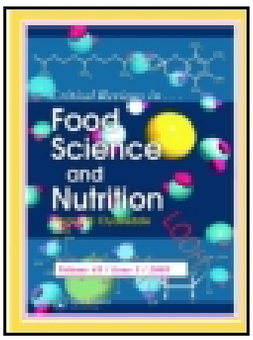

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Coffee Consumption and Disease Correlations

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ABSTRACT

Coffee is one of the most widely consumed beverages in the world. It has primarily consumed due to its stimulant effect and unique taste since the ancient times. Afterwards, its consumption has been historically associated with a lower risk of some diseases such as type 2 diabetes mellitus, obesity, cardiovascular disease and some type of cancer and thus it has also consumed due to health benefits. It contains many bioactive compounds such as caffeine, chlorogenic acids and diterpenoid alcohols which have so far been associated with many potential health benefits. For example, caffeine reduces risk of developing neurodegenerative disease and chlorogenic acids (CGA) and diterpene alcohols have many health benefits such as antioxidant and chemo-preventive. Coffee also have harmful effects. For example, diterpenoid alcohols increases serum homocysteine and cholesterol levels and thus it has adverse effects on cardiovascular system. Overall, the study that supports the health benefits of coffee is increasing. But, it is thought-provoking that the association with health benefits of coffee consumption and frequency at different levels in each study. For this reason, we aimed to examine the health effect of the coffee and how much consumption is to investigate whether it meets the claimed health benefits.

Keywords

Coffee; caffeine; chlorogenic acid; kahweol; cafestol; diseases

Introduction

Coffee is one of the most common consumed beverages around the world due to its stimulative effect and desirable bitter taste (Ramalakshmi & Raghavan, 1999; Nosáľová et al., 2011; You et al., 2011). Although its consumption historically has been related to negative health outcome, recent study shows that it might have health benefits (de Mejia & Ramirez-Mares, 2014). Coffee has health benefits due to the content of caffeine, cafestol, kahweol, chlorogenic acid and micronutrient (potassium, magnesium, niacin and vitamin E) (Higdon & Frei, 2006). Because of these potential health benefits, coffee has recently become the focus of studies (Messina et al., 2015). Coffee, specially green coffee, is rich in chlorogenic acid (CGA), which is a type of polyphenol (Revuelta-Iniesta & Al-Dujaili, 2014) and CGA has many health benefits such as antibacterial, antifungal, antiviral, antioxidant, chemo-preventive and other biological activities (Bharath, Sowmya, & Mehta, 2015). In addition, it is rich in caffeine (Butt & Sultan, 2011) and caffeine reduces the risk of developing neurodegenerative diseases such as Alzheimer's and Parkinson disease with psychostimulant effect (Cappelletti, Daria, Sani, & Aromatario, 2015) and increases resting energy expenditure by stimulating lipolysis with the effect of increasing sympathetic activity (Glade, 2010). Due to its bioactive compounds, coffee generally acts as anti-obesity, anti-diabetic, hepatoprotective, antioxidant, pro-oxidant, anti-genotoxic, anti-inflammatory, cytotoxic and immunomodulator agent and invasion, metastasis, angiogenesis, cell cycle progression and cell proliferation inhibitor (Chen, Teoh, Chitturi, & Farrell, 2014; El-Abhar & Schaalan, 2014; Gaascht, Dicato, & Diederich, 2015; Pan, Tung, Yang, Li, & Ho, 2016). Until now, several studies have pointed out that coffee has effects on many chronic diseases including cancer, obesity, cardiovascular diseases and neurodegenerative disease and

further studies has required (Costa et al., 2010; Ding et al., 2013; Gavrieli et al., 2013; Ding et al., 2014; Schmit et al., 2016). Despite these health benefits, excessive coffee consumption is linked to the risk of cardiovascular diseases due to the presence of cholesterol-increasing agents (Butt & Sultan, 2011). As a result, in accordance with studies in recent years, moderate coffee consumption (3-4 cup/day) is reported to be good for human health (George, Ramalakshmi, & Mohan Rao, 2008).

Coffee and its components

Beverages are a substantial part of daily nutrition and coffee takes up significant place among those (Tofalo, Renda, De Caterina, & Suzzi, 2016). Coffee is earned a reputation for its stimulative effect and delicious taste after roasting (Nosáľová et al., 2011). Coffee fruit belongs to the genus *Coffea* (*Rubiacea* family) which has a different species more than ninety. But, only two them, *Coffea arabica* (approximately %60 of the world's production) and *Coffea canephora* (approximately %40 of the world's production) are commonly cultivated in the world and have significant economical value (Şemen, Mercan, Yayla, & Açıkkol, 2017). Coffee contains carbohydrates, lipids, vitamins, nitrogenous compounds, isoflavonoids and micronutrients (Akash, Rehman, & Chen, 2014). Hydroxycinnamic acids (p-coumaric, caffeic and ferulic acid), methylxanthines (theophylline, caffeine and theobromine), flavonoids (anthocyanin and catechins), tocopherols, diterpene alcohols (kahweol and cafestol), melanoidins and chlorogenic acids (p-coumaroylquinic, feruloylquinic and caffeoylquinic acids) is found as bioactive compounds in coffee (de Mejia & Ramirez-Mares, 2014). The most known of bioactive compounds found in coffee is shown in Figure 1 (Godos et al., 2014).

Caffeine (1,3,7- trimethylxanthine), one of bioactive compounds found in coffee, is a methylated purine base formed as a product of purine degradation (Volk & Creighton, 2013). It is completely absorbed by small intestine and stomach within 45 minutes after its consumption and reaches its highest concentrations in the blood stream between fifteen and one hundred twenty minutes. When absorbed, it is distributed throughout the human body and is metabolised in the liver. A reaction catalyzed through cytochrome P450 oxidase enzyme system separates methyl 1 and 7 groups of caffeine and ultimately three metilxanthine occur. These metilxanthine are paraxanthine (%84), theobromine (%12) and theophylline (%4) (Pimentel, Micheletti, & Nehlig, 2014). Because caffeine and adenosine have similar structures, it is an adenosine receptor antagonist and therefore has impact on the peripheral and central nervous system (Gaspar & Ramos, 2016). Caffeine not only stimulates the central nervous system but also rises blood pressure, wakefulness and metabolic rate; reduces DNA degradation and hydroxyl radicals (Tofalo et al., 2016). In addition to caffeine, kahweol and cafestol known as diterpene molecules reduces risk of colorectal cancer (Lee, Chae, & Shim, 2012). Furthermore cafestol, by increasing the activity of glutathione-S-transferase, increases degradation of toxic compounds, protects against aflatoxin induced genotoxicity and thus exerts hepatoprotective effect (Kurzrock & Speer, 2001). However, two diterpenes (kahweol and cafestol) have also adverse health effect such as increasing LDL and total cholesterol (Penson, Serban, Ursoniu, & Banach, 2016). Among diterpene molecules, cafestol reduces the activity and expression of cholesterol 7-alpha-hydroxylase, which is the rate-limiting enzyme in bile acid synthesis, and thus exerts cholesterol-increasing effect (Karabudak, Türközü, & Köksal, 2015). Fortunately, with the filtration process, the levels of kahweol and cafestol in coffee are significantly reduced (Zhang, Linforth, Fisk,

2012). As a result, while diterpene molecules have negative effect such as increasing blood lipid levels, also have positive effect such as antioxidant activity and protection from cancer (Silva, Borges, Santos, & Alves, 2012). Another bioactive compound of coffee, chlorogenic acid (CGA) is often associated with anti-inflammatory, anti-bacterial, anti-hypertensive and antioxidant activity. In addition, CGA exerts inhibitory effects on fat accumulation and modulator effects on glucose metabolism (Farah, Monteiro, Donangelo, & Lafay, 2008). By stimulating glucose uptake in both insulin sensitive and non-insulin sensitive adiposity, CGA plays a role in glucose metabolism and also by decreasing serum and hepatic triglyceride, LDL cholesterol and LDL oxidation levels, activating lipid metabolism in liver and inhibiting lipid absorption in small intestine plays a role in lipid metabolism (Meng, Cao, Feng, Peng, & Hu, 2013).

Coffee and disease correlations

It is suggested that coffee might prevent many chronic diseases such as some of cancer type, type 2 diabetes mellitus, cardiovascular, renal, neurological and liver diseases and endocrine disorders (Nosáľová et al., 2011).

Immune system diseases and coffee

There is little data about the effects of oral administration of coffee on immune response and allergy (Goto, Yamaki, Shinmoto, & Takano-Ishikawa, 2009). Coffee is rich in polyphenols and it is known that polyphenols may impact immune function and chronic inflammation (Loftfield et al., 2015). Cellulose, galactomannan and arabinogalactan proteins (AGP), which are polysaccharide constituents in coffee, account for approximately 50% of dry weight of coffee bean. Among these, APGs have prebiotic, cholesterol-lowering, emulsifier, immunumodulatory properties (Capek, Matulová, Navarini, & Suggi-Liverani, 2010).

Type 2 arabinogalactan fraction increases proliferation of splenocytes and peritoneal macrophages, activates production IFN-γ, T_H-1 type cytokines and IL-12, and thus it is thought that it inhibits dermatitis and may provide an effective activity for allergic reactions (Capek et al., 2014). At the same time, another bioactive compounds found in coffee, kahweol have anti-inflammation effects. This action of kahweol is attributed to its ability to inhibit inducible nitric oxide synthase and macrophage cyclooxygenase-2 expression and its modulator effect on NF-kappa-β expression (Cárdenas, Quesada, & Medina, 2014). Coffee extract suppresses mitogen-induced tryptophan degradation and neopterin formation in human peripheral blood mononuclear cells and thus it is suggested that coffee extract has anti-inflammation and immunosuppression property (Gostner et al., 2015). Lopez-Garcia et al. (2006) reported a relationship between higher coffee consumption and lower endothelial dysfunction or plasma concentration of many markers of inflammation (Lopez-Garcia, van Dam, Qi, & Hu, 2006). In addition, lower circulating levels of inflammation marker among individuals who consume coffee is partly mediated the association of coffee drinking with cancer and other chronic diseases (Loftfield et al., 2015).

Cancer and coffee

The International Agency for Research on Cancer (IARC) has categorized coffee as non-carcinogenic to humans (IARC, 2016). Its consumption and various cancer risks have been extensively studied (Hashibe et al., 2015). According to many studies doing for anticancer property of coffee, kahweol found in coffee has been shown as one of the main compounds responsible for cancer chemoprevention (Park, Song, & Jeong, 2016). Kahweol is antioxidant and protects DNA against hydrogen peroxide-induced oxidative stress by cleaning reactive oxygen species (ROS) and stimulates hem oxygenase-1 for control intracellular ROS levels

(Cárdenas et al., 2014). In addition to kahweol, polyphenols found in coffee such as chlorogenic acid has also antioxidant and anti-inflammation property (Fukushima et al., 2014). Furthermore, caffeic acid shows the ability to suppress DNA methylation in cancer cells and is connected with inactivation of several ways participated in tumorigenic process such as apoptosis, stress and inflammatory response and cell cycles regulation (Yu, Bao, Zou, & Dong, 2011). Coffee consumption also shows anticancer property through some transcription factors. Increased activation of the transcription factor Specificity protein 1 (Sp1) contribute to development of various types of cancer. It is shown that this transcription factors is significantly reduced in cells treatment with kahweol (Chae, Jeon, & Shim, 2014). Carcinogenesis is suppressed by activating NF-E2-related factor 2 (Nrf2), another transcription factor, (Sporn & Liby, 2012) and Nrf2 activation in human increases with coffee consumption (Volz et al., 2012). In summary, regulation of genes involved in the detoxification, metastasis, angiogenesis, apoptosis, inflammation and DNA repair process are recommended mechanisms for the mechanism responsible for chemopreventive effect of coffee (Oh et al., 2015). Coffee has anti-carcinogenic effect by showing inhibitory/suppressive effects at every step of carcinogenesis action process. Coffee prevents development of cancer by removing pro-carcinogen, inhibiting oxidative damage and stimulating cellular defense in the initiation phase of carcinogenesis; by promoting apoptosis, removing damaged cells and showing anti-inflammation effect in progression phase of carcinogenesis; by inhibiting metastasis, cell adhesion and invasion in metastasis phase of carcinogenesis (Bøhn, Blomhoff, & Paur, 2014).

Colorectal cancer and coffee

Colorectal cancer is a main cause of mortality and morbidity and is third most widely cancer in the world (Haggar, & Boushey, 2009). Up to now, surgery and adjuvant treatment have been seen as the most effective treatment. However, the mortality of colorectal cancer remains high, and therefore the application of chemopreventive recently has drawn attention as promising strategies for human cancers (Park et al., 2016). Coffee, commonly consumed beverage, is hypothesized to be protective in colorectal cancer because it contains many anti-carcinogenic compounds (Schmit, Rennert, Rennert, & Gruber, 2016) and studies gives results in the direction of supporting this hypothesis (Budhathoki, Iwasaki, Yamaji, Sasazuki, & Tsugane, 2015; Schmit et al., 2016; Yu et al., 2011). Coffee can protect against colorectal cancer by increasing the motility of large intestine in rectosigmoid region, releasing natural sterols and bile acids into colon, showing antioxidant activity with its cafestol and kahweol content and inhibiting colon cancer cell growth with its caffeine content (Nkondjock, 2009; Yu et al., 2011). According to Colorectal Cancer Report (2011), iron increases risk of colorectal cancer due to its catalytic activity on the generation of reactive oxygen species (WCRF/AICR, 2011). The presence of coffee polyphenols inhibits iron absorption and this can contribute to anti-carcinogenic action of coffee (Mascitelli & Goldstein, 2010). Furthermore, Kang et al. (2011) hypothesized that coffee protect against colorectal cancer at the molecular level and shown that caffeic acid targets colon cancer metastasis and kinases such as MEK1 or TOPK to suppress the transformation (Kang et al., 2011). But, in some studies, coffee consumption either not related to colorectal cancer risk or associated with increased risk of colorectal cancer (Groessl et al., 2016; Larsson, Bergkvist, Giovannucci, & Wolk, 2006; Naganuma et al., 2007)

Pancreas, liver cancer and coffee

Pancreas cancer is the eighth most widely reason of death from cancer in the world (Ran, Wang, & Sun, 2016). According to Pancreas Cancer Report (2012), coffee has no significant effect on pancreas cancer risk (WCRF/AICR, 2012). In some studies, either there was no important relationship between its consumption and pancreas cancer or there was a weak correlation between its consumption and increased risk of pancreas cancer (Genkinger et al., 2012; Turati et al., 2012; Bhoo–Pathy et al., 2013; Nie, Xing, Huang, Wang, & Liu, 2016). But, some studies have found an inverse relationship between coffee and risk of pancreas cancer (Dong, Zou, & Yu, 2011; Ran et al., 2016).

Primary liver cancer is also known as hepatocellular carcinoma and is the one of the most lethal cancers worldwide (Darvesh, Aggarwal, & Bishayee, 2012). It has been put forward that coffee consumption may have a protective effect against liver cancer (Wierzejska, 2015) and according to a report published by World Cancer Research Fund International (2015) high its consumption is a possible safeguard against liver cancer (WCRF, 2015). It has a this effect against hepatocellular carcinoma by inhibiting the activity of phase 1 activating enzyme and early mutagenic events through stimulating phase 2 detoxifying enzymes and with anti-inflammatory, antioxidant and anti-fibrotic property (Masterton & Hayes, 2010). A meta analysis found that its consumption may be related to reduced risk of liver cancer (Sang, Chang, Li, & Jiang, 2013). Aleksandrova et al. (2015) suggested that there is an inverse relationship between the risk of hepatocellular carcinoma and coffee consumption and this relationship is potentially mediated by inflammation, metabolic, liver damage and iron metabolism biomarkers (Aleksandrova et al., 2015). Studies have also shown that it might have impact on the liver enzymes. In a study conducted by Chinwe et al. (2013), daily 3-4 cups unfiltered coffee

consumption increased alanine aminotransferase (ALT) levels and filtered coffee consumption decreased alkaline phosphatase and bilirubin levels in healthy individuals (Chinwe, Johnkennedy, Hope, Constance, & Helen, 2013). Low levels of markers of liver damage including gamma-glutamyl transferase enzyme and alanine transaminase enzyme is defined with coffee consumption. Thus, coffee consumption is linked to a reduced risk of cirrhosis, a risk factor for the development of liver cancer (Manne & Saab, 2015). Klatsky et al. (2006) found a relationship between coffee consumption and lower prevalence of elevated ALT (alanine aminotransferase) and AST (aspartate aminotransferase) enzyme levels. This result supports the hypothesis that coffee is protective against liver disease such as cirrhosis (Klatsky, Morton, Udaltsova, & Friedman, 2006).

Breast cancer and coffee

Among risk factors known to be responsible for approximately 10-15% of breast cancer incidence takes place lifestyle factors including dietary factors (Pathy et al., 2010). There is very little study showing the relationship between reduced risk of breast cancer and coffee consumption (Li et al., 2011; Jiang, Wu, & Jiang, 2013). Moreover, most studies suggested that there is no relationship between breast cancer risk and coffee consumption (Ganmaa et al., 2008; Fagherazzi, Touillaud, Boutron-Ruault, Clavel-Chapelon, & Romieu, 2011; Li et al., 2013). In addition, the Breast Cancer Report (2010) doesn't mention a relationship between breast cancer and coffee (WCRF/AICR, 2010). However, studies that found an inverse relationship between breast cancer and coffee consumption have suggested some mechanism for this relationship. While the consumption of high-caffeine-containing beverages such as coffee is inversely related to testosterone hormone bioavailability and is affirmatively associated with sex hormone binding

globulin and these hormonal changes positively affect breast cancer risk (Yu et al., 2011). Jernström et al. (2003) found that regular coffee consumption significantly increase the ratio of 2OHE (2-hydroxyestrone) to 16-alphaOHE (16-alpha-hydroxyestrone) and suggested a inversely relationship between this ratio and risk of breast cancer (Jernström, Klug, Sepkovic, Bradlow, & Narod, 2003). Another study found that there is a statistically substantial decrease in the risk of breast cancer among women consuming 6 or more cups/day of coffee and shown that caffeine in coffee protects against risk of breast cancer in women with BRCA1/2 gene mutation (Nkondjock et al., 2006). Kotsopoulos et al. (2007) also found protective effect of coffee against breast cancer among women with BCAR1 mutation (Kotsopoulos et al., 2007).

Prostate cancer and coffee

Prostate cancer is the most common cancer worldwide affecting the health of male population, especially in developed countries (Cao et al., 2013). Until today, the association between higher coffee consumption and lower prostate cancer has been shown in many studies (Wilson et al., 2011; Cao et al., 2013; Li et al., 2013; Lu et al., 2014; Liu et al., 2015; Tverdal, 2015). This inverse relationship is been associated with potentially chemopreventive compounds such as kahweol, cafestol, chlorogenic acid and caffeic acid in coffee (Geybels, Neuhouser, Wright, Stott-Miller, & Stanford, 2013). This compounds exerts anti-carcinogenic properties by stimulating phase 2 enzyme through kahweol and cafestol (Lai et al., 2013), showing antioxidant activity through chlorogenic acids (Kamiyama, Moon, Jang, & Shibamoto, 2015) and inhibiting DNA methylation through caffeic acid (Lee & Zhu, 2006). In addition, its consumption is positively associated with serum levels of total testosterone and sex hormones and thus may affect the risk of prostate cancer (Li et al., 2013).

Parkinson disease and coffee

Parkinson's disease is one of the widely common neurodegenerative disease worldwide. Coffee and its major bioactive compounds such as caffeine consumption provide a protective effect on Parkinson's disease (Yamada-Fowler & Söderkvist, 2015). Although the exact mechanism of coffee on Parkinson's disease is unknown, it is thought that this mechanism is mediated by caffeine effect on adenosine A2 receptor (Prakash & Tan, 2011). Caffeine acts as an adenosine receptor antagonist by inhibiting adenosine A2 receptors and stimulates the central nervous system (Hu, Bidel, Jousilahti, Antikainen, & Tuomilehto, 2007). Caffeine has neuroprotective effect because of its ability to inhibit adenosine A2 receptors concentrated in dopamine rich areas in the brain (Martyn & Gale, 2003). Caffeine has also neuroprotective effects by reducing MTP-induced neurotoxicity in animal models of Parkinson's disease (Derkinderen, Shannon, & Brundin, 2014). In a review study, it is suggested that consumption of 2-3 cups of coffee per day could protect against Parkinson's and Alzheimer's disease (Gönder & Şanlıer, 2014).

Type 2 diabetes mellitus and coffee

High coffee consumption is associated with lower risk of type 2 diabetes mellitus and better glucose tolerance (Van Dam, Willett, Manson, & Hu, 2006). More than twenty prospective cohort studies conducted in USA, Asia and Europe showed an inverse relationship between type 2 diabetes and coffee consumption (Alperet et al., 2016). At the same time there is little information about the mechanism responsible for this relationship (Fernandez-Gomez et al., 2016). Caffeine, chlorogenic acids and magnesium, etc. compounds in coffee can affect glucose metabolism (Muley, Muley, & Shah, 2012). Theophylline, the metabolism product of caffeine in liver, exerts anti-diabetic activity by controlling glucose metabolism (Pimentel, Zemdegs,

Theodoro, & Mota, 2009). Chlorogenic acids exerts anti-diabetic activity by reducing glucose output from liver, exhibiting its anti-oxidative properties, reducing glucose absorption in the intestine through inhibiting the enzyme glucose-6-phosphate translocase, (Ding, Bhupathiraju, Chen, van Dam, & Hu, 2014) inhibiting gut incretin hormones and protecting pancreatic beta cells against oxidative stress through antioxidant property (Pereira, Parker, & Folsom, 2006). Trigonelline exerts anti-diabetic activity by modulating enzymes in involved in glucose and lipid metabolism such as glycokinase, glucose-6-Pase, fatty acid synthetase and carnitine palmitoyltransferase (Santos & Lima, 2016) and magnesium may acts on diabetes by improving insulin secretion and sensitivity (van Dam & Feskens, 2002). Yarmolinsky et al. (2015) suggested that coffee has a protective effect on the risk of adult-onset diabetes and this effect is mainly mediated by postprandial glucose homeostasis (Yarmolinsky et al., 2015). There is increasing evidence that regularly 3-4 cup/day coffee consumption is associated with lower risk of type 2 diabetes mellitus (Santos & Lima, 2016). The effects of coffee on type 2 diabetes mellitus are shown in Figure 2 (Akash et al., 2014).

Cardiovascular disease and coffee

Coffee is both positively and negatively associated with cardiovascular disease (Bøhn, Ward, Hodgson, & Croft, 2012). A number of mechanism have been proposed to explain the harmful and protective effects of certain compounds of coffee on cardiovascular disease development. Coffee has negative effects on cardiovascular diseases in the form of increasing blood pressure, serum lipid levels and serum homocysteine levels (Cornelis & El-Sohemy, 2007). Firstly, Olthof et al. (2001) found that chlorogenic acids, which are compounds of coffee, increase the total homocysteine levels in plasma (Olthof, Hollman, Zock, & Katan, 2001). Homocysteine is known

to induce cardiovascular problems through unfavorable effect on the smooth muscle cells and cardiovascular endothelium (Ganguly & Alam, 2015). Secondly, caffeine in coffee is the main compound increase acute blood pressure (O'Keefe et al., 2013). It has been suggested that caffeine increases blood pressure by stimulating the sympathetic nervous system and increasing release of norepinephrine with activation of renin-angiotensin system and direct effect on the adrenal medulla (Geleijnse, 2008). As a result of a randomized study, caffeine increased blood pressure in healthy normative young men and women (Farag et al., 2010). Finally, diterpenoid alkaloids (kahweol and cafestol) known as coffee fats in coffee are main compounds responsible for increasing blood lipids (Shateri & Djafarian, 2016) and filtration of coffee reduces these compounds (Bidel & Tuomilehto, 2012). As a result of a meta-analysis study, consumption of unfiltered coffee has been found to increase serum levels of LDL and total cholesterol (Jee et al., 2001). Kahweol and cafestol increases serum cholesterol levels by reducing LDL receptor activity. This causes accumulation of LDL cholesterol outside the cells and supports the development of atherosclerosis (Bidel & Tuomilehto, 2012). Besides the negative effects on blood lipid levels, diterpenes have positive physiological effects such as hepatoprotective and antioxidant effects (Dias, de Faria-Machado, Mercadante, Bragagnolo, & de Toledo Benassi, 2014). As a result of a meta-analysis by Ding et al. (2013), 3-5 cups/day (moderate) consumption was related to lower risk of cardiovascular disease and ≥6 cups/day (heavy) consumption was not related to cardiovascular disease risk (Ding, Bhupathiraju, Satija, van Dam, & Hu, 2013).

Obesity and coffee

The intake of coffee polyphenols decreases dietary-induced obesity by increasing energy expenditure through suppressing transcription factor sterol regulatory element binding protein 1c

(SREBP-1c), which are controls the expression of lipogenic enzymes such as stearoyl coa desaturase 1 and acetyl coa carboxylase in the liver and adipose tissue (Murase et al., 2011). Nagao et al. (2009) suggested that regularly consumption of chlorogenic acid, the main coffee polyphenol, reduces body fat, especially the abdominal fat including visceral fat (Nagao et al., 2009). While caffeine in coffee suppresses fat absorption, chlorogenic acid causes decrease in hepatic triglyceride levels (Shimoda, Seki, & Aitani, 2006). Cho et al. (2010) shown that chlorogenic acid and caffeic acid exhibit anti-obesity effects by decreasing cholesterol and fatty acid biosynthesis and altering plasma adipokine levels while increasing PPAR-alpha expression and fatty acid oxidation in the liver (Cho et al., 2010). In another study, Gavrielli et al. (2013) found that moderate coffee consumption effectively reduced energy intake all day and after meals (Gavrieli et al., 2013). In addition coffee consumption has potentially beneficial effects on some metabolic risk factors such as hypertension, abdominal obesity and hyperglycemia (Song, Oh, Lee, & Cho, 2016). Therefore, coffee consumption is associated with a lower risk of metabolic syndrome (Nordestgaard, Thomsen, & Nordestgaard, 2015). It has also been shown that green coffee extract has anti-obesity activity with reducing body fat accumulation by regulating adipogenesis and genes and proteins associated with lipid metabolism in white adipose tissue and liver and thus leads to loss of body weight (Onakpoya, Terry, & Ernst, 2010; Choi et al., 2016). The effects of coffee on obesity are shown in Figure 3 (Pimentel et al., 2014).

Coffee consumption recommendations

According to EFSA recommendations, pregnant and lactating women can consume caffeine provided they don't exceed 200 mg/day of caffeine consumption. That is, the consumption of coffee is likely to be less than two cups per day. In addition, according to EFSA

recommendations, consumption of caffeine is safe until 400 mg/day caffeine consumption in healthy adults. As a result, in line with an active lifestyle and a healthy diet, moderate coffee consumption (3-5 cups/day) is associated with a wide range of desired physiological effects and for healthy adults (other than pregnant and lactating women) this amount of consumption is safe (Efsa Panel on Dietetic Products & Allergies, 2015). EFSA recommended consumption amounts for the effects of coffee and its components on health are given in Table 1 (Efsa Panel on Dietetic Products & Allergies, 2011a, 2011b).

Studies showing the relationship between coffee and health are given in Table 2.

Conclusions and Recommendations

Coffee is widely consumed throughout the world. Its health benefits depend on caffeine, chlorogenic acids, caffeic acid, kahweol, cafestol and so on compounds. Regular coffee consumption of 3-5 cups/day (moderate consumption) can reduce risk of type 2 diabetes mellitus, Alzheimer's, Parkinson's and cardiovascular diseases and exerts optimal protective effects. It is known that coffee oils, cafestol and kahweol, increase LDL and total cholesterol levels. However, with the filtration of coffee, the content of kahweol and cafestol in coffee significantly reduces and filtered coffee consumption may not be associated with an increase in serum cholesterol levels. At the same time, kahweol is also responsible for beneficial effects such as anti-oxidant and anti-inflammatory effects. As a result, consumption of 2 cups (200 mg caffeine) per day for pregnant and lactating women and 3-5 cups (400 mg caffeine) per day for adults will be beneficial.

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Table 1. EFSA recommended consumption amounts for the effects of coffee and its components on health (Efsa Panel on Dietetic Products & Allergies, 2011a, 2011b)

Health effects	Coffee components and health effects	Consumption amounts for health effects
Maintenance of body weight	Coffee Glucose homeostasis	3 cups/day coffee
	Coffee-chlorogenic acids Glucose homeostasis	180 mg/day chlorogenic acid 1,5 cups/day coffee
	Coffee-caffeine Fat metabolism and energy expenditure	Minimum 150 mg/day caffeine
	Coffee-caffeine Thermogenesis support	Minimum 300 mg/day caffeine (at least 3 portions)
Protection of cancer	Coffee Protection of oxidative stress	1-2 cups/day coffee
Cognitive health	Coffee-caffeine Cognitive performance	Minimum 32 mg/day caffeine

Table 2. Studies showing the relationship between coffee and health

Diseases	Study types	Coffee consumption (min-max)	Health effects of coffee consumption	References
Colorectal cancer	2 prospective cohort study	1-3 times/ m. ≥6 times/day	Regular caffeinated coffee consumption ⇒ ↓ not associated with risk of colon and rectal cancer Regular decaffeinated coffee consumption ⇒ risk of rectal cancer↓	Michels, Willett, Fuchs, and Giovannucci, 2005
Colorectal cancer	2 prospective cohort study	Consumption (-) ≥4 cups/day	Coffee consumption ⇒ ↓ not associated with risk of colorectal cancer	Larsson et al., 2006
Colorectal cancer	Prospective cohort study	Consumption (-) ≥5 cups/day	Coffee consumption ⇒ not associated with risk of colorectal cancer	Naganuma et al., 2007
Colorectal cancer	Meta analyze study	-	+1 cup/day coffee consumption ⇒ 3% reduction in risk of colorectal cancer	Yu et al., 2011
Colorectal cancer	Prospective cohort study	Consumption (-) ≥6 cups/day	Coffee consumption ⇒ risk of colon cancer ↓ Decaffeinated coffee consumption ⇒ risk of rectal cancer ↓	Sinha et al., 2012
Colorectal cancer	Meta analyze	Consumption (-) ≥8 cups/day	Coffee consumption ⇒ risk of colon and colorectal cancer↓	Li, Ma, Zhang, Zheng, and Wang, 2013
Colorectal cancer	Cohort study	<1 cup/day ≥4 cups/day	Coffee consumption ⇒ risk of colon cancer ↑ (men), not associated with risk of colorectal cancer (women)	Yamada et al., 2014
Colorectal cancer	Case control study	<1 cup/week ≥10 cups/day	Coffee consumption ↑ ⇒ risk of colorectal cancer ↓	Budhathoki et al., 2015
Colorectal cancer	Observational cohort study	0-4 cups/day ≥4 cups/day	Regular moderate/high decaffeinated coffee consumption⇒risk of colorectal cancer↑(postmenopausal women)	Groessl et al., 2016
Colorectal cancer	Case control study	<1 serving/d. ≥2,5 serving/d.	Coffee consumption ⇒ 26% reduction in risk of colorectal cancer Coffee consumption ↑ ⇒ risk of colorectal cancer ↓	Schmit et al., 2016
Pancreas cancer	Cohort study	Consumption (-) ≥3 cups/day	Coffee consumption ⇒ risk of pancreas cancer ↓ (men)	Luo et al., 2007
Pancreas cancer	Meta analyze	Consumption (-) ≥7 cups/day	Coffee consumption ↑ ⇒ risk of pancreas cancer ↓	Dong et al., 2011
Pancreas cancer	Meta analyze	-	High coffee consumption ⇒ not associated with risk of pancreas cancer	Turati et al., 2012

Pancreas cancer	Prospective study	Consumption (-) ≥6 cups/day	Caffeinated or decaffeinated coffee consumption ⇒ not associated with risk of pancreas cancer	Guertin et al., 2015
Pancreas cancer	Meta analyze	-	+1 cup/day coffee consumption ⇒ 1% increase in risk of colorectal cancer	Nie et al., 2016
Pancreas cancer	Meta analyze	Consumption (-) ≥10 cups/day	Coffee consumption ↑ ⇒ risk of pancreas cancer ↓	Ran et al., 2016
Diseases	Study types	Coffee consumption (min-max)	Health effects of coffee consumption	References
Liver cancer	2 prospective studies	Consumption (-) ≥1 cup/day	Coffee consumption ⇒ risk of liver cancer ↓	Shimazu et al., 2005
Liver cancer	Meta analyze study	-	Coffee consumption ↑ ⇒ risk of liver cancer ↓	Larsson and Wolk, 2007
Liver cancer	Cohort analyze study	<1 cup/day ≥3 cups/day	Coffee consumption ↑ ⇒ risk of liver cancer ↓	Inoue et al., 2009
Liver cancer	Prospective cohort study	Consumption (-) ≥3 cups/day	≥3 cups/day coffee consumption ⇒ 44% reduction in risk of liver cancer	Johnson et al., 2011
Liver cancer	Meta analyze study	Consumption (-) ≥8 cups/day	Coffee consumption ↑ ⇒ risk of liver cancer ↓ High coffee consumption ⇒ 50% reduction in risk of liver cancer	Sang et al., 2013
Liver cancer	Prospective study	<2 cups/day ≥4 cups/day	Coffee consumption ↑ ⇒ risk of liver cancer ↓	Aleksandrova et al., 2015
Liver cancer	Cohort study	Consumption (-) ≥3 cups/day	≥3 cups/day coffee consumption ⇒ 50% reduction in risk of liver cancer	Petrick et al., 2015
Liver cancer	Cohort study	Consumption (-) ≥4 cups/day	2-3 cups/day coffee consumption ⇒ 38% reduction in risk of liver cancer ≥4 cups/day coffee consumption ⇒ 41% reduction in risk of liver cancer	Setiawan et al., 2015
Breast cancer	Cohort study	<1 cup/month ≥4 cups/day	Coffee consumption ⇒ not associated with risk of breast cancer	Ganmaa et al., 2008
Breast cancer	Meta analyze	Consumption (-) ≥7 cups/day	Coffee consumption ↑ ⇒ associated with risk of breast cancer	Tang, Zhou, Wang, and Yu, 2009
Breast cancer	Prospective cohort study	Consumption (-) ≥3 cups/day	Coffee consumption ⇒ not associated with risk of breast cancer	Fagherazzi et al., 2011
Breast cancer	Case control study	<1 cups/day >5 cups/day	High coffee consumption ⇒ estrogen receptor negative breast cancer ↓ (postmenopausal women)	Li et al., 2011
Breast cancer	Meta analyze	-	Coffee consumption ⇒ not associated with risk of breast cancer	Li et al., 2013

Breast cancer	Meta analyze	Consumption (-) ≥10 cups/day	+2 cups/day coffee consumption ⇒ 2% reduction in risk of breast cancer (poorly)	Jiang et al., 2013
Prostate cancer	Meta analyze	Consumption (-) ≥7 cups/day	Regular coffee consumption ⇒ 12% reduction in risk of prostate cancer	Wilson et al., 2011
Prostate cancer	Prospective cohort study	Consumption (-) ≥5 cups/day	≥3 cups/day coffee consumption ⇒ 37% reduction in risk of prostate cancer	Cao et al., 2013

Diseases	Study types	Coffee consumption (min-max)	Health effects of coffee consumption	References
Prostate cancer	Meta analyze	Consumption (-) 6-9 cups/day	High coffee consumption ⇒ risk of lethal prostate cancer ↓	Lu et al., 2014
Prostate cancer	Meta analyze	Consumption (-) ≥7 cups/day	Coffee consumption ⇒ risk of prostate cancer ↓	Liu et al., 2015
Prostate cancer	Prospective study	Consumption (-) ≥9 cups/day	Coffee consumption ↑ ⇒ risk of prostate cancer ↓	Tverdal, 2015
Oral cancer	Cohort study	Consumption (-) ≥1 cup/day	Coffee consumption ↑ ⇒ risk of oral, pharynx and esophagus cancer ↓	Naganuma et al., 2008
Endometrial cancer	Meta analyze	Consumption (-) ≥8 cups/day	Coffee consumption ↑ ⇒ risk of endometrial cancer ↓	Zhou, Luo, Li, Li, and Zhou, 2015
Parkinson's disease	Prospective cohort study	-	Coffee consumption ↑ ⇒ risk of Parkinson disease ↓	Ross et al., 2000
Parkinson's disease	2 cohort studies	Consumption (-) ≥6 cups/day	Coffee consumption ↑ ⇒ risk of Parkinson disease ↓ (men) Moderate coffee consumption (1-3 cups/day) ⇒ protection on risk of Parkinson disease	Ascherio et al., 2001
Parkinson's disease	Meta analyze	-	Coffee consumption ↑ ⇒ risk of Parkinson disease ↓	Hernán et al., 2002
Parkinson's disease	Cohort study	Consumption (-) ≥6 cups/day	Coffee consumption ↑ ⇒ Parkinson disease mortality ↓ (men)	Ascherio et al., 2004
Parkinson's disease	Prospective study	Consumption (-) ≥10 cups/day	Coffee consumption ↑ ⇒ risk of Parkinson disease ↓	Sääksjärvi et al., 2008
Parkinson's disease	Meta analyze	Consumption (-) ≥6 cups/day	Coffee consumption ↑ ⇒ risk of Parkinson disease ↓	Costa, Lunet, Santos, Santos, and Vaz-Carneiro, 2010
Diabetes mellitus	Cohort study	<2 cups/day >7 cups/day	Coffee consumption ↑ ⇒ risk of type 2 diabetes mellitus ↓	Vandam and Feskens, 2002
Diabetes	Prospective	Consumption (-)	Long term coffee consumption ⇒	Salazar-Martinez

mellitus	cohort study	≥6 cups/day	risk of type 2 diabetes mellitus ↓	et al., 2004
Diabetes mellitus	Systematic review	Consumption (-) ≥10 cups/day	Moderate coffee consumption (≥4 cups/day) ⇒ risk of type 2 diabetes mellitus ↓	Pimentel et al., 2009
Diabetes mellitus	Systematic review	Consumption (-) ≥10 cups/day	Coffee consumption ↑ ⇒ risk of type 2 diabetes mellitus ↓	Muley et al., 2012
Diabetes mellitus	Meta analyze	Consumption (-) ≥12 cups/day	Coffee consumption ↑ ⇒ risk of type 2 diabetes mellitus ↓	Ding et al., 2014

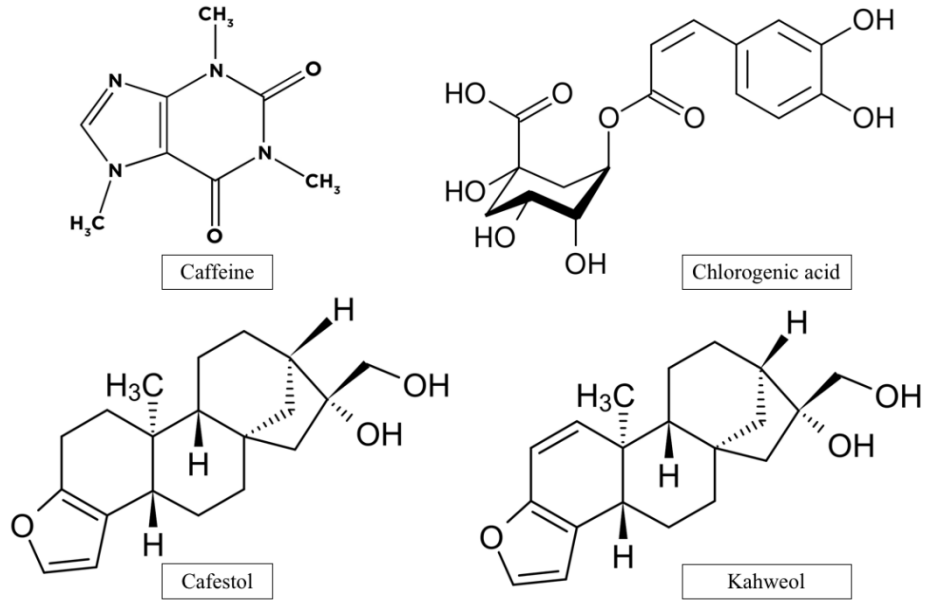

Figure 1. Chemical formula of bioactive compounds found in coffee (Godos et al., 2014)

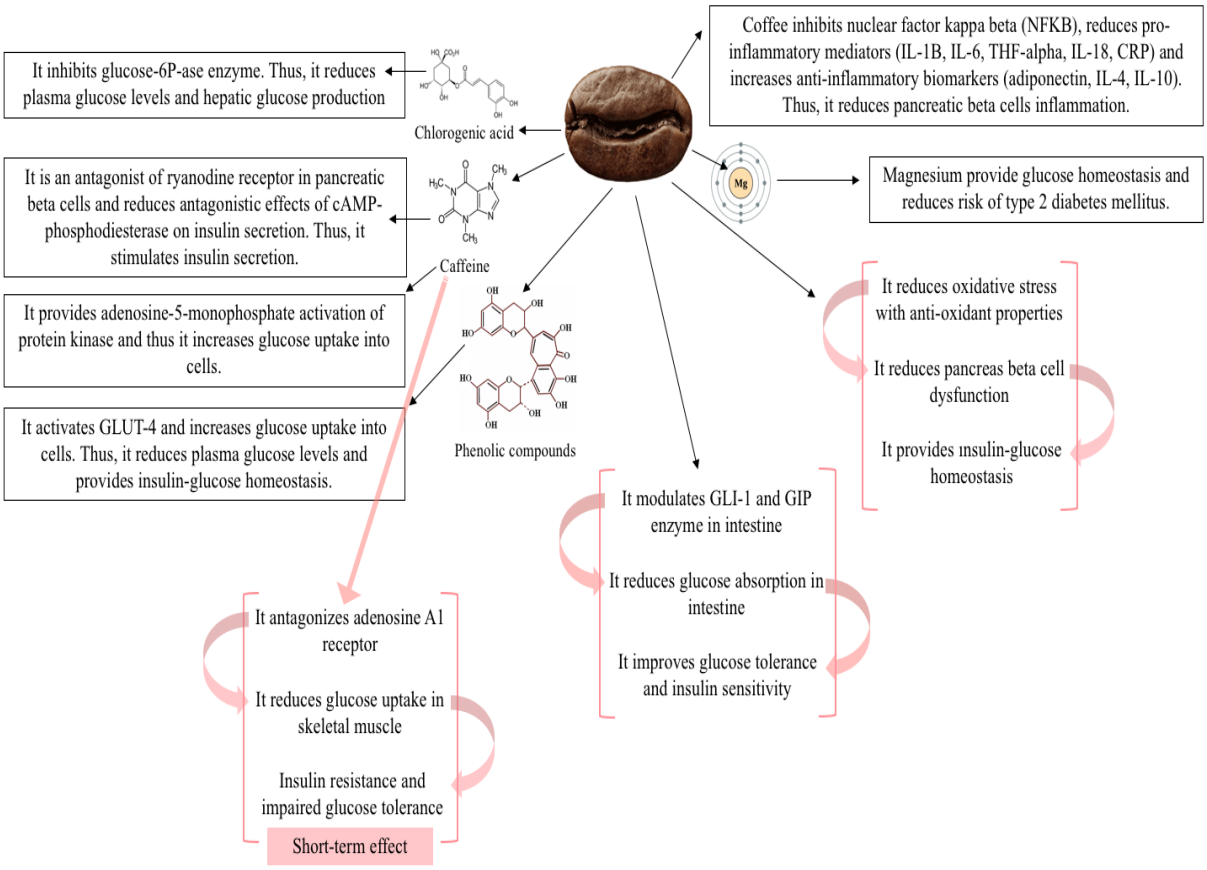

Figure 2. The effects of coffee on type 2 diabetes mellitus (Akash et al., 2014)

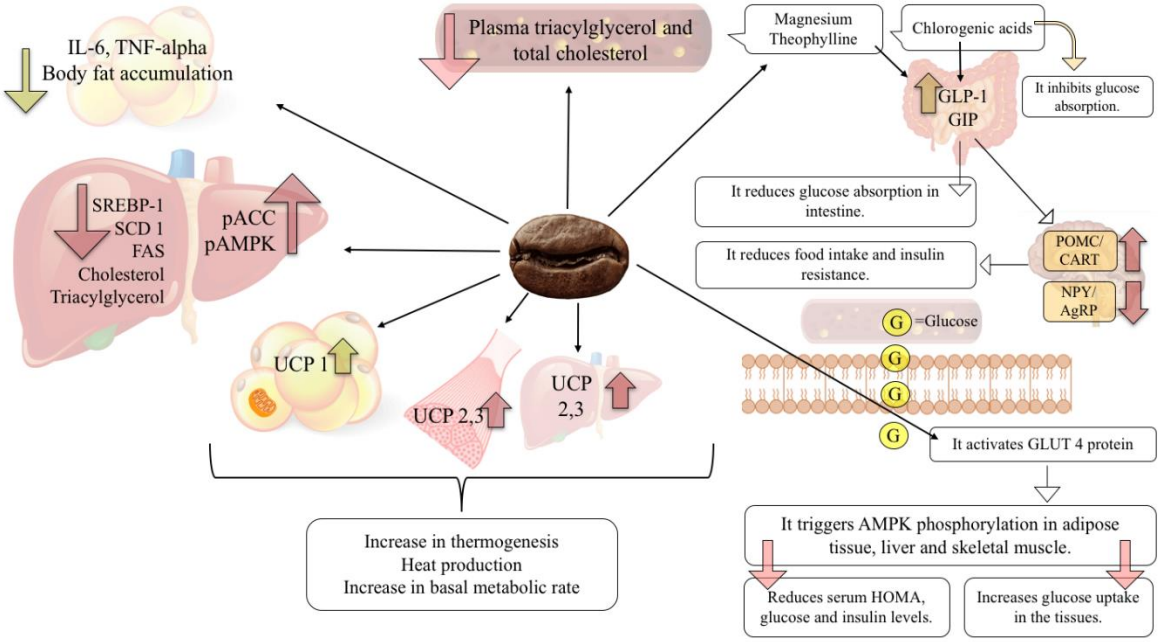

Figure 3. The effects of coffee on obesity (Pimentel et al., 2014)