et al., 2010).

Stroke: Coffee consumption may reduce the risk of stroke. The meta-analysis of seven prospective studies demonstrated that 1 to 3 cups coffee consumption was associated with reduced stroke risk. Other hand, it has been observed that more than 6 cups of coffee consumption did not reduce the stroke risk in another study. According to researchers, the coffee is not associated with high stroke risk but habitual moderate coffee may provide protective effects (D'Elia et al., 2012).

Cardiovascular heart diseases: The studies that have investigated the association between coffee consumption and coronary heart diseases are contradictory. In a meta-analysis with case-control and cohort studies, the coffee consumption was significant associated with cardiovascular heart diseases in short-term but same relationship could not be observed in long-term (Greenberg et al., 2007). The

researchers detected that coffee consumption reduced CVD risks and inflammatory diseases in only post menopausal women because of its antioxidant and antiinflammatory properties (Andersen et al., 2006). But in 21 cohort prospectivestudies, it has been observed that moderate coffee consumption reduced CVD risks in long-term. Also the adults consuming moderate coffee had lower CVD risk compared to those who less consumed (Wu et al., 2009). In another study including patients with STEMI history, there was no cardiac arrhythmia increase in patients due to vagal tonus activation. The researchers agree that the coffee consumption may be confident the patients with STEMI history (Richardson et al., 2009). In conclusion, there are contradictions between studies and the prospective cohort studies have not found significant associations between coffee consumption and CVD risk (Higdon and Frei, 2006).

Heart Failure (HF): There was interesting association between HF risk and coffee consumption. In a recently study, more or less coffee consumption increased HF risk but 4 cups of coffee consumption daily reduced HF risk. But the patients were not categorized according to their sex, age, MI or DM history in this study (Mostofsky et al., 2012).

Table 1. The cardiovascular effects of coffee on human health

The acute effects of coffee are transient on blood pressure and it may not increase the risk of hipertension on chronic coffee consumers.
Coffee may reduce the development of T2DM risk.
The effect of coffee on serum lipid levels varies according to types of cooking.
Although there is no strong evidence that coffee reduced high stroke risk, moderate coffee consumption may be protective against stroke.
There are contradictory claims about association between coffee and CVD risk. But coffee may reduce CVD risk in post menopausal women because of reduced inflammation.
Coffee consumption is confident for patients with STEMI history.
The effects of coffee on HF changes as dose dependent
Coffee can reduce all-cause deaths by reducing cardiovascular risk.
Coffeine does not cause serious ventricular and supraventricular cardiac arrhythmias. Also, there is no association between AF and coffee consumption.

Cardiovascular mortality: The coffee was found to be protective on cardiovascular mortality in elderly patients in a study (Greenberg et al., 2007). In another study, the participants with no cancer and no CVD history were included and they were followed during long-term. The results of the study, it has been observed showed that coffee consumption reduced all-cause mortality due to moderately reduced risk of CV disease mortality. Also decaffeinated coffee slightly reduced in all-cause and CV disease mortality (Lopez-Garcia et al., 2008).

Cardiac Arrhythmia: The recent studies demonstrated that coffee consumption did not increase arrhythmia risk. In a study, habitual coffee consumption was inversely associated with hospitalization due to cardiac arrhythmia during long-term follow-up (Klatsky et al., 2011). According to recent studies, high doses coffee consumption did not effect heartbeat rate, available rhythm and did not cause serious ventricular and supraventricular arrhythmias (Newcombe et al., 1988). More recently, two prospective studies could find no association between coffee and the risk of atrial fibrillation development atrial fibrillation (Wilhelmsen et al., 2001).

The other effects of coffee on human health

Cancers: Many studies have shown that the coffee consumption was associated with reduced cancer risks but these studies were mostly case-control studies (Nawrot et al., 2003). In the result of the metaanalysis of 17 trials, four or more cups daily coffee consumption caused by 24% reduction of colorectal cancer risk (Giovannucci et al., 1998). A prospective cohort study indicated that increased coffee consumption was negatively correlated with hepatocellular carcinoma risk (Inoue et al., 2005).

Cirrhosis: Coffee consumption was inversely associated with risk of cirrhosis in several case-control studies. A study in Norway, the death from cirrhosis was found by 40% lower in patients consuming two cups of coffee daily compared to those who never consumed (Tverdal et al., 2003).

Parkinson disease: Studies in animal models submitted suggested that caffeine consumption decreased the risk of Parkinson's disease by

protecting against dopaminergic neurotoxicity (Schwarzschild et al., 2002). In a cohort study, the coffee consumption prevented the death from Parkinson diseases in men but not woman. Perhaps eustrogen replacement therapy may decrease the benefit of coaffeinein women (Ascherio and Chen, 2003).

Bone fracture: It is claimed that highmuch coffee consumption provoked by 14% more bone fracture because of negative effects on calcium absorption and bone mineral density (Lee et al., 2014; Heaney, 2002; Hallström 2013). However, the researchers explored that 400mgcoffee consumption daily might not damage the calcium absorption and bone mineral density (Wikoff et al., 2017).

Antiinflammatory and antioxidant effects: Several studies have reported that coffee has antinflammatory and antioxidant effects due to bioactive components such as especially caffeine and chlorogenic acid. The researchers agree that coffee may prevent lipid peroxidation, DNA damage and it may reduce the expression of pro-inflammatory cytokines (Sukyong et al., 2018).

Table 2. The other effects of coffee on human health

It has anti-inflammatory and antioxidant effects.
It decreases the risk of suicide and the symptoms of depression.
It reduces the death from cirrhosis
It is associated with lower colorectal cancer risks.
It has benefict effects on Parkinson disease.
It may have negative effects on bone mineral density and may reduce calcium absorption to bone.

Suicide, anxiety and depression: Each cup of coffee can reduce the risk of suicide by 24% (Kawachi et al., 1996). Also, the coffee consumption may relieve the depression symptoms and it is associated with lower risk of anxiety (Tse et al., 2009; Wang et al., 2016).

Adverse effect of coffee and caffeine:

The coffee may cause tachycardia, palpitations, insomnia, restlessness, nervousness, tremor,

headache, abdominal pain, nausea, vomiting, diarrhea and diuresis depending on caffeine component of coffee (Engebretsen et al., 2001). Caffeine may cause withdrawal symptoms including headaches, fatigue, drowsiness, and irritability, difficulty concentrating and depressed mood in consuming long-term consumption (Dews et al., 1999). Caffeine may increase the adverse effects of sympathetic agents and acetaminophen. It may inhibit antipsychotic agents' elimination and metabolism (Mendelsohn, 2001).

CONCLUSION

Although coffee is one of the most consumed drinks and it has rich bioactive components, the studies on human health are still controversial. Therefore, health professionals should be aware of the effects and side effects of coffee consumption and should be careful. Also randomized controlled prospective and high-evidence studies that will clearly demonstrate the effects of coffee consumption on heart and human health are needed.

REFERENCES

Andersen LF, Jacobs D, Carlsen M, Blomhoff R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. *Am J Clin Nutr* 2006;83(5):1039-46.

Arab L. Epidemiologic evidence on coffee and cancer. *Nutr Cancer* 2010; 62:271-83.

Arion WJ, Canfield WK, Ramos FC, Schindler PW, Burger HJ, Hemmerle H et al. Chlorogenic acid and hydroxynitrobenzaldehyde: New inhibitors of hepatic glucose 6-phosphatase. *Arch Biochem Biophys* 1997; 339:315-22.

Ascherio A, Chen H. Caffeinated clues from epidemiology of Parkinson's disease. *Neurology* 2003; 61:51-4.

Bae JH, Park JH, Im SS, Song DY. Coffee and health. *Integr Med Res* 2014; 3:189-91.

Bonita JS, Mandarano M, Shuta D, Vinson J. Coffee and cardiovascular disease: in vitro, cellular, animal, and human studies. *Pharmacol Res* 2007; 55:187-98.

Boswell-Smith V, Spina D et al. Phosphodiesterase inhibitors. *Br J Pharmacol* 2009; 147:252-7.

Van Sag Bil Derg 2019;12(2):25-31

Carlsson S, Hammar N, Grill V, Kaprio J. Coffee consumption and risk of type 2 diabetes in Finnish twins. *Int J Epidemiol* 2004; 33:616-7.

Chung TW, Moon SK, Chang YC, Ko JH, Lee YC, Cho G et al. Novel and therapeutic effect of caffeic acid and caffeic acid phenylesteron hepatocarcinoma cells: complete regression of hepatoma growth and metastasis by dual mechanism. *FASEB J*. 2004; 18:1670-81.

D'Elia L, Cairella G, Garbagnati F, Scalfi L, Strazzullo P. Moderate coffee consumption is associated with lower risk of stroke: meta-analysis of prospective studies. *J Hypertens* 2012 ;e107.

DeRoos B, Sawyer JK, Katan MB, Rudel LL. Validity of animal models for the cholesterol-raising effects of coffee diterpenes in human subjects. *Proc Nutr Soc* 1999;58: 551-7.

Dews PB, Curtis GL, Hanford KJ, O'Brien CP. The frequency of caffeine withdrawal in a population-based survey and in a controlled, blinded pilot experiment. *J Clin Pharmacol* 1999; 39:1221-32.

Engebretsen KM, Harris CR. Caffeine and related non-prescription sympathomimetics. *Clin Toxicol* 2001; 310-5.

Ferré S, Fredholm BB, Morelli M, Popoli P, Fuxe K. Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. *Trends Neuro Sci* 1997; 20: 482-7.

Frost-Meyer NJ, Logomarsino JV. Impact of coffee components on inflammatory markers: A review. *J Funct Foods* 2012;4: 819-30.

Gilbert RM, Marshman JA, Schwieder M, Berg R. Caffeine content of beverages as consumed. *Can Med Assoc J* 1976; 114: 205-8.

Giovannucci E. Meta-analysis of coffee consumption and risk of colorectal cancer. *Am J Epidemiol* 1998; 147:1043-52.

Glei M, Kirmse A, Habermann N, Persin C, Pool-Zobel BL. Bread enriched with green coffee extract has chemoprotective and antigenotoxic activities in human cells. *Nutr Cancer* 2006; 56:182-92.

Greenberg J, Dunbar C, Roseanne S, Kokolis R, Kokolis S, Kassotis J. Caffeinated beverage intake and the risk of heart disease mortality in the elderly: a prospective analysis. *Am J Clin Nutr* 2007;85(2):392-8.

Bak AA, Grobbee DE. The effect on serum cholesterol levels of coffee brewed by filtering or boiling. *N Engl J Med* 1989; 321:1432-7.

- Gross G, Jaccaud E, Huggett AC. Analysis of the content of the diterpenes cafestol and kahweolin coffee brews. *Food Chem Toxicol* 1997; 35:547-54.
- Hallström H, Byberg L, Glynn A, Lemming EW, Wolk A, Michaëlsson K. Long-term coffee consumption in relation to fracture risk and bone mineral density in women. *Am J Epidemiol* 2013; 178:898-909.
- Heaney R. Effects of caffeine on bone and the calcium economy. *Food Chem Toxicol* 2002; 40:1263-70.
- Higdon JV and Frei B. Coffee and health: A review of recent human research. *Food Sci Nutr* 2006; 46:101-23.
- Holtzman SG, Mante S, Minneman KP. Role of adenosine in caffeine tolerance. *J Pharmacol Exp Ther* 1991; 256:62-8.
- Huber WW, McDaniel LP, Kaderlik KR, Teitel CH, Lang NP, Kadlubar FF. Chemoprotection against the formation of colon DNA adducts from the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazol[4,5-b] pyridine (PhIP) in the rat. *Mutat Res* 1997; 376: 115-22.
- Husemoen LL, ThomsenTF, Fenger M, JorgensenT. Effect of lifestyle factors on plasma total homocysteine concentrations in relation to MTHFR (C677T) genotype. *Eur J Clin Nutr* 2004; 58:1142-50.
- Inoue M, YoshimiI, SobueT, Tsugane S. Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: A prospective study in Japan. *J Nation Cancer Inst* 2005;97(293):293-300.
- International Coffee Organization (ICO). Coffee Market Report, December 2018; ICO: London, UK, 2018; (Available online:<http://www.ico.org/Market-Report-18-19-e.asp>, accessed on 11 February2019).
- International Coffee Organization (ICO). Infographics on the Global Coffee Trade (Available online: <http://www.ico.org/coffee-trade-statistics-infographics.asp>? Section =Statistics, assessed on 1 March 2016).
- Kawachi I, Willett WC, Colditz GA, Stampfer MJ, Speizer FE. A prospective study of coffee drinking and suicide in women. *Arch Intern Med* 1996; 156:521-5.
- Klatsky AL, Hasan AS, Armstrong MA, Udaltsova N, Morton C. Coffee, caffeine, and risk of hospitalization for arrhythmias. *Perm J* 2011; 15:19-25.
- Lee DR, Lee J, Rota M, Lee J, Ahn HS, Park SM et al. Coffee consumption and risk of fractures: A systematic review and dose-response meta-analysis. *Bone* 2014; 63:20-8.
- Lopez-Garcia E, van Dam RM, Willett WC, Rimm EB, Manson JE, Stampfer MJ et al. Coffee consumption and coronary heart disease in men and women: A prospective cohort study. *Circulation* 2006; 113:2045-53.
- Lopez-Garcia E, van Dam RM, Li TY, Rodriguez-Artalejo F, Hu FB. The relationship of coffee consumption with mortality. *Ann Intern Med* 2008; 148:904-14.
- Louarn J, Dussert S, Guyot B, Hamon S, Noiro M. Caffeine, trigonelline, chlorogenic acids and sucrose diversity in wild *Coffea arabica* L. and *C. canephora* P. accessions. *Food Chem* 2001; 75:223-30.
- Martini D, Tassotti M, Riso P, Del Rio D, Brighenti F et al. Coffee consumption and oxidative stress: A review of human intervention studies. *Molecules* 2016;21(8); 979:210809979.
- Mendelsohn MJ. Monoamine oxidase inhibitors. *Clin Toxicol* 2001;546-57.
- Mesas AE, Leon-Munoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. *Am J Clin Nutr* 2011; 94:1113-26.
- Mitani T, NaganoT, Harada K, Yamashita Y, Ashida H. Caffeine-stimulated intestinal epithelial cells suppress lipid accumulation in adipocytes. *J Nutr Sci Vitaminol* 2017; 63: 331-338.
- Mohan Rao C, Ciudad CJ, Noé V, Izquierdo-Pulido M. Coffee polyphenols change the expression of STAT5B and ATF-2 modifying cyclin D1 levels in cancer cells. *Oxid Med Cell Longev* 2012; Article ID:390385,17.
- Mostofsky E, Rice MS, Levitan EB, Mittleman MA. Habitual coffee consumption and risk of heart failure: a dose-response meta-analysis. *Circ Heart Fail* 2012; 5:401-5.
- Namdar M, Schepis T, Koepfli P, Gaemperli O, Siegrist PT, Grathwohl R et al. Caffeine impairs myocardial blood flow response to physical exercise in patients with coronary artery disease as well as in age-matched controls. *PLoS ONE* 2009; 4:1-6.
- Namdar OG, Modell JG, Hariharan M. Caffeine and human cerebral blood flow: A positron emission tomography study. *Life Sci* 1990; 47:1141-6.
- Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. Effects of caffeine on

- human health. *Food Addit Contam* 2003; 20:1-30.
- Newcombe PF, Renton KW, Rautaharju PM, Spencer CA, Montague TJ. High-dose caffeine and cardiac rate and rhythm in normal subjects. *Chest* 1988; 94:90-4.
- Richardson T, Baker J, Thomas PW, Meckes C, Rozkovec A, Kerr D. Randomized control trial investigating the influence of coffee on heart rate variability in patients with ST-segment elevation myocardial infarction. *Q J Med* 2009; 102:555-61.
- Robertson WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA* 2005; 294:2330-5.
- Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. *J Clin Invest* 1981; 67:1111-7.
- Sato Y, Itagaki S, Kurokawa T, Ogura J, Kobayashi M, Hirano T et al. *In vitro* and *in vivo* antioxidant properties of chlorogenic acid and caffeic acid. *Int J Pharm* 2011; 403:136-8.
- Schwarzschild MA, Chen J, Ascherio A. Caffeinated clues and the promise of adenosine A(2A) antagonists in PD. *Neurology* 2002;58:1154-60.
- Shin HS, Satsu H, Bae MJ, Zhao Z, Ogiwara H, Totsuka M et al. Anti-inflammatory effect of chlorogenic acid on the IL-8 production in Caco-2 cells and the dextran sulphate sodium-induced colitis symptoms in C57BL/6 mice. *Food Chem* 2015; 168:167-75.
- Spiller MA. The chemical components of coffee. *Prog Clin Biol Res* 1984; 158:91-147.
- Choi S, Jung S, Ko KS. Effects of coffee extracts with different roasting degrees on antioxidant and anti-inflammatory systems in mice. *Nutrients* 2018;10(3):363.
- Tse WS, Chan CC, Shiu SY, Chung PY, Cheng SH. Caffeinated coffee enhances co-operative behavior in the mixed motive game in healthy volunteers. *Nutr Neurosci* 2009;12: 21-7.
- Tverdal A, Skurtveit S. Coffee intake and mortality from liver cirrhosis. *Ann Epidemiol* 2003; 13:419-23.
- Upadhyay R, Mohan Rao LJ. An outlook on chlorogenic acids-occurrence, chemistry, technology, and biological activities. *Crit Rev Food Sci Nutr* 2013; 53:968-84.
- Urgert R, van Vliet T, Zock PL, Katan MB. Heavy coffee consumption and plasma homocysteine: A randomized controlled trial in healthy volunteers. *Am J Clin Nutr* 2000; 72:1107-10 .
- Urgert R, Katan MB. The cholesterol-raising factor from coffee beans. *Ann Rev Nutr* 1997; 17:305-24.
- Van Dam RM, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* 2002; 360:1477-8.
- Wang L, Shen X, WuY, Zhang D. Coffee and caffeine consumption and depression: A meta-analysis of observational studies. *Aust N Z J Psychiatry* 2016; 50:228-42.
- Wedick NM, Brennan AM, Sun Q, Hu FB, Mantzoros CS, Van Dam RM. Effects of caffeinated and decaffeinated coffee on biological risk factors for type 2 diabetes: A randomized controlled trial. *Nutr J* 2011; 10:93-101.
- Welsch CA, Lachance PA, Wasserman BP. Dietary phenolic compounds: Inhibition of Na⁺-dependent D-glucose uptake in rat intestinal brush border membrane vesicles. *J Nutr* 1989; 119:1698-704.
- Wikoff D, Welsh BT, Henderson R, Brorby GP, Britt J, Myers E et al. Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. *Food Chem Toxicol* 2017; 109:585-648.
- Wilhelmsen L, Rosengren A, Lappas, G. Hospitalizations for atrial fibrillation in the general male population: Morbidity and risk factors. *J Intern Med* 2001; 250:382-9.
- Wu JN, Ho SC, Zhou C, Ling WH, Chen WQ, Wang CL et al. Coffee consumption and risk of coronary heart diseases: a meta-analysis of 21 prospective cohortstudies. *Int J Cardiol* 2009; 137:216-25.