FOOD and HEALTH

FOOD and HEALTH
E-ISSN 2602-2834

Food Health 8(4), 344-358 (2022) • https://doi.org/10.3153/FH22032 Review Article

Coffee: Health effects and various disease treatments

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Cite this article as:
Vo, T.S., Vo, T.T.B.C. Vo, T.T.T.N. (2022). Coffee: Health effects and various disease treatments. *Food and Health,* 8(4), 344-358. https://doi.org/10.3153/FH22032

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Submitted: 12.03.2022
Revision requested: 27.04.2022
Last revision received: 25.06.2021
Accepted: 06.07.2022
Published online: 22.09.2022

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Available online at
http://jfhs.scientificwebjournals.com

ABSTRACT

To respond the growing demands for consuming natural foods, biochemical compounds originated from natural sources can be one of significant purposes for numerous researchers. In this review, we summarize the literatures regarding to the health effects of coffee consumption toward various human disease treatments, i.e., diabetes, cancer, liver diseases, and neurodegenerative diseases. The consumption of natural products is being common and considered significantly, for example, the potentially functional features of biochemical compounds contained in coffee have significantly contributed to clinical treatments of different human diseases. The experimental and epidemiologic evidences are indicated in this review to probably contribute to elucidate the protective effects of coffee consumption on several human diseases; besides, it is not still certain whether the consumption of coffee should be recommended to patients in some cases. Moreover, the chemical features and health benefits of coffee are introduced shortly, which can support readers understanding in detail to the benefits and the roles of coffee compounds.

Keywords: Coffee, Disease treatment, Diabetes, Liver diseases, Parkinson's disease, Alzheimer's disease

Introduction

Coffee drink (Figure 1) is one of the most widely used beverages in the world, which contains several biochemical compounds that may influence the uptake and the metabolism of glucose (Ejaz et al., 2004). So far, numerous researches have been conducted to demonstrate the beneficial health effects of coffee on various diseases (Ngueta, 2020). Indeed, coffee showed its beneficial effects in irregular/regular coffee drinkers by changing mood, enhancing cognitive performance and endurance with exercises (Campbell et al., 2013). However, the extraction of coffee soluble from the roasted and ground coffee bean is a complex operation and brewing/cooking method plays an important role on the extraction and amount of the key compounds in the coffee drink. For instance, Ilkay et al. provided in detail how the roasting level and brewing techniques affect the key compounds, physicochemical attributes, and health of coffee beverage (Gök, 2021). More notably, coffee is utilized to support in sports that is useful for a significantly improved performance of athletes after the consumption of coffee (Mc Naughton et al., 2008). Coffee, as is known, is one of the most essential sources of caffeine, although soft and energy drinks also contain a significant part of caffeine. Its consumption probably increases alertness and enhances the performance of manual works, i.e., driving and encoding of new information (Gök, 2021).

Coffee contains over a thousand compounds including caffeine, sugars, polysaccharides, chlorogenic acids, aromatics, phenols, organic acids, and etc. (Table 1); nonetheless, the exact content of bioactive compounds containing in coffee can differently depend to the species, farming processes and preparation of final product, i.e., blend, roast, or brew (Yesil and Yilmaz, 2013). The use of coffee was first reported that it could provide a beneficial health effect against the cirrhosis development, similarly for an inverse relationship with total and non-cancer related mortality, as well as uncertainty over caffeine content and the information of coffee preparation techniques (Gök, 2021).

According to the epidemiological studies, the use of coffee could reduce the risk of liver enzyme disorder and decrease death rate and hospitalisations in all cirrhotic patients (Ruhl and Everhart, 2005). Besides liver diseases, the consumption of coffee also effectively resulted in treating other diseases, i.e., diabetes, cancer, neurodegenerative diseases, and so on. Hence, it is truly important to clearly understand the biochemical compounds and bioactive functions containing in coffee, aiming to apply it in bioactive and pharmacological applications after its reliability has been demonstrated. Thereby, we hope that it is an effective approach for various disease treatments, and its chemical components and beneficial health effects will be briefly summarized in several disease treatments.

Figure 1. Schematic illustration of the coffee drink.

Table 1. Background of chemical compositions containing in coffee.

Chemical compositions	Background
Lipids	Coffee oil (triglycerides, unsaponifiables and sterols/tocopherols) and diterpenes (cafestol and kahweol).
Minerals	Phosphorus and potassium. Magnesium, sodium, calcium, and sulfur.
Proteins	Peptides and free amino acids, i.e., regard to the coffee flavor.
Caffeine	Alkaloid, using as a psychoactive stimulant of the central nervous system.
Chlorogenic acids	Using as an ester compound of the caffeic acid. They are assumed to cause gastrointestinal discomfort at some people with higher coffee consumption, and can cause a slight reduction in blood pressure and have been investigated concerning an anti-inflammatory effect, and an antioxidant effect.
Trignonelline	Alkaloid. When roasting it can partly metabolize to niacin.
Carbohydrates	Common carbohydrates: fructose, glucose, mannose, arabinose, and rhamnose and oligosaccharides, raffinose and stachyose. Other ones: • *Sucrose*: Important for coffee flavor and quality. • *Polysaccharides*: The main polysaccharides in coffee are galactomannan and arabinogalactan (soluble compounds). • *Lignin*: A class of complex organic polymers, structural material in the support tissue of plants, important for the formation of cell walls.
Productions of caramelizations and condensation	Substances, influencing the color, and aroma of coffee.

Chemistry and General Properties of Coffee

So far, coffee is one of the most common beverages in the world, as well as its beneficial effects have been demonstrated to human health. Besides, coffee contains lots of chemicals, for example, vitamins, lipids, carbohydrates, nitrogenous compounds, minerals, alkaloids and micronutrients, which significantly depends on the variety and processes. Table 1 listed in detail for information of availably chemical compositions containing in coffee. Chemical structure of principal compounds contained in coffee is shown in Figure 2. Among these chemicals, the main components containing in coffee are caffeine, cafestol and kahweol, chlorogenic acid, ferulic acid, and micronutrients, at same time that the major polyphenols in coffee contributes to making coffee as a real functional food. Besides, it reveals promising anti-oxidative properties owing to their beneficial activities, especially for ferulic acid and chlorogenic acid (Higdon and Frei, 2006). More specifically, chlorogenic acid containing in roasted coffee is considered as a major antioxidant in the diet (Yanagimoto et al., 2004), whereas diterpenes cafestol and kahweol are contained much in boiled or unfiltered coffee.

Chlorogenic acid, as is known, is a phenolic compound (a family of polyphenols), which is reached from the combination of (L)-quinic acid and caffeic acid to be concerned as anti-oxidative agent. Meanwhile, ferulic acid is also a phenolic acid (a derivative of trans-cinnamic acid) and available in coffee, which can intervene in the expression and cytotoxic enzymes' activity (i.e., caspases, nitric oxide synthase, and cyclooxygenase-2), aiming to apply it in treating cardiovascular, neurodegenerative and diabetic disorders (Perumpail et al., 2018).

For chlorogenic acids containing in green coffee, there are some major subclasses including caffeoylquinic acids, dicaffeoylquinic acids, *p*-coumaroylquinic acids, feruloylquinic acids, and caffeoylferuloylquinic acids (Chu, 2012). Among them, 5-caffeoylquinic acid reaches ~60.0% of the total chlorogenic acids content, and thus is named as chlorogenic acid due to a commercial standard, at same time that dicaffeoylquinic acids are known as potent inhibitors contributing against various viruses (Chu, 2012). Concomitantly, caffeine-contained coffee (1,3,7-trimethylxanthine) favors to increase peroxiredoxin-1, which has positive effects on reactive oxygen species and lowering oxidative stress at hepatocytes level (Perumpail et al., 2018). Thereby, the coupling influences of

caffeine- and polyphenols-contained coffee on hepatocytes probably reduce insulin resistance, which is revealed as an anti-fibrotic effect on the liver through the effective investigations on obese rats (Watanabe et al., 2017).

Additionally, chlorogenic acids can be completely degraded with severely roasting conditions that is mainly due to its thermal instability, leading to forming bioactive lactones in medium roasting process and degrading then. Concomitantly, several volatile compounds are formed, and these acids are partially incorporated into melanoidines' backbones during coffee roasting process (Chu, 2012). Meanwhile, caffeine is not affected much during coffee roasting process, as well as this methylxanthine is heat stable. Trigonelline is considered as an alkaloid and obtained from enzymatic methylation of nicotinic acid, which is also degraded during this roasting process, yielding several compounds regarding nicotinic acid (3%) (Hirakawa et al., 2005). Overall, the various chemical composition-contained coffee is truly modified significantly from combinations of the coffee roasting techniques, regard with the species and other factors, i.e., agricultural processes, degree of fruit ripeness, and storage conditions (Chu, 2012).

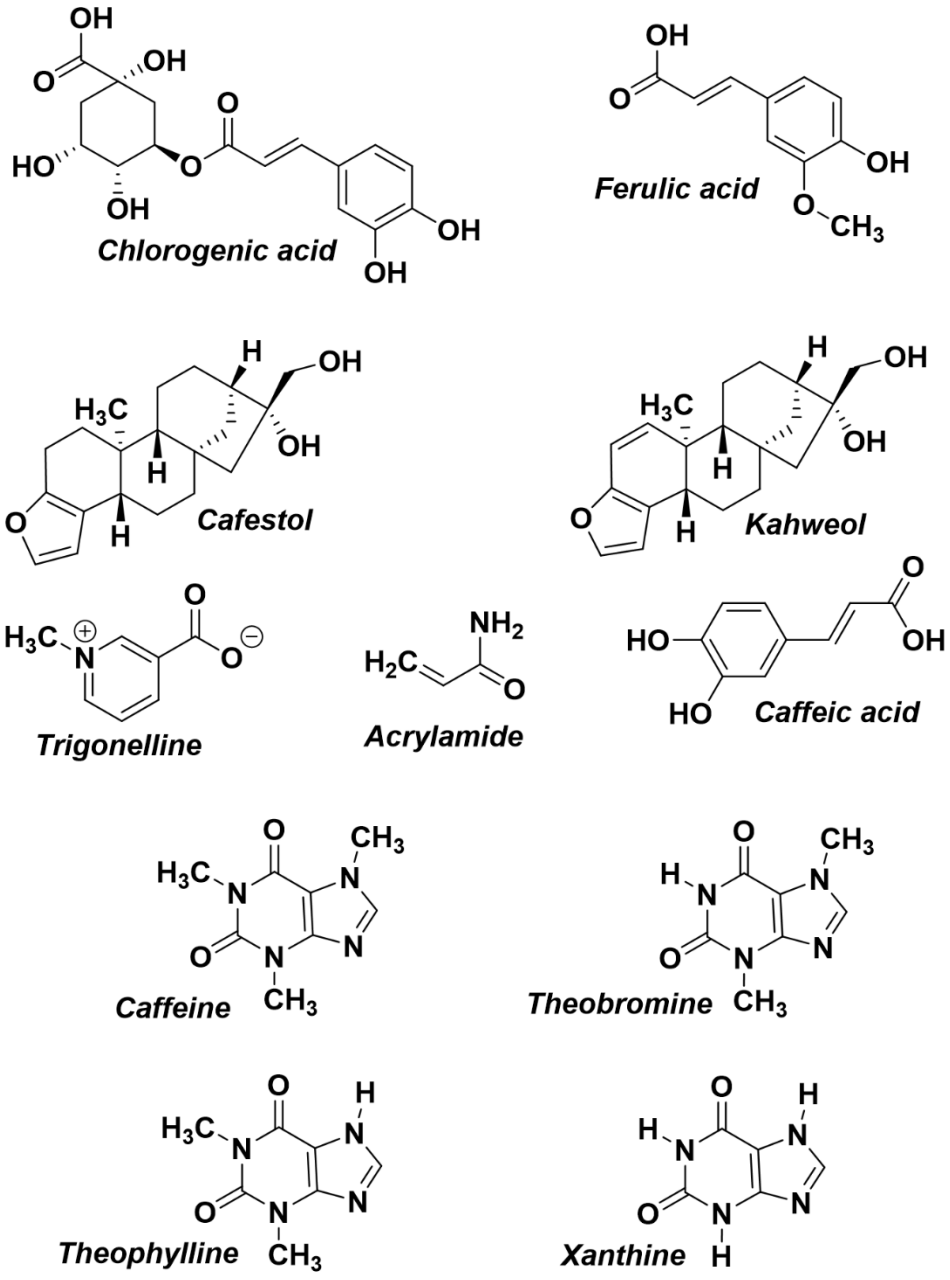

Figure 2. Chemical structure of the principal compounds contained in coffee.

More notably, caffeine is able to be the most well-known bioactive compound contained in coffee. Caffeine is an alkaloid and can be well absorbed in the stomach, which is metabolized in the liver (after 45-60 min of absorption period) to be converted into dimethylxanthines, i.e., xanthine, theobromine, theophylline, leading to enhancing its beneficial health effects. In other words, caffeine is quickly absorbed from the gastrointestinal way and well distributes in all tissues consisting of brain (Higdon and Frei, 2006); similarly, the caffeine consumption could lower a risk of raised aminotransferases, as well as its obviously hepatoprotective effect is to against liver disease (Ruhl and Everhart, 2005). Caffeine is concerned to be the purines, which acts as a psychostimulant in the central nervous system. It means that its stimulant ability can reduce the adenosine transmission in the different regions of brain (Fisone et al., 2004), as well as it probably lowers the sleeps and stimulate the heart muscle (Farah et al., 2006). Caffeine also induce to a bronchodilation and a peripheral vasodilation that can be due to its positive inotropic effect leading to increasing the contractility and efficiency of the heart. Moreover, it well stimulates digestion through promoting peristalsis, and which attains the diuretic effects on kidney (Maughan and Griffin, 2003). It could synergistically combine with phenylpropanolamine to be associated with severe hypertension, stroke and myocardial infarction. Additionally, the anti-fibrotic influences of coffee is controlled by lowering growth factor and connective tissue one (Chen et al., 2014), whereas tocopherols and chlorogenic acid in coffee showed anti-oxidative activities.

Moreover, cafestol and kahweol in coffee are pentacyclic diterpene alcohols, increasing cholesterol level, but they can be served as an anti-carcinogenic effect. Their amount containing in filtered coffee can be reduced but still maintain an amount of chlorogenic acid and caffeine to probably provide the maximum health benefit (Torres and Harrison, 2013). Their bioactive derivatives can be salts or esters of saturated and un-saturated fatty acids (~20.0%) (Chu, 2012); in particular, cafestol (0.2-0.6%, wt.) is a primary compound of unsaponifiable fraction of coffee oil, while kahweol (less abundant) is unstable to light, heat, oxygen, and acids . For acrylamide, it is found in coffee beans during the roasting process, and its content in coffee has a significant difference, besides, dietary acrylamide exposure in animal is higher than that in human studies. These coffee diterpenes revealed as hepatoprotective and anti-carcinogenic properties in vitro; however, these compounds are highly consumed, leading to elevating levels of homocysteine and low-density lipoprotein in human plasma that can indirectly induced to the cardiovascular diseases' risk (Chu, 2012). Therefore, coffee is served as non-toxic and highly promising compounds to apply for beneficial health effects and various disease treatments based on an appropriately utilized dose and each studying aim.

Health Effects and Various Disease Treatments of Coffee

As mentioned above, coffee is one of the most widely used beverages in the world. Roasted coffee accommodates chlorogenic acids that is known as a major antioxidant in the diet (Yanagimoto et al., 2004), whereas the diterpenes cafestol and kahweol can obtain after boiling or un-filtering coffee . With the concomitant existence of these components and other bioactive compounds containing in the coffee, the beneficial health effects and various disease treatments of coffee have been investigated as well (Grosso et al., 2017, Poole et al., 2017), especially for cancer, diabetes, liver diseases, Alzheimer's disease, and Parkinson's disease. Among these diseases, an inverse relationship between the use of coffee and liver cancer has long been recognized (Bravi et al., 2013, Godos et al., 2017); however, its mechanisms regarding these anti-carcinogenic influences have yet to be explained in detail. They are induced from liver enzymes to probably lead to cirrhosis and hepatocellular carcinoma; besides, the γ-glutamyltransferase of 2,494 male self-defense officials was ~30.0% lower in who drank coffee (≥ five cups/day) compared to nondrinkers , at same time that the inverse relationship between coffee and γ-glutamyltransferase was limited and stronger in alcohol drinkers. Also, chlorogenic acids and caffeic acids showed anti-oxidative effects in vitro (Iwai et al., 2004), while caffeine while caffeine has been reported regarding to its psychostimulant and positive short-term effects on attention and mental condition (i.e., cognition and memory) (Hameleers et al., 2000). From several researches, 3,5-icaffeoylquinic acid (family of chlorogenic acids) was utilized to be a potent inhibitor of the human immunodeficiency virus integrase , at same time that dicaffeoylquinic acids could be used to investigate against influenza and herpes virus, as well as regarded to other anti-bacterial properties (Antonio et al., 2010). Besides, chlorogenic acids probably impacted to mobility and replication of murine macrophages, anti-mutagenic properties, inhibition of glucose-6-phosphatase in lowering blood glucose and other mechanisms. Also, trigonelline has recently been considered an anti-bacterial agent to be against a cariogenic bacterium, i.e., Streptococcus mutants (Antonio et al., 2010).

Liver Cancer and Liver Diseases

Liver cancer, as is known, is a common malignancy worldwide, which can cause cancer deaths (Ferlay, 2004), especially for chronic infection with hepatitis B (HBV) or C (HCV) viruses and alcohol consumption (Franceschi et al.,

2006, Llovet et al., 2021). In general, coffee contains lots of biologically active components, especially for anti-tumor effects, at same time that trigonelline has well impeded the cancer cells' invasiveness in vitro (Hirakawa et al., 2005). Several investigations were conducted on animal models indicating that the direct use of coffee had the barring influences against the chemical carcinogenesis in liver tissue; concomitantly, several epidemiological investigations indicated on the inverse relation between the effects of coffee and liver cancer regarding serum liver enzyme activity, as well as the inconsistent relation with the incidence of liver cirrhosis.

To further clarify this approach, Sang et al. conducted an investigation of prospective–cohort and case–control studies, resulting that the use of coffee could relate to a reduced risk of liver cancer; nevertheless, this should be treated with caution more (Sang et al., 2013). Whereas, Shimazu et al. carried out an available data analysis of 2 cohort studies, including 22,404 people with the frequency consumption of coffee (10,588 men and 11,816 women) and 38,703 people with other health habits (18,869 men and 19,834 women), who were ≥40 years old and no previous history of cancer (Shimazu et al., 2005). It manifested that the consumption of coffee significantly contributed to a decreased incidence of liver cancer, and which is truly need more investigations to elucidate the role of coffee in prevention of liver cancer. Additionally, Loftfield et al. also demonstrated that coffee has been consistently involved to reducing risk of liver cancer and chronic liver disease, which based on serum metabolites in case-control studies of liver cancer (221 people) and fatal liver disease (242 people) (Loftfield et al., 2020).

Moreover, hepatocellular carcinoma can be also added into other digestive tract cancers regarding to beneficial health effects of coffee drinking has been suggested (i.e., oral-pharyngeal and oesophageal-colorectal cancers) (Tavani and La Vecchia, 2004). The use of coffee has been suggested to reduce the risk for hepatocellular carcinoma; nonetheless, controversy exists about the exactly used dose. Bhurwal et al. (Bhurwal et al., 2020) investigated the association of coffee utilization and risk of hepatocellular carcinoma and/or liver cancer (20 people, one cup/day), evaluating that the relationship between the use of coffee with hepatocellular carcinoma or liver cancer development along with the suitably used amount of coffee to probably prevent hepatocellular carcinoma or liver cancer. Also, more highly used doses of coffee have better benefits in terms of risk reduction, but further biological and epidemiological investigations are truly necessary to be required to demonstrate the exact mechanism and determine specific subgroups (i.e., HBV- or HCV-related hepatocellular carcinoma). Concomitantly, Freedman et al. also examined the relationship between the use of coffee and liver disease progression in individuals with advanced HCV–related liver disease (766 people), suggesting that the regular utilization of coffee related to lowering the disease progression (Freedman et al., 2009). As such, coffee consumption probably reduced the fibrosis progression's risk in HCV and improved the interferon based anti-HCV therapy (Freedman et al., 2011, Freedman et al., 2009), at same time that it also protected against the hepatocellular carcinoma development (Johnson et al., 2011). In other studies, 59 people with alcohol-related cirrhosis drank the coffee (≥ four cups/day), manifesting that it reached about five fold lower the risk of non-coffee drinkers , as well as the use of coffee was also inversely involved to the risk of cirrhosis death (Komorita et al., 2020, Teramoto et al., 2021). Besides, a case-control study (115 people) indicated an inverse relation between the use of coffee and the risk of cirrhosis, especially for a favorable health effect of coffee on alcohol-related cirrhosis risk. This was similar with another bigger study (274 people and 458 controls), which revealed a strong inverse relation between coffee drinking and cirrhosis, meaning a relative risk of 0.16 for coffee drinkers (≥ four cups/day) comparing to non-coffee drinkers.

In general, coffee contains lots of bioactive compounds that probably reach beneficial health effects on the liver, which probably based on their antioxidant and anti-inflammatory properties, defense mechanisms, and angiogenesis inhibition to favor the tumors' growth with oxygen and nutrients (Bohn et al., 2014). Also, the use of decaffeinated coffee in an animal model was able to decrease liver fibrosis, steatosis, and inflammation (Vitaglione et al., 2010).

Non-Alcoholic Fatty Liver Diseases and Diabetes

For non-alcoholic fatty liver disease, it is a highly common condition and signalized in the initial stages by hepatic steatosis. In another word, this disease is originated from hepatic fat accumulation (>5.0%), which is not due to excess alcohol consumption or other established liver diseases (Friedman et al., 2018). This disease is a phenomenon of alterations scaling from simple hepatic steatosis to non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma; besides, the liver biopsy non-alcoholic steatohepatitis can be classified with the degree of fibrosis, i.e., mild fibrosis, significant fibrosis, advanced fibrosis and cirrhosis. Some clinical meta-analysis indicated that potentially bioactive compounds (i.e., vitamin, silymarin, resveratrol, curcumin, etc.) exert positive influences on this disease that was probably attributed to their anti-inflammatory or antioxidant properties (Vo et al., 2021a, b, Vo et al.); nonetheless, it could be also significantly involved to the differently used doses, formulation issues, or tested duration.

Among them, the consumption of coffee containing caffeine could reduce lipid infiltration in the liver via anti-inflammatory, anti-oxidation, and fatty acid metabolism-related mechanisms. Also, the utilization of coffee can be beneficial in treatment of non-alcoholic fatty liver disease based on a direct effect on the liver and beneficial systemic metabolic influences. Needed, coffee has plenty of potentially bioactive properties, i.e., anti-inflammatory, antioxidant, and anti-fibrotic properties, which reported a reverse relationship between the coffee utilization and non-alcoholic steatohepatitis on base of a dose-dependent manner (Chen et al., 2014). A daily used coffee drink (n=177, > two cups/day, ~6 months) was associated with significantly lower odds of liver fibrosis (Modi et al., 2010), similarly with a non-alcoholic steatohepatitis specific cohort (n=306, > two cups/day, 2 years) (Molloy et al., 2012). At the same time, it revealed that non-alcoholic fatty liver-associated patients (n=5,147) drank the coffee liquid (> three cups/day, 7 years) resulting a lower fibrosis score (Zelber-Sagi et al., 2015), and the coffee consumption (≥ three cups/day) could also decrease the growing hepatocellular carcinoma's risk in 63,257 people (~44.0%) (Johnson et al., 2011). In other studies, it manifested that caffeine decreased intrahepatic fat accumulation in rat models, but they did not definite clearly its used dose based on animal weight (Fang et al., 2019, Helal et al., 2018).

In addition to caffeine, coffee contains the other biochemical compounds, and which are especially rich in polyphenols, i.e., chlorogenic acids, was responsible for its beneficial health effects. Thereby, Velázquez et al. conducted an investigation of green coffee extract and caffeine effects (5.00 mg/day) on hepatic lipids in female rat models with steatosis (Velázquez et al., 2020). As a result, a low dose of caffeine did not decrease hepatic steatosis in these rat models, but the same used dose of green coffee extract led to lowering liver triglyceride levels. Trovato et al. surveyed the drinking espresso coffee in 161 obese women and 34 men after bariatric surgery, which explained clearly in its beneficial health effect (Trovato et al., 2013).

Theoretically, coffee is used to can protect the liver on base of increased PPAR-α mediated fatty acid oxidation and protective antioxidants, and reduced collagen deposition (Carvalhana et al., 2012), so the use of caffeine-contained coffee significantly related to lower the hepatic fibrosis' risk in patients with non-alcoholic steatohepatitis. Molloy et al. also surveyed 400 non-alcoholic fatty liver-associated patients, suggesting that greater use of coffee significantly reduced risk of advanced fibrosis (Molloy et al., 2012). However, the exactly used dose of coffee regarding the greatest risk reduction was not still clear. The case of 782 non-alcoholic fatty liver-associated adults also showed a lowered risk for advanced non-alcoholic steatohepatitis through regularly drank coffee, especially in patients with low levels of insulin resistance (Bambha et al., 2014). Besides, the use of coffee could protect against the development of metabolic syndrome and non-alcoholic fatty liver disease conducted in experimental and clinical models (Yesil and Yilmaz, 2013) (i.e., 3 animal studies and 11 epidemiological and clinical studies). Thereby, the health effects of coffee on liver disease are multiple factors, as well as which is truly necessary to elucidate further, especially for the use of filtered unsweetened coffee was be able to be a rational extension to diet and exercise in the fatty liver-associated patients (Chen et al., 2014, Yesil and Yilmaz, 2013).

More interestingly, caffeine could lower the gene expression of the transcription factors Sterol regulatory element-binding protein 1c and 2 in HepG2 cells regarding to the combination of cholesterol and triglycerides in the liver (Quan et al., 2013), which was able to cause the reduction of 3-hydroxy 3-methylglutaryl CoA reductase and low-density lipoprotein receptor in an appropriately used dose. In another study, the utilization of caffeine could improve liver damage induced by a high-fat diet in animal models (Helal et al., 2018), which was evaluated on base of alanine/aspartate aminotransferase, albumin, bilirubin, triglycerides and cholesterol. As result, it showed that the use of caffeine lowered elevated serum levels of alanine/aspartate aminotransferase, bilirubin/hepatic mRNA expression of fatty acid synthase and acetyl CoA carboxylase. Furthermore, the use of coffee also impacted to an improvement of insulin sensitivity (Bohn et al., 2014) and lowered risks of metabolic syndrome and type 2 diabetes (Tunnicliffe and Shearer, 2008). Diabetes is considered as an auto-inflammatory syndrome with plenty of possible disorders, i.e., insulin resistance, hyperglycemia, dyslipidemia, impaired β-cell functioning and insulin secretion (Bosun-Arije et al., 2020, Hussain and Chowdhury, 2019), which also accelerates liver fibrosis and inflammation. Generally, the traditional anti-diabetic agents probably induce several potentially adverse occurrences (Bosun-Arije et al., 2020, Hussain and Chowdhury, 2019), at same time that there are also some natural anti-inflammatory agents with anti-diabetic effects to be able to against type 2 diabetes (Akash et al., 2013), and their limitations in short biological half-life (Akash et al., 2012). Besides, coffee can be well used to protect liver cancer through improving the insulin sensitivity as well as lowering the risk of diabetes (Tunnicliffe and Shearer, 2008). Recently, several researches have indicated a significantly reduced risk of cardiovascular disease and type 2 diabetes in coffee drinkers (Ding et al., 2014). Specifically, some biochemical components of coffee are able to ameliorate type 2 diabetes symptoms through impacting glucose regulation,

i.e., the effects of chlorogenic acid on glucose-6-phosphatase, the beneficial influences of caffeine on insulin secretion, and the antioxidant activity of polyphenols on α-glucosidase (Tuomilehto et al., 2004).

Neurodegenerative Diseases

Mitochondrial dysfunction and oxidative stress are considered as prior occurrences in neurodegenerative diseases (NDDs), i.e., Alzheimer's disease (AD), Parkinson's disease (PD), and so on. In fact, mitochondria are essential factors in cellular function grounded on their energy produced and their major role in cell physiology. Also, neurons significantly relate to this energy production, so the mitochondrial dysfunction can induce deadly influences regarding to neuronal function and survival that are due to their high energy demand and reduced glycolytic capacity. Especially, the use of coffee has protectively affected in these NDDs through epidemiological and clinical studies (Beghi et al., 2011), for example, the protective effects of aqueous coffee extract investigated effectively on amyloid-beta (Aβ) peptide toxicity in the AD (Dostal et al., 2010).

More specifically, AD is known as the most typical dementia on base of a gradual descent of cognitive functions and memory deficiencies (Reitz and Mayeux, 2014), meaning that it involves to extra-neuronal deposition of Aβ protein in the formation of plaques and intra-neuronal aggregation of the hyper-phosphorylated microtubule-associated protein tau in the cortex, hippocampus and amygdala (Lloret et al., 2015). Moreover, a neuro-inflammatory constituent regarded strongly to the AD (Ikonomovic et al., 2008). In other words, the presence of Aβ oligomers probably leads to microglia-mediated neuro-inflammatory response, which can induce the neuronal-loss and -toxicity (Pan et al., 2011). As such, microglia reactivity is occurred not only in the brain, but also in the retinas of AD animal models (Ning et al., 2008), at same time that activation is also considered as a consequence or a cause of the AD. Thereby, interventions are suitably selected to control the microglia reactivity that probably delay the AD progression.

Interestingly, the use of caffeine can favor for reducing the cognitive decline in AD patients and healthy subjects with advanced age (Ritchie et al., 2007). This approach was also investigated in AD animal models, which showed that the use of caffeine could effectively reach in amelioration of cognitive impairments and dementia (Arendash et al., 2009, Eskelinen and Kivipelto, 2010), at same time that increased caffeine amounts in the plasma could reduce levels of inflammatory cytokine in the hippocampus (Cao et al., 2009). Notably, caffeine was also used in a mouse model with AD-like tau pathology reducing some oxidative stress and pro-inflammatory markers in the hippocampus, as well as which interfered the spatial memory deficits' development (Laurent et al., 2014). Concomitantly, caffeine could be applied to well protect against AD-associated blood-brain barrier dysfunction (Chen et al., 2010) and probably control an increase in AD-associated inflammatory mediators (Farkas et al., 2003).

More notably, the use of caffeine significantly improved memory deficits and reduced the expression of reactive oxygen species, pro-inflammatory cytokines TNF, IL-1β, and further granted anti-apoptotic effects (Ullah et al., 2015) in an animal model with age-related central nervous system alterations; at the same time, the caffeine actions were mediated through A2aR blockade, indicating that this blockade based on pharmacological features and genetic inactivation well provided neuroprotection against Aβ toxicity (Canas et al., 2009). As such, these demonstrated the use of caffeine reached desired and potential properties to apply for the AD treatment.

For the cased of PD, it is considered as the second most common NDD based on a progressive loss of dopaminergic neurons with the Lewy bodies' occurrence, which leads to appearing resting tremor, muscular rigidity, bradykinesia and postural instability (Klockgether, 2004). Concomitantly, this PD has been also coupled with oxidative stress and chronic neuro-inflammation inducing the blood-brain barrier disruption, meaning that the brain can be susceptible to cause oxidative stress because of the high oxygen consumption (Hald and Lotharius, 2005). Notably, the oxidative stress could be a main cause inducing the neuronal damage in the PD based on postmortem human samples (Jenner and Olanow, 2006). Moreover, plenty of currently epidemiological studies have been also significantly investigated the use of caffeine to favor reducing risk of developing PD (Rodrigues et al., 2015). For instance, the daily use of caffeine could attenuate microglia reactivity and prevent the blood-brain barrier dysregulation in the MPTP mouse model, which led to reducing dopaminergic neuronal loss (Chen et al., 2008). The caffeine also probably depress the inflammatory procedure and microglial cell expression in the later neurodegenerative processes suggesting its ability to delay or arrest neuro-inflammation and neurodegeneration (Chen et al., 2008); besides, the lowly used doses of caffeine can invert functional motor deficiencies in the PD animal models probably involving to the A2AR antagonism (Bata-Garcia et al., 2010). Furthermore, the long- and short-term use of caffeine also impacted to acetylcholine and its receptors in the brain, at same time that the acetylcholine response displayed no trend to tolerance (Acquas et al., 2002). In case of long-term use of caffeine to mice, it indica-

ted that it could increase the number of muscarinic and nicotinic receptors in the brain, as well as probably increased their cholinergic function.

So far, the potential benefits and roles of coffee are attracting interests in treatment of age-related NDDs. In particular, Fisicaro et al. conducted the evaluation between various quantities of used mocha coffee (two cups/day) and performance of cognitive-mood in 300 non-demented patients with subcortical ischemic vascular disease (Fisicaro et al., 2021), indicating that daily use of mocha coffee involved to higher cognitive-mood performance, similarly with a dose-response association to probably identify the factors regarding vascular dementia and geriatric depression. However, there are some limitations occurred during this investigation, i.e., the drinking habit can become an effect of cognitive performance rather than causally regarded (Arab et al., 2013). The caffeine could significantly contribute to the evaluation, but the other potential compounds contained in the coffee, i.e., flavonoids, were missed and need further investigation. Besides, trigonelline could also recreate axons and dendrites in animal models, which led to probably improving memory (Tohda et al., 2005).

Coronavirus Disease 2019

As known, the first cases of coronavirus disease 2019 (COVID-19) were reported in Wuhan (China) at the end of 2019, which is as an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Especially, handwashing (i.e., soap and water/warm water-based handwashing, or alcohol-based hand sanitizers) and wearing masks (i.e., cloth masks, medical masks, N95 respirators, and surgical masks) are considered as one of the ways that can prevent the influenza virus infection (Vo et al., 2020a, b). People in the world are now self-isolating at their homes, the use of supplement products probably support enhancing the immune system and prevent SARS-CoV-2 infection through the daily diet, that may reduce the COVID-19 infection risk and a recovery in SARS-CoV-2 infection cases (Vo et al., 2021a, b, Vo et al.). Moreover, 1,3,7-trimethylxanthine is known as the most common psychoactive drug worldwide, which is used effectively on the tolerance to central hypovolemia (Zores and Rebeaud, 2020) and the prevention of hypotension-related syncope (Pizzey et al., 2020), at same time that the exposure to lower body negative pressure led to decreasing significantly blood pressure was conducted in coffee-used 13 patients, which contained caffeine and 1,3,7-trimethylxanthine. It means that syncope is caused by a decrease in blood flow, especially from low blood pressure, so its control can allow a better perfusion of the brain and a reduced risk of syncope. Interestingly, Belaroussi et al. performed a pedagogic comparative investigation aiming to evaluate the effect of active part (1,3,7-trimethylxanthine) contained in the coffee for the treatment of 93 COVID-19 infected patients (Belaroussi et al., 2020), meaning that this pedagogic investigation aimed to highlight potential biases in research on COVID-19 treatment. However, this study cannot be still concluded for any association between coffee or 1,3,7-trimethylxanthine and COVID-19.

Conclusion

In brief, coffee is one of the widely used beverages in the world, which was also applied effectively for treating various human diseases to assess correspondingly its beneficial health effects. For liver diseases, the health effect of coffee is almost undoubtable on liver cancer risk, chronic liver diseases, and etc., indicating that it is not only one specific benefit to liver cancer, but also a favorable effect on a whole of liver functions. Nonetheless, prospective mechanisms have not still been determined in detail and need to be resolved further in this approach. Coffee could also directly affect to the pathogenesis of type 2 diabetes and non-alcoholic fatty liver disease, revealing that the use of coffee imparted the advantageous effects to stop the pathogenesis of these diseases. Besides, this approach also needs to be concerned further to be an alternate supplement along with other anti-diabetic agents, while the effects of caffeine to neuro-inflammation is truly important to be elucidated more. Interestingly, the biochemical compounds of coffee could also be known as a preventive and therapeutic role in the neurodegenerative diseases, i.e., Alzheimer's and Parkinson's diseases. It means that these potentially functional features have contributed to antioxidant, anti-apoptotic, and etc.; concomitantly, the clinical studies with long-term approach should be recommended more in the future.

Compliance with Ethical Standard

Conflict of interests: The author declares that for this article they have no actual, potential, or perceived conflict of interests.

Ethics committee approval: The author declares that this study does not include any experiments with human or animal subjects; therefore, no ethics committee approval is needed.

Funding disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgments: -

Disclosure: -

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