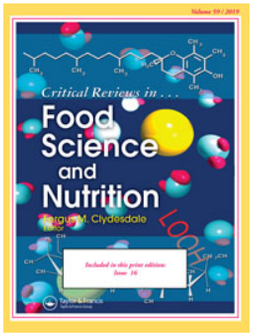

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Consumption of green coffee and the risk of chronic diseases

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ABSTRACT

Green coffee contains macro nutrients such as carbohydrates, protein, fat, as well as minor components such as caffeine, trigonelin and chlorogenic acid. Phenolics, chlorogenic acids and brown pigments are sources of natural antixodants. High polypehonic materials found in green coffee and especially chlorogenic acid in it have an important place. It is considered that; green coffee has effects on body mass, blood glucose and lipid levels, blood pressure, prevention from cardiovascular diseases which is based on chlorogenic acid consisting antioxidant activity. However, many topics like toxicological effects, doses, amounts, usage in the body, advantages and disadvantages, etc. of these active molecules need to be examined. For these reasons this article was rewieved to evaluate health effects of green coffee.

KEYWORDS

Green coffee; caffeine; phenolics; chlorogenic acid; antioxidant activity; diseases

1. Introduction

The pleasant taste and odour of the coffee, being a natural antioxidant source due to the polyphenols it contains have made it one of the most popular beverages consumed in the world after water. Every year more than 800 billions cup of coffee have been consumed in the world (Yüceşen 2012). Which is why coffee is consumed at all hours of the day and night by people, especially after meals (Gómez-Juaristi et al. 2018). With the proliferation of specialty coffee establishments, restaurants and snacks, coffee consumption is also increasing rapidly. Depending on the augmentation of special coffee enterprises, restaurants and fast food chains, coffee consumption is also increasing rapidly (Bozkurt 2012). Coffee containing more than 700 compounds which are responsible for its aromatic and unique taste, is one of the most consumed beverage in the world (Wolska et al. 2017; Jeszka-Skowron et al. 2016a). At the same time, it is the most important nutritional product that is traded and consumed in the world and it is ranked as the second after crude oil among all raw materials (Getachew and Chun 2016). World coffee production has shown an increase about 100% since 1950 (Nogaim et al. 2013).

Coffee belongs to *Rubiaceae* family, grows in areas which are rainy, have average 18–24°C temperatures and never seen frost event. Although *Rubiaceae* family has many subgenus and subspecies, *Coffea arabica* and *Coffea canephora (robusta)* are the species gained importance in commercially speaking (Bozkurt 2012). About 90 % of coffee production is formed by *Coffee arabica* while this ratio is 9 % in Canephora (*Coffee robusta*). (Kemsley, Ruault, and Wilson 1995).

Coffee has a widespread impact on public health with its preventive health effects (Sarriá et al. 2018). As a functional food with antioxidant properties, coffee reduces the incidence of cancer, diabetes and liver diseases, protects against Parkinson's disease and reduces mortality risk (Jeszka-Skowron et al. 2016a; Stelmach, Pohl, and Madeja 2015). Especially in recent years, green coffee which is defined as a functional food due to the components it contains has become a popular product that consumption of it is becoming increasingly widepread (Dziki et al. 2015).

Green coffee is form of raw, unroasted, unprocessed and natural coffee fruit (Şemen et al. 2017). Nowadays, green coffee which is favoured by people whom have effort on weight loss, is preferred because of antioxidant and other sanatory properties. Reducing the risk of disease and preventive property of coffee is associated with rich phytochemicals such as caffeine, chlorogenic acid and caffeic acid in its composition (İştar et al. 2016).

Green coffee bean extract has a hypotensive effect in mice and reduces visceral fat and body weight. These effects are linked not only to chlorogenic acids and their derivatives but also to bioactive compounds such as caffeine, theophylline and theobromine, cafestol, kahweol, tocopherols and trigonellin (Jeszka-Skowron et al. 2017). In addition, green coffee beans contain hydroxycinnamic acids such as caffeic and ferulic acids and quinic acid esters called chlorogenic acids (CGAs). These components exhibit anti-inflammatory and antimutagenic effects that prevent tumors, chronic disorders such as cardiovascular and rheumatologic diseases (Budryn, Zaczyńska, and Rachwał-Rosiak 2016; Tajik et al. 2017). Moreover they have antiviral, antioxidant, antibacterial (Brahat, Sowmya, and Mehta 2015), antifungal and antimycotoxigenic (Suárez-Quiroz et al. 2013) properties. Furthermore, it has been found that CGAs can modulate lipid metabolism and glucose in both genetic disorders and disorders associated with healthy

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metabolism (Naveed et al. 2018). For this reason green coffee which is evaluated as a functional food itself should also be used in new functional food development.

In 2017 a study conducted by Zain and colleagues in production of a functional bread with the addition of green coffee beans, powdered green coffee beans were added at the ratios of 3, 5 and 7 % into the bread dough. They have reported that, as the amount of green coffee bean added to dough increased, the total phenolic content, antioxidant activity increased while the sensory properties were adversely effected. They have also reported that the usage of green coffee bean is appropriate for functional bread production but more studies are required to determine the optimum amount (Zain, Baba, and Shori 2017). In a similar study, the addition of green coffee flour in bread making increased the phenolic content of the bread and improved its protection ability against lipid oxidation. *In vitro* digestion led to the release of phenolics from the bread and caused significant qualitative changes. According to the results of the research, it has been found that the bioaccessibility and bioavailability of phenolic compounds are provided *in vitro*. However, the influence of the food matrix and its interaction with CGAs also play an important role in the bioactivity of the functional product. According to the results obtained, it is reported that the qualitative composition plays an important role in the formation of phenolic fraction antioxidant potential; in addition to this, potential synergism between caffeine and low molecular weight antioxidants is also important (Świeca et al. 2017).

In another study in which soy milk was enriched with green coffee extract, it was demonstrated that the level of the phenolic substance and the antioxidant capacity in the milk was increased. In addition it has been reported that, the phenolic antioxidants obtained from soy milk drinks supplemented with green coffee extract are highly accessible *in vitro*; herewith the consumption of soy milk supplemented with green coffee extract may combine the health benefits of green coffee and soya bean compounds. On a side note, it is notified that the inclusion of green coffee extract especially in high doses has a positive effect on nutritional properties; also provides increase in protein and starch digestibility (Seczyk, Świeca, and Gawlik-Dziki 2017).

1.1. Composition of green coffee

Traditionally, green coffee is produced by wet or dry processing of coffee fruit (cherry). Wet processing is the process of extracting most of the essence and the pulp of coffee fruit by pressing. However, most of the fruit pulp remains on the parchment and these residues are degraded by fermantation and afterwards they are dried. The parchment and the testa are peeled. In the dry processing process, all the coffee beans are dried before all the layers around the seeds are removed. The dry processing process is often applied in areas where particularly climatic contiditions are suitable for sun drying (Kleinwächter, Bytof, and Selmar 2015).

The chemical composition of green coffee is characterized by the presence of caffeine, which could reach 1.45 % and 2.38 % in *C. arabica* and *C. canephora*, respectively. (Babova, Occhipinti, and Maffei 2016). The main components of the green coffee beans are; polysaccharides, proteins and fats, while minor components are caffeine, trigonelin, chlorogenic acid, simple sugars (especially sucrose), free amino acids (Wei and Tanokura 2015). Approximately half weight of dry coffee beans are formed by polysaccharides. The content of polysaccharide in the Green Robusta bean is 48 % and is mainly composed of arabinogalactan, mannan and cellulose. Polysaccharide profiles of the Arabica and Robusta green coffee benas are similar. The main difference between them is; the arabinogalactan content of Robusta beans is 3 % higher than that of Arabica. Although the polymeric carbohydrate content of Arabica beans is lower than that of Robusta beans, the low molecular weight carbohydrate content (especially sucrose) of the Arabica beans is higher (Bradbury and Halliday 1990). Sucrose is the most common simple carbohydrate in green coffee beans. It participates in the Maillard reaction during the roasting of the coffee bean. The sucrose content of Arabica green coffee beans are higher that that of Robusta. Sucrose forms 9 % of dry weight of the green coffee beans. Arabica green coffee bean (mean 73 mg/g dry weight) contains significantly at higher concentration of sucrose than Robusta (mean 45 mg/g dry weight). During roasting, sucrose gives a typical aroma and color to the coffee. Glucose, fructose and galactose are found at significantly lower concentrations in the green coffee bean (Murkovic and Derler 2006). Proteins, peptides and free amino acids are the nitrogenous flavor precursors of green coffee beans. Flavor and dark color (brown) of the coffee are formed as a result of Maillard reactions. Maillard reaction; is a nonenzymatic browning reaction taking place between the carbonyl group of a reducing sugar and amino acids, peptides or the free amino groups of proteins. The amino acid content of Robusta is higher than that of Arabica. Alanine is the most common amino acid in both 2 types of coffee, followed by asparagine. Asparagine is important for being the determining material of the amount of acrylamide formation during the roasting process. The oil content of green coffee bean is 7–17 %. The oil content of Arabica (mean 15 %) is higher than Robusta (mean 10 %). A great majority of green coffee lipids is formed by coffee oil in bean endosperm which is composed by triglycerides, phospholipids, sterols, tocopherols, characteristic diterpenes of coffee (cafestol, kahweol), fatty acid esters (Oestreich-Janzen 2010; Albertina de Oliveira et al. 2018). 100 g of green coffee beans contain about 1–2 g (40 % of total mineral content) of potassium. The ratio of phosphorus of coffee is 4 % of total mineral content. Sodium, magnesium, calcium, sulphure are the other minerals in coffee. The amount of other minerals except for magnesium is not different for Arabica and Robusta. (*C. arabica* 2.5–6 mg/100 g; *C. canephora* 1–3 mg/100 g) (Farah 2012). Caffeine (1,3,7-trimethylxanthine) is a derivative of xanthine. It is an important factor in the formation of characteristic bitter aroma of the coffee. The caffeine content of green coffee on dry weight basis is; 2.2–2.8 % for Robusta coffee and 0.6–1.2 % for Arabica coffee. Trigonine is a derivative of pyridine presents in the green coffee bean. It contributes to the formation of aroma products during roasting of coffee (Perrone, Marino Donangelo, and Farah 2008). Green coffee contains 53–76 mg/200 ml of trigonelin and the content of trigonellin in Robutsa coffee is higher than that of Arabica (Minamisawa, Yoshida, and Takai 2004).

Green (or raw) coffee is the main source of CGAs in nature (5–12 g/100 g) (Farah and Donangelo 2006). Chlorogenic acids are used to label a transhydroxycinnamic acid family, one of the most important groups of phenolic compounds found in abundant amounts in many plants (Budryn et al. 2014). Chlorogenic acids (CGA) are phenolic compounds formed by the esterification of cinnamic acids, such as caffeic, ferulic, and *p*-coumaric acids, with (−)-quinic acid (Shearer et al. 2003). Chlorogenic acid has 9 main isomers. Three of them is CQA (3-,4-,5-CQA), three of them is diCQA (3,4,-3,5-,4,5- diCQA) and the other three of them is FQA (3-,4-,5-FQA). The green coffee bean is one of the important sources of chlorogenic acid and 5-CQA forms 50 % (based on dry weight) of total CGAs in green coffee beans. Chlorogenic acid contents of green coffee beans are 3.40–7.24 % for *C. arabica* and 5.17–14.4 % for *C. canephora* (*robusta*) (Narita and Inouye 2015).

1.2. Green coffee and health effect

Although some possible negative effects, such as spontaneous abortion and stillbirth have been suggested during pregnancy (Bech et al. 2005), habitual coffee consumption has been associated with a substantially lower risk of mortality (Happonen et al. 2008) as well as degenerative, progressive and chronic diseases, including Alzheimer's disease (Lindsay et al. 2002), Parkinson's disease (Ascherio et al. 2004), type 2 diabetes (Van Dam, and Hu 2005), and coronary heart disease (Lopez-Garcia et al. 2006).

1.3. Green coffee and ıts effect on blood glucose level

It is considered that the worldwide prevalence of Type 2 diabetes is increasing, and by 2030 the number of individuals with Type 2 diabetes is expected to reach 366 million (Sarriá et al. 2016). Recent studies have shown that green coffee may have effects on glucose metabolism. Green coffee serves as glucose usage stimulant and mitochondrial activator by caffeine. Caffeic acid reduces oxidative stress and takes charge in axon regeneration with trigonellin dentrit. On the other hand, chlorogenic acid plays an important role in glucose homeostasis as well as in reducing oxidative stress. It has been reported that green coffee extract in rats fed on a high fat diet; may protect against oxidative stress of β-cells, reduce tiglycerides, glucose and oxidized glutathione levels, have antidiabetic effect, even be useful for reducing metabolic syndrome by prevention and treatment of type 2 diabetes (Budryn et al. 2017). In an another study, decaffeinated green coffee bean extracts were given to 50 healthy men and women aged between 18–70 years for 40 days without diet and exercise changes. In prospective, open-label, pilot clinical trial; each of them containing 200 mg green coffee beans extracts were (GCBE) given to individuals 3 tablet /day. After 40 days of GCBE intervention, glycaemia was reduced after glucose tolerance test, before intervention, also it is reported that mean body weight loss was approximately 1361 g (without dieting and exercise changes) for the entire group after the intervention (Blum, Lemaire, and Lafay 2007). In a study in which 500 mg/kg of decaffeinated green coffee bean extract (DGCBE) with 2 g/kg of sucrose/maltose/soluble starch/glucose together was given to 6-week-old rats, 30 minutes after the administration blood glucose levels were measured low contrast to control group. It has been stated that DGCBE does not have an effect on the glucose tolerance curve when it is given alone. On the part of the study working on volunteers, 45 healthy individuals aged between 20–50 years were consumed a test drink (100 or 300 mg decaffeinated green coffee bean extract / 200 mL water or only water as a control) with a snack containing 2 pieces of rice and seaweed for 1 week. 30 minutes after consumption of drink containing decaffeinated green coffee bean extract plasma glucose was found to be low compared to control (Iwai et al. 2012). In an another study, the effect of once-use of different coffee products on glucose absorption was investigated. Individuals' blood glucose levels were analyzed by calculating the total area under the curve (AUC) using linear trapezoidal rule. It has been reported that, after the consumption of green coffee bean extract there was a decrease in AUC when it is compared after the consumption of control drink, but there was not such an effect observed after consumption of caffeinated instant coffee or decaffeinated instant coffee (Thom 2007). In a randomized, controlled cross-over study of 52 healthy men and women aged between 18 and 55 who were not diagnosed with diabetes, individuals consumed at a ratio of 35:65 green/roasted coffee mixture or water or isotonic drink as a control every 8 weeks. In coffee intervention, the subjects consumed 6 g of coffee (3 cups) containing a total of 510.6 mg of hydroxycinnamic acid (chlorogenic acid) and 120 mg of caffeine per day. After coffee intervention, the calculated HOMA-IR values for evaluating fasting blood glucose levels and insulin resistance were found to be low, the calculated QUICKI values for assessing insulin sensitivity were found to be high and this was reported to improve insulin sensitivity. As a result, it has been stated that consumption of regular green/roasted coffee mixture may be suggested to prevent type 2 diabetes risk (Sarriá et al. 2016). Chlorogenic acid in the green coffee bean should inhibit glucose-6-phosphatase activity by inhibiting glucose absoption from the small intestine (Thom 2007). It could be considered that the effect of it on blood glucose level is shown by this mechanism.

1.4. Green coffee and effect on blood lipids

Green coffee bean extract supplementation in overweight and obese patients with nonalcoholic fatty liver disease was found to have a positive effect on liver enzymes, insulin resistance and glucose and lipid metabolism at the end of eight weeks in a randomized controlled trial. It has been reported that these beneficial effects of the green coffee bean extract may depend on the possibility of reducing insulin sensitivity and improving anti-inflammatory, antioxidant properties (Shahmohammadi et al. 2017).

In a similar study in which green coffee extract was investigated on lipid metabolism, 400 mg of green coffee extract was given to 10 healthy adult subjects for 30 days and urine samples were taken every day. It has been observed that the urine composition was different between the process in which the green coffee extract was used and before. Markers for treatment are carnitine derivatives and dicarboxylic acids as well as metabolites of polyphenol administration, such as hypercarboxylic acid, benzoic acid derivatives, dihydroferulic and

dihydrocinapic acid sulphate. On the other hand, no changes in allantoin and 8-OHdG levels were observed. The results have shown that green coffee extract is effective on lipid metabolism. Green coffee beans are thought to play an active role in controlling blood lipid levels while participants' body weights were not changed (Peron et al. 2018).

Coffee and tea are the most frequently used beverages prepared from plants worldwide; they are consumed primarily for their taste and flavour, but are also considered to be healthy for several organs and tissues, including the liver. Conflicting data were also reported on the association between coffee intake and the severity of liver damage in NAFLD patients. Two cross-sectional studies showed that a large amount of coffee was protective towards histologically diagnosed liver fibrosis (Anty et al. 2012; Molloy et al. 2012).

1.5. Green coffee and antıoxıdant effect

Coffee is a complex beverage composed of many bioactive compounds that have been found to exert many physiological effects. Caffeine, an important component of coffee, has potent antioxidant activities and the capabilities to inhibit oxidative DNA damage, modulate the apoptotic response and regulate the cell-cycle checkpoint function. In addition, the coffee components cafestol and kahweol are two specific diterpenes that have been shown to have a broad range of bioactive properties resulting in a reduction in carcinogen-induced genotoxicity (Li et al. 2013; Cavin et al. 2002; Banerjee et al. 2014; Ferk et al. 2014). Chlorogenic acid, a phenolic compound found in green coffee, has antioxidant activity and has the ability to trap superoxide anions or hydroxyl radicals (Morishita and Ohnishi 2001). This compound has so many beneficial effects on health including having *in vitro* free radical scavenging property and preventing the propagation of oxidative process (Castro et al. 2018). Cholorogenic acids are strong reactive oxygen species (ROS) scavengers. ROS are produced physiologically during various cellular processes such as aerobic metabolism and should be harmful when the amount is high. Even though ROS are known to be harmful, in order to sustain cellular homeostasis through redox cell signalling, they must be at a certain level (Priftis et al. 2018). Chlorogenic acids are obtained from esterification of quinic acid with one or more derivatives of transcinnamic acid. The most common chlorogenic acids in coffee are caffeoylquinic acid acid monoesters, especially 5- caffeoylquinic acid (Castro et al. 2018). In an *in vivo* study, it was determined that the green coffee bean extract had a positive effect on the longevity and delayed aging of *Caenorhabditis elegans*. These positive effects have been reported to be due to the high level of chlorogenic acid that the green coffee bean extract has (Amigoni et al. 2017). A study involving the first 4 weeks of purging, followed by 4 weeks of coffee consumption followed by a second purging period was performed on thirty-three healthy subjects and the individuals consumed 750 mL of freshly infused filter coffee (contains 580 mg/L CQA and 720 mg/L caffeine) per day containing green coffee bean extracts as well as roasted coffee beans. During the period of coffee consumption, it has been determined that oxidative DNA damage was decreased, glutathione level and glutathione reductase activity were increased (Bakuradze et al. 2011). In an another study, 29 females and males consumed instant coffee containing 4 × 200 mL (800 mL/day) green and roasted coffee bean extract, in addition at the same amount of water as control, for 5 days. A 200 mL cup of coffee consumed by individuals was containing 300 mg of chlorogenic acid and the individuals applied these interventions at intervals of 5 weeks of purging period. As a result, it was detected that 8-isoprostaglandin F2α and 3-nitrotyrosine which are the markers of oxidative stress in urine were decreased and total antioxidant capacity was partially increased (Hoelzl et al. 2010).

1.6. Green coffee and effect on blood pressure

Many diseases linked with cardiovascular disease such as diabetes, hyperlipidemia, hypertension, obesity are associated with excessive pro-oxidant production and/or endogenous antioxidant suppression (Goszcz et al. 2015). Polyphenols are the most common antioxidants in human nutrition and are prevalently found in fruits, vegetables, grains, dry legumes, chocolate and beverages such as tea, coffee or wine (Medina-Remo et al. 2014). Chlorogenic acid is one of the most common polyphenols, while green coffee is one of the richest sources of chlorogenic acid. In a randomized, double-blind, placebo-controlled study using a green coffee bean extract instead of chlorogenic acid, 28 individuals without any diseases consumed drink containing 140 mg of CGA (CGA group) and placebo drink (placebo group) for 12 weeks. Only fruit and vegetable juices were given to the placebo group while 125 mL of green coffee extract (GCE) (0.48 g) and fruit-vegetable juices were consumed in CGA group's daily diet. Systolic and diastolic blood pressures have been reported to be significantly reduced in the CGA group compared to the placebo group (Watanabe et al. 2006). In an another study, participants consumed 40 grams of green and black coffee per day for 4 days dividing into 4 cups during the day. The green coffee (GC) and black coffee (BC) used were given as 10 g/100 mL of water. It has been found that the green cup reduced the systolic blood pressure compared to the baseline and the black cup partially reduced the blood pressure but the difference was not significant. After intervention with GC, cortisol level decreased by 39 %; after BC intervention, cortisol level increased by 5 %. The levels of cortisone were increased and the proportion of free cortisol/cortisone in the urine was significantly reduced. The significant decrease in the ratio of cortisol/cortisone after GC and BC consumption has shown that coffee consumption inhibits 11β-HSD1 enzyme activity. The chlorogenic acid presents in GC has an inhibitory effect on the 11β-HSD1 enzyme. This situation may explain the higher effect of GC on the urinary free cortisol/cortisone ratio (Revuelta-Iniesta and Al-Dujaili 2014). In Japan, 46 mg, 93 mg, 185 mg of green coffee bean extracts (GCBE) were added to the diets of 117 subjects with mild hypertension for 28 days in the multicentered (8-center), randomized, double blind, placebo-controlled, parallel group study. Individuals consumed soy sauce flavored soup containing green coffee bean extract (test diet) or a placebo diet in the breakfast. This soup was containing 0 mg (placebo), 46 mg, 93 mg or 185 mg of GCBE. The contents of chlorogenic acid in these four mixtures were 0 mg, 25 mg, 50 mg and 100 mg, respectively. When the reductions in systolic and diastolic blood pressures were compared to the

placebo group at the end of 28-day of study, significant differences were found between the 93 mg of GCBE group and 185 mg of GCBE group (Kozuma et al. 2005).

The role of reactive oxygen species in hypertension is remarkable. The levels of hydrogen peroxide and superoxide anions increase in uncontrolled hypertensive patients. Superoxide anions react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), inhibit NO bioavailability in endothelial tissues. CGA intake can improve NO bioavailability in hypertensive patients. By this way, ferulic acid, the metabolite of 5-CQA, is able to capture superoxide and exhibit hypotensive effects (Watanabe et al. 2006).

In a study conducted on 20 healthy male subjects, the individuals consumed 125 mL of drinks containing green coffee bean extract (GCBE) (140 mg chlorogenic acid) or drinks non-containing GCBE for 4 months. It was detected that, there was no change in systolic and diastolic blood pressures after individuals' GCBE containing drink consumption compared to the initial, also there was no difference between the test group and the placebo group. In this study, it was reported that GCBE does not show hypotensive effect. However, the average reactive hyperemia rate of the group consuming GCBE containing drinks was found to be higher than the initial which was also higher than that of the placebo group, and it was stated that the GCBE developed vasoreactivity of GCE (Ochiai et al. 2004). Moreover, in a cross-over study of 20 healthy individuals (10 males, 10 females), 2 g of chlorogenic acid, 4 g of black tea, 440 mg of quercetin-3-rutinoside or placebo were administered to each individual in random order for 7 days in addition to the individuals' diets. Two grams of chlorogenic acid dissolving in hot water was consumed only before lunch. In addition, blood samples were taken from each individual twice on 7th day of each intervention, first in morning when fasting (20 hours after taking supplement) and second after meal (4–5 hours after taking supplements). Total homocysteine in the postprandial plasma of individuals consuming chlorogenic acid compared to placebo was 12 % higher; total homocysteine was increased by 4 % in fasting plasma, and fasting plasma folate concentration was decreased by 8 % (Olthof et al. 2001).

1.7. Green coffee and effect on the loss of body weight

It is known that green coffee effects the body weight, green coffee extract has a hypotensive effect in mice, decreases visceral fat and body weight (Jeszka-Skowron et al. 2016a). In a conducted study, an unpurified diet containing 0.5 % or 1 % coffee bean extract, 0.05 % or 0.1 % caffeine added diet; 15 % or 0.3 % chlorogenic acid added diet were given to 6-week-old mice for 14 days. During the intervention, it was detected that the amount of the dietary intakes of the mice were not reduced, and the coffee bean extract (0.5 % and 1 %) reduced the body weight of the mice. The hepatic triglyceride levels of the mice were reduced after 13 days of coffee extract (100 and 200 mg/kg/day), caffeine (10 and 20 mg/kg/day) and chlorogenic acid (30 and 60 mg/kg/day) intervention (Shimoda, Seki, and Aitani 2006). In a study investigating the protective and therapeutic effect of chlorogenic acid in rats fed a high fat diet (HFD) (60% of the energy is fat); 6-week-old mice were fed either on a high fat diet or on a normal diet for the first phase for 15 weeks and intraperitoneal chlorogenic acid (100 mg/kg) or dimethylsulfoxide (DMSO) were given for control twice a week (normal diyet+DMSO, HFD+DMSO, HFD+CGA). In the second phase, chlorogenic acid (100 mg/kg) or dimethyl sulfoxide was given twice a week for 6 weeks to obese mice (average body weight 50 g) and the protective effect of chlorogenic acid on diet induced obesity was assessed. The mean body weight of mice in the HFD+CGA group was found to be 16 g less than in the HFD+DMSO (HFD control group) group. Body composition analysis results showed that CGA blocked the increase in fat mass without altering lean body mass in HFD fed mice. CGA; decreased hepatic lipids, plasma triglyceride and cholesterol levels significantly, and fasting blood glucose was found to be much lower in mice treated with CGA than in the HFD control group. It has also been reported that chlorogenic acid intervention improved insulin sensitivity and obesity-associated hyperinsulinemia in obese mice (Ma, Gao and Liu 2015).

In an another study, 12 individuals consumed coffee containing green coffee bean extract (each 2200 mg of package containing 200 mg of green coffee extract) or caffeinated instant coffee. At the end of 12 weeks it was found that those who consume coffee containing green coffee bean extract had a greater body weight reduction than those who consume normal instant coffee. It has been stated that the percentage of body fat in the group consuming coffee containing the green coffee bean extract showed a decline for the duration of the study, which means that approximately 80 % of the body weight loss in the individuals took its source from fat loss (Thom 2007). In a further study, 50 overwieght individuals between the age of 19–75 years were divided into 2 groups and given 2 capsules/day green coffee bean extract (each capsule containing 200 mg of green coffee bean extract) or placebo for 60 days. The decrease in body weight was found to be higher in the green coffee bean extract group than in the placebo group. Furthermore, the body mass index of the group to which green coffee bean extract was given decreased and the ratio of muscle mass/fat mass increased (Dellalibera, Lemaire, and Lafay 2006). A randomized, double-blind, placebo-controlled, comparative, independent market research study was conducted on 42 healthy, medium weight (BMI 25–30 kg/m^2) individuals for 4 weeks. Individuals participating in the study consumed 1 cup (pack)/day (3 g coffee/day) of coffee containing green coffee bean extract (180 mg green coffee bean extract / 3 g coffee, containing 2.7% chlorogenic acid) or normal instant coffee. It has been found that body weight loss in the individuals who consume coffee containing green coffee bean extract is higher than those who consume normal instant coffee (Ayton Global Research 2009). In the other conducted study, 48 mice were divided into groups and high fat diet, high fat + decaffeinated green coffee bean extract added diet, high fat + 5-caffeolquinic acid (5-CQA) added diet and the control diets were given for 11 weeks. As a result, the body weight gain and the visceral fat weight of the mice were found to decrease fed with the green coffee bean extract (Song, Choi, and Park 2014).

In a further study, lipid catabolism of 3-caffeoquinic acid in the green coffee extract and effects on regulation of body fat in obese rats induced by high-fat diets were researched. For this purpose, rats were fed a high fat diet for 4 weeks. Then, the rats were fed with high fat diet, high fat diet with 50, 100, 200 mg/kg

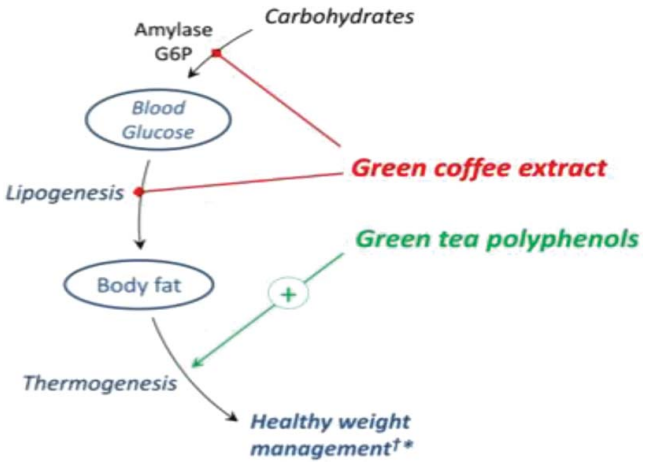

Figure 1. Green coffee bean extract moderates the breakdown of carbohydrate to its lipogenic substrate, glucose.

green coffee bean extract with high fat diet for 6 weeks. In the result of the study it was observed that rats treated with the green coffee bean extract had a lower fat mass and significantly relative body weight and fat mass were reduced compared to rats fed the high fat diet alone. The active compound 3-caffeolquinic acid in green coffee bean extract is thought to reduce lipogenesis in obesity and body fat accumulation through regulation of adipogenesis (Choi et al. 2016).

In a meta-analysis of the effect of the green coffee extract on weight loss, the researchers evaluated 2160 articles on the subject. As a result of this evaluation, the 2155 article was excluded because of the reasons such as incorrect title, usage of summary, not being defined as food supplement providing weight loss, etc. One of the five articles was excluded from the evaluation for the reason which was a non-random work while the other one was excluded for the reason which was just a study on normal wight people. Three randomized clinical trials were evaluated statistically. It was reported that more precise and long-term studies have been necessary to clarify the effect of the green coffee extract on weight loss and its clinical safety (Onakpoya, Terry, and Ernst 2011).

Green coffee bean extract moderates the breakdown of carbohydrate to its lipogenic substrate, glucose showed in Figure 1.

1.8. Green coffee and cancer

The International Agency for Research on Cancer (IARC) classified coffee as non-carcinogenic to humans (IARC 2016). Several epidemiological studies have investigated whether coffee consumption induce or promote cancer, although the question remains unclear. Many studies have revealed the protective association between coffee consumption and the risk of certain cancers (Nishi et al. 1996; Schilter et al. 2001). Coffee is also a major source of the chlorogenic acid that contributes to its antioxidant effect (Rodriguez de Sotillo and Hadley 2002). Intake of chlorogenic acid has been shown to reduce glucose concentrations (Shearer et al. 2003). Chronic hyperinsulinemia and insulin resistance are confirmed markers of high risk for some cancer sites (Renehan, Roberts, and Dive 2008).

According to many studies for anti-cancer properties of coffee, kahweol in coffee content is regarded as one of the main compounds responsible for cancer chemoprevention (Park, Song, and Jeong 2016). The antioxidant kahweol protects the DNA against oxidative stress causing hydrogen peroxides through the cleansing of reactive oxygen species and triggers hem-oxygenase-1 to control levels of intracellular reactive oxygen species (ROS) (Cárdenas, Quesada, and Medina 2014). In addition to kahweol, polyphenols (such as chlorogenic acid) in coffee have antioxidant and anti-inflammatory properties, too (Fukushima et al. 2014). In addition, caffeic acid has the ability to inhibit DNA methylation in human cancer cells and is associated with inactivation of various pathways involved in tumorigenic processes such as cell cycle regulation, inflammatory and stress responses and apoptosis (Yu et al. 2011).

Hypermethylation of DNA is a common feature in tumor cells and is a key epigenetic mechanism for suppressing various genes including those encoding tumor suppressor proteins, DNA repair enzymes and receptors. Caffeic acid has the ability to inhibit DNA methylation in human cancer cells and is associated with inactivation of various pathways involved in tumorigenic processes such as cell cycle regulation, inflammatory and stress responses and apoptosis (Yu et al. 2011). Genes-specific hypermethylation is known to be associated with the inactivation of various pathways involving tumorigenic process including cell cycle regulation, inflammatory and stress response and apoptosis. Caffeic acid, the major component of coffee, has been shown to inhibit DNA methylation in cultured MCF-7 and MAD-MB-231 human cancer cells (Vucic, Brown, and Lam 2008). At the same time, coffee consumption also shows anti-cancer properties through some transcription factors. Increased activation of transcription factor specificity protein 1 (Sp1) contributes to development of various types of cancer. In a study of rats, it was shown that caffeol and cafestol-containing diet reduced the DNA binding rate as well as reduced CYP450 enzyme activity, induced GST expression and thus served for with AFB1 detoxification (Abdel-Wahhab, Ahmed and Hagazi 2006).

It was reported that, a cup of coffee increase daily, reduces the risk of death due to cancer by 3% (Happonen et al. 2008), while moderate level coffee consumption has protective effects on kidney (Lee et al. 2017), liver (Larsson and Wolk 2007), pancreas (Ran, Wang, and Sun 2016), colorectal (Schmit et al. 2016), breast (Jiang, Wu, and Jiang 2013), prostate (Tverdal 2015) cancers. In a study investigating the antiproliferative and cytotoxic effects of green coffee and yerba mate extracts, it was detected that green coffee extracts at the ratios of 100 and 1000 μg/mL showed inhibitive effects on the proliferation of cancerous cells. Regular consumption of green coffee and/or mate has been reported to have antiproliferative effects on cancer cells (Amigo-Benavent et al. 2017).

1.9. Green coffee and effect on neurologıc dıseases

The effects of caffeine on Alzheimer's disease are explained by different mechanisms. The first is that caffeine can reduce beta amyloid accumulation by blocking the pathway that increases beta secretase secretion in the brain. The second mechanism is that caffeine can suppress GSK-3 isoforms associated with tau hyperphosphorylation and presenilin 1/gamma secretase activation (Arendash et al. 2009). Caffeine can inhibit beta amyloid

induced neurotoxicity in cerebral neurons by stimulating cholinergic neurotransmitter secretion as an adenosine receptor antagonist (Gelder et al. 2007). It is also mentioned that caffeine is also therapeutically effective in Alzheimer's disease due to being potent antiinflammatory agent, antioxidant, mitochondrial activator, neuronal activation and stimulation of glucose utilization of it (Arendash and Cao 2010). In addition to beneficial effects of caffeine, latests studies on chlorogenic acid the main component of green coffee beans have shown a protective role for this compound in neurons. For this reason it should be said that, chlorogenic acid taken with green coffee, is useful to protect against neurodegenerative diseases such as ischemic stroke (Jeszka-Skowron, Stanisz, and Paz De Peña 2016b).

In a study conducted by Cao et al. (2011), it was found that plasma level of granulocyte-colony stimulating factor (GCSF) increased significantly in caffeinated coffee-consuming rats, but caffeine solution alone or decaffeinated coffee did not show this effect. Since oxidative stress/free radical damage and chronic inflammation in the brain are critical processes in the pathogenesis of Alzheimer's, coffee can be effective in these two pathogenic conditions with antioxidant and anti-inflammatory components of it such as chlorogenic acid. In a study conducted by Eskelinen et al. (2009), on 1409 individuals, daily coffee consumption of middle-aged individuals was examined and in the elderly period of individuals; 61 dementia cases were detected in which 48 of them were Alzheimer's type. It was detected that those who consumed medium-level coffee during the middle age period had a 62–64 % lower risk of Alzheimer's disease in old age than those consuming low amounts of coffee. Apart from caffeine, phenolic compounds, diterpenes, magnesium is also among the coffee components that can reduce Alzheimer's risk. Coffee consumption is associated with a low risk of diabetes, and magnesium in the coffee may increase insulin sensitivity. Diabetes is one of the factor that increases the risk of dementia. Insulin resistance in type 2 diabetes results in reduction of amyloid beta breakdown. Similar to magnesium, chlorogenic acid can also gain favor to Alzheimer's indirectly availing in glucose homeostasis (Ho et al. 2012).

Since one of the mechanisms involved in the pathogenesis of Parkinson's disease is oxidative stress, coffee can be beneficial because of its ability to raise plasma antioxidant levels. Adenosine A2 receptors are important targets in basal ganglia disorders such as Parkinson's. Caffeine can protect dopaminergic neurons from excitotoxic components by inactivating adenosine A2 receptors (Hu et al. 2007; Sääksjärvi et al. 2008). As a result of a meta-analysis, it was determined that those who consume 3 cups of coffee a day had a lower risk of Parkinson's disease, but no change in risk after 3 cups of coffee (Li et al. 2013). In another study of 29335 Fin individuals aged 25 to 74 years and whom not diagnosed Parkinson's disease before, occurence of the illness was observed in 102 men and 98 women after 13 years of follow-up. Considering many factors such as age, gender, body mass index, physical activity, alcohol and tea consumption, those who consumed 1–4 cups or more than 5 cups a day had ratios of 47 % and 60 % lower risk of incidence of Parkinson's disease respectively compared to those never consumed coffee. It has been determined that the risk ratio for men and women is approximately the same (Hu et al. 2007).

In an another study conducted on 1372 individuals with multiple sclerosis, individuals who consumed regular coffee had lower risk of recurrence than those who never consume coffee. Consumers who consume coffee on a daily basis are taking caffeine in significant amounts. Caffeine suppresses the production of proinflammatory cytokines and has neuroprotective properties through the inhibition of phosphodiesterase by being an adenosine receptor antagonist (D'hooghe et al. 2012). However, the number of studies conducted to associate between MS and coffee consumption is inadequate.

Studies showing the relationship between coffee and health are given in Table 1.

Caffeine is one of the stimulants of the central nervous system. Excessive consumption of tea and coffee can change the efficacy of nonepileptic drugs and Alzheimer's drugs (Jankiewicz et al. 2007). Caffeine intake in rats has been shown to induce the microsomal enzyme system. Increasing epileptic seizures depending on taking caffeine at high doses has been shown in animal studies (Tchekalarova, Kubová, and Mareš 2013). The caffeine contents of tea, coffee, chocolate and coke are approximately 50 mg/250 mL, 60–80 mg/250 mL, 20 mg/100 g and 20–30 mg/200 mL, respectively (Wierzejska 2012). One of the components that interact with drugs other than the caffeine in the contents of these foods is also referred to as polyphenols (Alshatwi et al. 2016).

In an another study, the interaction between the plasma caffeine concentration increased with caffeine and antiepileptic drugs was investigated and as a result the protective effect of antiepileptic drugs against epileptic seizures together with acute or chronic caffeine intake has been found to decrease significantly. Therefore, caffeine limitation is extremely important in epileptic patients. In addition, caffeine has been one of the most commonly used compounds mediacally worldwide, by the effects on the central nervous system via adenosine receptors. In a study conducted with rats, caffeine was investigated on six different antidepressants and caffeine at dosages of 10, 20 and 50 mg/kg was found to increase antidepressant activity of the drugs, but this did not cause an effect on locomotor activity of the patient rats. However, only two antidepressant drugs (paroxetine and imipramine) interacted with caffeine and changes were occured in plasma and brain tissue concentrations (Szopa et al. 2016).

In an another study, it was investigated whether caffeine effects anticholinesterase and antioxidant properties of donepezil used in the management of Alzheimer's disease. In the study, caffeine has been shown to have synergistic effect with donepezil and to increase anticholinesterase activity. It was also found that the activity of anticholinesterase was higher in the groups given 50 mg and 100 mg of caffeine compared to the other groups. As a result of the study, it was determined that low levels of caffeine consumption contribute to the antioxidant properties of donepezil; medium levels of caffeine intake has been shown to decrease anticholinesterase activity of donepezil and increase antioxidant properties (Oboh, Ogunsuyi,

Table 1. Studies showing the relationship between coffee and health.

Diseases	Study types	Coffee consumption (min-max)	Health effects of coffee consumption	References
Colorectal cancer	Meta analyze	Consumption (−)≥8 cups/day	Coffee consumption ⇒ risk of colon and colorectal cancer	Li et al. 2013b
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	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, Wang, and Sun 2016
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	Meta analyze	—	Coffee consumption ⇒ not associated with risk of breast cancer	Li et al. 2013a
Breast cancer	Meta analyze	Consumption (−) ≥10 cups/day	+2 cups/day coffee consumption ⇒ 2% reduction in risk of breast cancer (poorly)	Jiang, Wu and Jiang 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
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
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 et al. 2010
Diabetes mellitus	Systematic review	Consumption (−) ≥10 cups/day	Coffee consumption ↑ ⇒ risk of type 2 diabetes mellitus ↓	Muley, Muley and Shah 2012
Diabetes mellitus	Meta analyze	Consumption (−) ≥12 cups/day	Coffee consumption ↑ ⇒ risk of type 2 diabetes mellitus ↓	Ding et al. 2014
Metabolic syndrome		Normal diet, high fat diet or high fat diet supplemented with 0,5% w/w green coffee bean extract rich in chlorogenic acid 12 weeks Ten healthy adult daily 400 mg of dry green coffee bean extract	Coffee bean extract did not attenuate rich in chlorogenic acid -induced obesity, glucose intolerance, insulin resistance or systemic oxidative stress Markers related to treatment were assigned to metabolites belonging to the pathways of fatty acid metabolism, showing an influence of green coffee extract on lipid metabolism	Li Kwok Cheong et al. 2014 Peron et al. 2018
Blood pressure		Untreated patients with mild hypertension were consumption 180 mL of fluid containing 46, 93 or 185 mg of chlorogenic acids during 28 days Mild essential hypertension person. Test coffee containing 82,172 and 99 mg chlorogenic acids consumption	Sistolic and diastolic blood pressure↓ Sistolic and diastolic blood pressure↓	Kozuma et al. 2005 Yamaguchi et al. 2008

and Olonisola 2017). In an another study, interaction between caffeine consumption and antihypertensive drug was examined. In the study, antihypertensive individuals were divided into groups, after 2-daya coffee and caffeine-free diet consumption, 300 mlx2 coffee or the maximum recommended dose of felodipine (10 mg) or coffee and felodipine together were given to the groups. At the end of the study individuals who received coffee and felodipine were found to have higher blood pressures than individuals who received only felodipine. It has also been observed that individuals receiving felodipine had reduction in blood pressure was interrupted with coffee consumption and two-fold increase in the concentration of felodipine was necessary in order to ensure the progress in blood pressure reduction (Bailey et al. 2016).

Table 2. Potential drug interactions of active ingredients of coffee (*Coffea arabica*).

Herbal Products	Active Compounds	Potential Drug Interactions
Coffee (*Coffea arabica*)	• Purine alkoloids (caffeine, theobromine and theophyllin) • Trigonelline • Carbonisation products of hemicelluloses • Caffeic and ferulic esters of quinic acid • Norditerpen glycoside ester	• May decrease absorption of some drugs. • May increase stimulant effect of the plant ineracting with oral contraseptives and cinolon antibiotics

Potential drug interactions of active ingredients of coffee (*Coffea arabica*) are summarized in Table 2 (Anderson 2004).

2. Result and suggestions

It is known that, green coffee reduces blood pressure in mild hpertensive individuals, provides body wieght loss in obese and mild-weighed individuals and decreases the post-prandial increase in blood glucose. These are thought to come across by the effect of chlorogenic acid in the green coffee. Furthermore, studies have shown that green coffee has antioxidant activity. In addition to adequate and balanced nutrition, 3–4 cups/day green coffee may have beneficial effects on health, but attention should be paid to the amount of caffeine consumed and care should be taken not to exceed the daily maximum safe dose of 400 mg (EFSA 2015) for adult subjects as specified by the European Food Safety Authority. According to EFSA recommendations, pregnant and lactating women can consume caffeine in a way that does not exceed 200 mg/day of caffeine consumption, in other words, the consumption of coffee should be on the carpet as long as it is consumed less than 2 cups per day. According to EFSA recommendations, consumption of caffeine is safe for healthy adults until 400 mg/day caffeine consumption. As a result, 3–5 cups (medium) coffee consumption per day is associated with a wide range of desired physiological effects, consistent with an active lifestyle and a healthy diet, and this amount of consumption is safe for healthy adults (other than pregnant and lactating). As a result, 3–5 cups (medium level) coffee consumption per day in harmony with an active lifestyle and a healthy diet is associated with a wide range of desired physiological effects and the amount of this consumption is safe for healthy adults (except pregnants and lactatings) (EFSA 2015). EFSA recommended consumption amounts for the health effect of coffee and its components are given in Table 3 (EFSA 2011a; EFSA 2011b). Average daily intakes vary among people are given in Table 4 (EFSA 2011a; EFSA 2011b)

Furthermore, due to the fact that some individuals have side effects such as headache, nausea, etc., more studies are needed on more subjects worked on more individuals to determine the effective and reliable dose of green coffee.

Table 3. EFSA recommended consumption amounts for the health effect of coffee and its components (EFSA 2011a; EFSA 2011b).

Health effect	Coffee compound/ coffee activity	Consumption amount for effect on health
Body mass maintaining	Coffee	3 cup/day coffee
	Glucose homeostatis Chlorogenic acid	180 mg chlorogenic acid
	Glucose homeostatis Caffeine	1.5 cup/day coffee At least 150 mg/day
	Lipid metabolism and spending energy Caffeine	At least 300 mg/day
	Supplying thermogenesis	(at least dividing 3 portion)
Protection from cancer	Coffee- protection from oxidative stress	1–2 cup/day
Cognitive health	Caffeine-cognitive performance	At least 32 mg/day

Table 4. Average daily intakes vary among people (EFSA 2011a; EFSA 2011b).

Age (year)	Daily intake (mg)
Very elderly (75 years and above)	22–417
Elderly (65–75 years)	23–362
Adults (18–65 years)	37–319
Adolescents (10–18 years)	0.4–1.4 mg/kg bw
Children (3–10 years)	0.2–2.0 mg/kg bw
Toddlers (12–36 months)	0–2.1 mg/kg bw

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