CHAPTER THREE

Chemical composition and health properties of coffee and coffee by-products

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Contents

Abstract

Coffee can be an ally in the fight against diseases such as type 2 diabetes, cancer, hepatic injury, cirrhosis, depression, suicidal behavior, and neurological and cardiovascular disorders. The properties of coffee also favor gastrointestinal tract and gut microbiota

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establishment. Coffee bioactive components include phenolic compounds (chlorogenic acids, cafestol and kahweol), alkaloids (caffeine and trigonelin), diterpenes (cafestol and kahweol) and other secondary metabolites. The image of coffee as a super functional food has helped to increase coffee consumption across the globe. This chapter addresses the main health promotion mechanisms associated with coffee consumption. Related topics on coffee production chain, world consumption and reuse of coffee by-products in the production of high-value-adding molecules with potential applications in the food industry are addressed and discussed.

1. Introduction

The popularity of coffee products is related to their unique sensory and pleasant flavor (Pereira et al., 2019). Coffee consumption has greatly increased all around the world. One of the reasons for this continuous increase includes the change in coffee's image as a functional food. Coffee bioactive components include phenolic compounds (chlorogenic acids, cafestol and kahweol), alkaloids (caffeine and trigonelin), diterpenes (cafestol and kahweol) and other secondary metabolites. Regular coffee consumption has been associated with a healthy profile in consumers. Improvements in mental alertness, reducing risk of disease development (type 2 diabetes, depression, suicidal behavior, cancer, hepatic injury, cirrhosis, and neurological and cardiovascular disorders), and positive effects on the gastrointestinal tract and gut microbiota are well documented benefits.

Coffee production starts during on-farm processing. In this step, coffee seeds are obtained with moisture between 10% and 12%, allowing the transport of coffee without quality loss. Coffee by-products are originated in the field-processing chain, where coffee seeds are separated from outer layers (skin, pulp, mucilage, and parchment). Coffee by-products represent about 50% of the fruit in dry weight. This residual biomass has been traditionally used for animal feed, fertilizer development and biotechnological transformation. More recently, the use of coffee by-products as functional ingredients has been an emerging sector in the food industry. Coffee by-products have been used as a source of phytochemicals, dietary fiber and caffeine for food supplementation.

The aim of this chapter is to describe the main health properties associated with coffee consumption. Initially, the coffee production chain and world consumption profile are described. Subsequently, the mechanisms

by which coffee consumption affects health in preventing disease are detailed. Finally, the use of coffee by-products in the production of high-value-adding molecules with potential applications in the food industry is exemplified.

2. Coffee production and consumption

Coffee production involves different operations, from on-farm processing to industrial operation, which turns raw fruit into finished coffee. In general, the collecting of coffee fruits and postharvesting steps are carried out by the coffee plantation owners and sent as green beans to different industries. The commercialization of coffee has a variety of end products, but the main ones are roasted beans and powdered coffee. The coffee drink is prepared by infusing hot water with roasted and ground coffee. Coffee can be prepared by filtration, percolation, or pressure. The coffee market has different ramifications with applications at many levels of consumption, from instant coffee to the use of single-capsule espresso machines.

2.1 The coffee markets

The world production of green coffee beans was 9.2 million tonnes with a market value of over 30 billion dollars in 2016 (FAO, 2015; OEC, 2017). The largest producer is Brazil with about 3 million tonnes, followed by Vietnam, Colombia, and Indonesia, as shown in Fig. 1. Only these largest coffee-producing countries account for 63% of world production. The coffee production has a major impact on the gross domestic product of producing countries, accounting for over 6.9% of the exportation of Colombia, 7.2% of Guatemala, 13% of Honduras, and 32% of Ethiopia (OEC, 2017). Coffee exported by producing countries is mostly based on raw green beans without any processing. Brazil, for example, obtained 87% of its green coffee export revenues and only 10% in instant coffee and 1% in coffee extract (ABIC, 2016).

Half of all green coffee beans produced in the world are imported by the United States, Germany, Italy and Japan (Fig. 1). Only the United States accounts for 21% of imports. Although some of the green beans are destined to serve the domestic market, some countries allocate some of the imported coffee to be re-exported with or without processing. As an example, Germany has no coffee plantation and is the fifth largest exporter of green coffee. In absolute terms, the United States and Brazil are the largest coffee consumers with 28% of green beans of the world. The consumption per

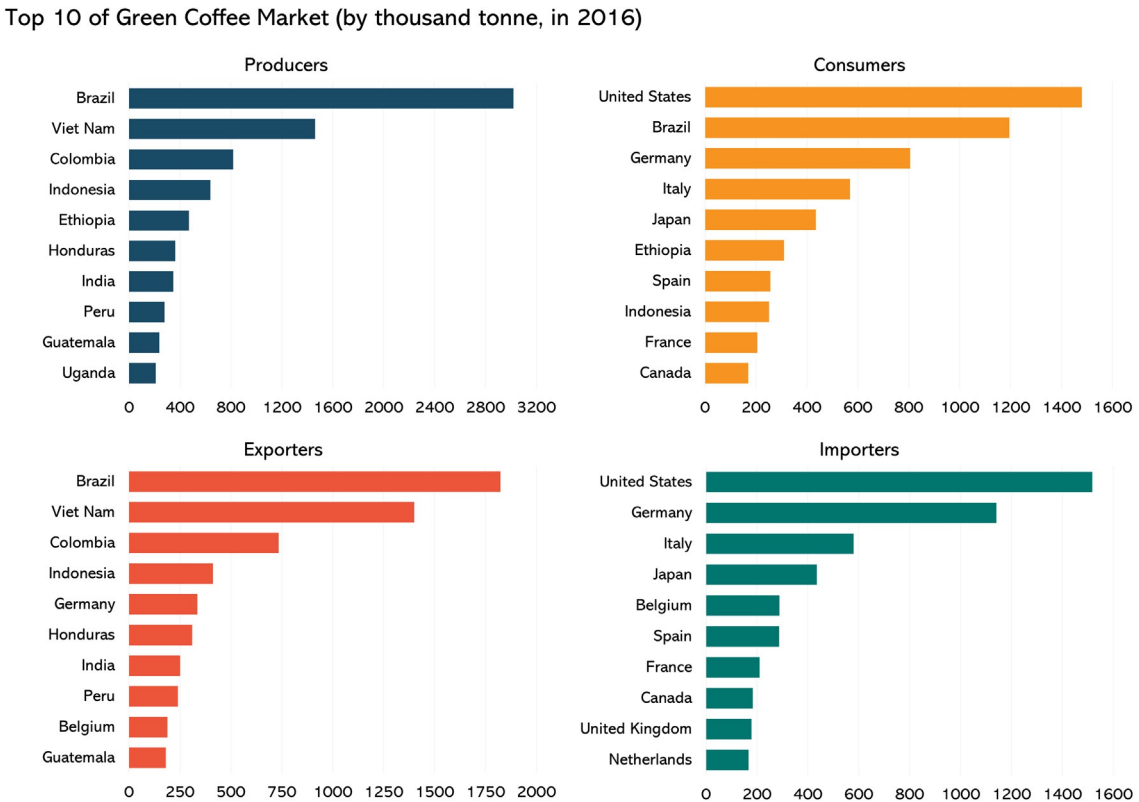

Fig. 1 The world's top coffee producing, consuming, exporting and importing nations according to FAOSTAT (2017).

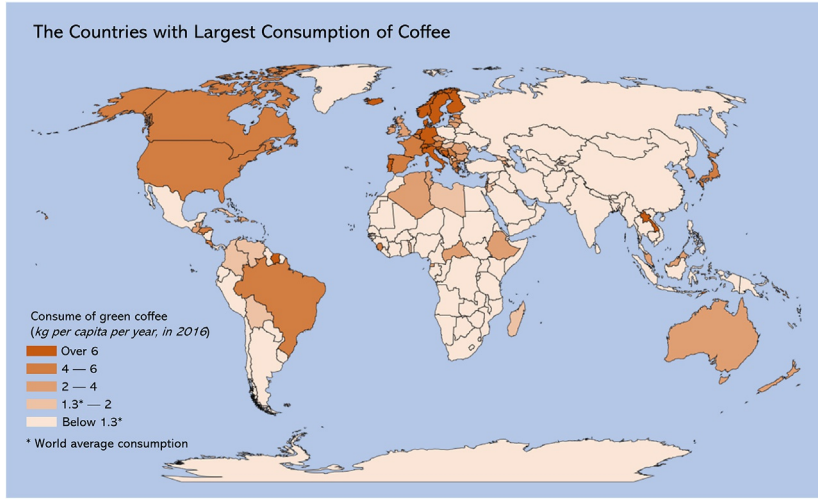

Fig. 2 The world's top coffee consuming nations per capita.

American and Brazilian persons are 4.5 and 5.8 kg of coffee per year, respectively. However, per capita consumption in European countries is higher, especially in northern European countries such as Finland, Sweden, Iceland, Norway, Denmark, and Austria, with a yearly consumption of coffee over of 6 kg per person. The average yearly consumption of coffee in the world is 1.3 kg per person. Fig. 2 shows the world's top coffee consuming nations per capita.

2.2 The coffee processing and by-product generation

Coffee processing involves different serial operations, including harvesting, washing, drying and pulping, to obtain coffee beans that meet industrial and commercial standards (Rezende, Rosado, & Gomes, 2007). These steps can generate residues with varying concentration and quantity that depends on the characteristics of the fruit used and the level of processing applied. The main coffee fruit structure is shown in Fig. 3. The mature fruit of the coffee tree has the husk, or exocarp, with shades ranging from yellow to red depending on the genotype of the species and green coloration when the fruit is premature. The mesocarp is a fleshy pulp and easily removable, composed mainly of carbohydrates, such as glucose, fructose, and pectin. The pectin layer, also known as mucilage, contains protein, fat, lipid minerals, tannins, polyphenols, and caffeine (Janissen & Huynh, 2018; Murthy & Naidu, 2012b). The endocarp or parchment is a polysaccharide layer like

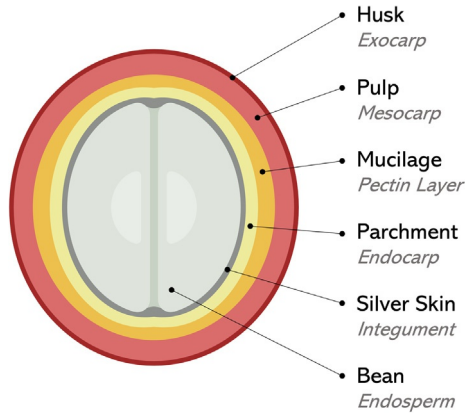

Fig. 3 Coffee fruit and its structure.

a thin, yellowish and easily shredded paper composed mainly of lignocellulose (Esquivel & Jiménez, 2012). The layer surrounding the bean is the integument, also called silverskin, and is composed of polysaccharides, such as cellulose and hemicelluloses, as well as monosaccharides, proteins, polyphenols and phenolic compounds with significant antioxidant activity (Farah & Ferreira dos Santos, 2014; Janissen & Huynh, 2018). The coffee bean is formed by two hemispheres of elliptical seeds that contain endosperm and embryos (Esquivel & Jiménez, 2012; Farah & Ferreira dos Santos, 2014).

The harvesting of the coffee fruit, regardless of the industrial method employed, consists of a mixture of fruits at different stages of ripeness in the same coffee tree: green (immature), cherry (ripe) and raisin (overripe) (Pezzopane, Pedro, De Camargo, & Thomaziello, 2003). Cherry fruit is the stage that gives the coffee bean better quality compared to green, because it has lower astringency and a higher content of volatile compounds, such as aldehydes, ketones, and higher alcohols (Pereira et al., 2019; Wintgens, 2004). Coffee quality, such as the appearance, hygiene and final quality of the beverage, directly impacts the value of the product (Silva, Lopes, Donzeles, & da Costa, 2011). Thus, harvesting begins when the coffee plantation reaches a maturation stage with a minimum prevalence of green fruits. Coffee harvesting can range from simpler methods using manual picking to mechanical processes with motorized stripping. This variation in the harvesting method depends mainly on access to technology and the size of the coffee plantation, with the manual picking being more used in the family coffee growing with an exclusive selection of ripe fruits and better-quality plots. Large producers use nonselective mechanical harvesting followed by

an extra step of sorting cherry, green and raisin fruits (Huch & Franz, 2015). During the harvesting of coffee fruits, regardless of the method used, dried and malformed fruits, leaves, branches and other impurities are also captured. A batch of coffee fruits harvested by stripping comprises about 6% of impurities (Silva et al., 2011). Thus, the fruits must be subjected to a process of separation of these impurities that can be done by manual screening or by precleaning machines, such as washers or screens with motorized fans.

Postharvest steps shall be started immediately to avoid fruit spoilage (Bee et al., 2005). Fig. 4 shows the schematic of coffee processing. Fruits with low-density may exhibit seed malformation, insects or microorganisms attack, or already have advanced stage of ripening, such as coffee. Better quality fruits are those with higher density, such as cherry coffee. A washing/separation step is used to sort out cherry fruits from low-density beans, in addition to removing thin material adhered to the surface and the withdrawal of foreign materials by density difference (Silva et al., 2011).

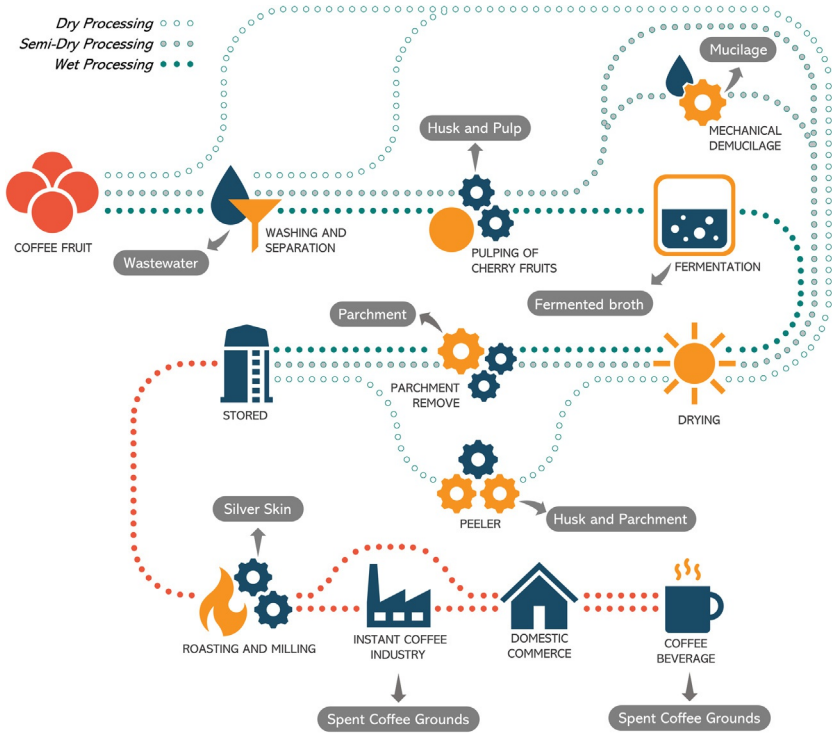

Fig. 4 Flowchart of the different types of coffee postharvest processing (dry, semi-dry and wet methods) showing the main residues generated.

Thus, cherry and green coffee are separated from fruits that float in water, also called float coffee, and pass through sieves to remove liquid effluent.

There are three postharvest processing routes: dry, wet, and semi-dry. During dry processing, the fruits are dried completely without removing the husk, pulp, and mucilage. When the washing/separation step is not used before drying, the dry route produces a batch containing a blend of cherry, green and float coffee. However, in high-quality coffee-growing commonly the float and green coffee are used for the dry route, while cherry coffee goes for the wet or semi-dry processing.

The outer layers of the coffee cherry fruit, namely, husk and pulp, can be easily removed by mechanical pulpers. In this process, the immature fruits remain intact due to the hardness of the outer layers and separated later from the pulped cherry bean. After separation, the green coffee is dried and husked in a similar process to the float coffee processing. Pulped cherry coffee still has mucilage, parchment, and silverskin that are firmly attached to the beans (De Bruyn et al., 2017). Demucilage can be performed by three different processes, one of them by the wet way by fermentation and two from the semi-dry way by mechanical demucilage method or direct drying. Wet processing involves the biological degradation of the mucilage by fermentation followed by bean washing and drying. In addition to the drying area, sun exposure time is dramatically reduced in wet and semi-dry processing to 8–10 days. In dry processing, the drying time is between 21 and 35 days (Bee et al., 2005).

Regardless of the dry, wet or semi-dry postharvest processing chosen, beans with a moisture content of approximately 65% need to reduce the final water content by 10–12% by direct sun exposure in yards or by using mechanical air dryers, as static, column, rotary, and forced air dryers (Pereira et al., 2019). The dryers are used in pulped bean and, especially, in demucilated beans since it requires shorter exposure time and has a lower wet mass when compared to whole fruits. In addition, the rapid drying of wet-processed beans is essential to avoid microbial contamination and thus to ensure the maintenance of coffee quality (Pereira et al., 2019). After drying two types of beans are formed: one processed by the dry route containing the whole bean with the husk; and another originated from the wet or semi-dry processing with the dry demucilated bean containing the parchment. The peel and parchment of the whole dried and demucilated bean, respectively, are removed by peelers specific to each type of processing. The dried coffee is then stored and ready for roasting.

During roasting, the beans go through different stages of heating causing, in addition to the expansion of the beans, chemical reactions that affect the

color, taste, and aroma. The first stage is the removal of water with the temperature at 180 °C and the humidity inside the bean decreasing to 2.5%. Then the temperature is raised to 200–300 °C and flavor development occurs through physicochemical transformation. The last step is cooling via cold air or water jets (Fadai, Melrose, Please, Schulman, & Van Gorder, 2017). Silverskin is the layer around the bean and difficult to remove. During roasting, the coffee beans expand, and the silverskin begins to break, leaving easily after shaking.

The coffee production chain can be divided into three main branches: bean production, roasting and milling industries, and instant coffee producers. Green coffee is usually exported directly without any processing. In other cases, the beans go through roasting and grinding to be sold to the consumer. In the instant coffee industry, dried coffee beans go through several processing steps that involve, in addition to roasting and grinding, extraction, aroma recovery, concentration, drying and agglomeration (Campos-Vega, Loarca-Piña, Vergara-Castañeda, & Oomah, 2015). The main waste generated in soluble coffee processing is spent coffee grounds. As beverage preparation, spent coffee grounds are the by-product of extracting soluble and volatile compounds from roasted coffee from pressurized hot water (Mussatto, Machado, Martins, & Teixeira, 2011). The extracted solution is concentrated and dried until soluble coffee is obtained. Spent coffee grounds correspond to about 50% of roasted coffee (Pujol et al., 2013).

3. Functional characteristics of coffee constituents

Green coffee beans present a complex composition with over 1000 phytochemicals of different chemical classes, including phenolic compounds (e.g., chlorogenic acids and its derivates), diterpenes (cafestol and kahweol), methylxanthines (e.g., caffeine, theobromine, and theophylline), nicotinic acid (vitamin B3), and trigonelline (Jeszka-Skowron, Zgoła-Grześkowiak, & Grześkowiak, 2015). This complex constitution has several implications for the health of coffee consumers. Chlorogenic acids (especially 5-caffeoylquinic acid) and diterpenes have a major contribution on the expression of enzymes involved in phase II metabolism responsible for the endogenous antioxidant defenses and anticarcinogenic activity through the inhibition of DNA methyltransferase (Cavin et al., 2002; Feng et al., 2005; Lee & Zhu, 2006). Trigonelline is an alkaloid with high bioavailability in coffee beans that shows hypoglycemic, neuroprotective,

and antibacterial activities (Ludwig, Clifford, Lean, Ashihara, & Crozier, 2014). In addition, several researches have demonstrated that the ingestion of caffeine induces lipolytic and thermogenic activities, increases metabolic rate through elevation of dopamine level, and improves protection against free radicals (Heckman, Weil, & de Mejia, 2010).

Apart the natural composition of green coffee beans, thermal reactions during the roasting processing allows the transformation of cell wall polysaccharides (e.g., cellulose, hemicellulose, arabinogalactan, and mannan), soluble carbohydrates (e.g., glucose, fructose, sucrose, xylose, rhamnose, galactose, and arabinose), nitrogen (N)-containing compounds, lipids (e.g., palmitic, linolenic, and linoleic acids), and proteins into molecules with numerous biological activities (Pereira et al., 2019). Phenylidanes, products originated from the breakdown of chlorogenic acid and lactones, show potent antioxidant effect and neuroprotective activity against the Alzheimer's disease pathology (Mancini, Wang, & Weaver, 2018). Nitrogenous macromolecular formed by the Maillard reaction has been associated with protective effect against oxidative stress in human cells, anticarcinogenic activity through inhibition of matrix metalloproteases, and antimicrobial action against both Gram-positive and -negative bacteria (Moreira, Nunes, Domingues, & Coimbra, 2012).

4. Metabolic and physiological effects on the human health

4.1 Type 2 diabetes risk reduction

Diabetes mellitus is an autoinflammatory disease driven by metabolic stress with significant loss of functional beta cells in the pancreas, which leads to hyperglycemia (Akash, Shen, Rehman, & Chen, 2012). Diabetes mellitus is considered as one of the leading life-threatening chronic diseases worldwide. A type 2 diabetes (T2D) is the most common type of diabetes, representing 90–95% of all cases (Verma & Hussain, 2017). Several studies report an inverse association between coffee consumption and T2D risk (Bhupathiraju et al., 2013; Jiang, Zhang, & Jiang, 2014; Salazar-Martinez et al., 2004; van Dam & Feskens, 2002). Coffee compounds are characterized by acting on pathophysiological marks of T2D, such as inflammation (Kolb & Mandrup-Poulsen, 2010), hyperglycemia (Manders, Pennings, Beckers, Aipassa, & van Loon, 2009) and oxidative stress (Njajou et al., 2009).

Decreased glucose tolerance is a condition of T2D, in which resistance to insulin sensitivity is increased in peripheral tissues in response to glucose (Akash, Rehman, Sun, & Chen, 2013). Caffeine has properties in glucose metabolism through increased insulin sensitivity and decreased glucose storage, reducing the extent of T2D (Johnston, Clifford, & Morgan, 2003; Muley, Muley, & Shah, 2012; Shearer, Sellars, Farah, Graham, & Wasserman, 2007; van Dijk et al., 2009). However, there is evidence that hypoglycemic potential is not regulated only by caffeine, but by the effect of other compounds present in coffee (Kato, Noda, Inoue, Kadowaki, & Tsugane, 2009). Also, the pro-inflammatory cytokines and chemokines are activated by the T2D. The suppression of such markers interrupts the inflammatory process.

Coffee compounds, such as chlorogenic acid, cafestol, trigonelin and kahweol, are reported to have strong anti-inflammatory properties. This substances are absorbed and act to significantly reduce the levels of the pro-inflammatory biomarker, such as interleukin (IL)-1 β, IL-6, tumor necrosis factor α, C-reactive protein, monocyte chemotactic protein 1, vascular cell adhesion molecule 1, C-peptides, endothelial-leukocyte adhesion molecule 1, and IL-18 (Akash, Rehman, & Chen, 2013; Fukushima, Kasuga, Nakao, Shimomura, & Matsuzawa, 2009; Pham et al., 2011; Williams et al., 2008; Wu, Willett, Hankinson, & Giovannucci, 2005; Zampelas, Panagiotakos, Pitsavos, Chrysohoou, & Stefanadis, 2004), and, consequently, increasing anti-inflammatory markers (adiponectin, IL-4, and IL-10) (Imatoh et al., 2011; Vitaglione et al., 2010). Caffeine acts by inhibiting lipopolysaccharide-induced cyclooxygenase-2, tumor necrosis factor-α and nitric oxide synthase expression (Kang et al., 2012). Pro-inflammatory biomarkers are activated on the tissue inflammation. These are stimulated via signaling activation, such as nuclear factor (NF)-κB (Feng et al., 2005). Chlorogenic acid, caffeic acid and kahweol have the ability to inhibit induced activation of NF-κB (Búfalo et al., 2013; Chung et al., 2004; Kim, Jung, & Jeong, 2004; Lee, Yoon, & Lee, 2012).

The target of T2D is the disruption of blood glucose homeostasis caused by a combination of insulin resistance and beta-cell insulin secretory dysfunction (Tajik, Tajik, Mack, & Enck, 2017). The implication of glucose uptake in peripheral tissues has resulted in increased plasma glucose levels leading to hyperglycemia (Shoelson, Lee, & Goldfine, 2006). Glucose transporter 4 (GLUT4) is responsible for regulating glucose levels in peripheral tissues by transferring glucose to cells via binding to insulin signaling (Holten et al., 2004). Coffee constituents stimulate insulin-mediated glucose uptake

through activation of GLUT4 and the insulin receptor by regulating plasma glucose levels (Prabhakar & Doble, 2009).

One of the factors that are related to T2D induction is magnesium micronutrient deficiency, developing hypomagnesemia. As a major compound of coffee beverage (7 mg per cup), magnesium acts as an essential cofactor for various enzymes involved in glucose metabolism (Belin & He, 2007). Coffee magnesium regulates glucose homeostasis and improves insulin sensitivity, thereby preventing T2D (Saris, Mervaala, Karppanen, Khawaja, & Lewenstam, 2000).

4.2 Neurological diseases prevention (Parkinson's, Alzheimer's, cognitive impairment and dementia)

Parkinson's disease is the second most common neurodegenerative disorder in aging society (Kasten, Chade, & Tanner, 2007). It is a debilitating disease with degeneration in dopaminergic and non-pharmacological neural systems, which affects the movement (Braak et al., 2003). The main cause of Parkinson's disease is still unclear, and studies suggest the possibility of genetic and environmental interaction. The pathological feature of the Parkinson's disease is the loss of pigmented neurons in the substantia nigra, locus coeruleus and other brain stem dopaminergic cell groups, resulting in the absence of the dopamine neurotransmitter in these cell areas (Sveinbjörnsdóttir et al., 2000). Current theories of how this neuronal loss occurs include inflammation, mitochondrial dysfunction, protein management imbalance and oxidative stress (Schapira & Jenner, 2011).

Recent studies show a significant inverse association between coffee caffeine intake and the risk of developing Parkinson's disease (Cho, Choi, Kim, & Kim, 2018; Moccia et al., 2016; Prakash & Tan, 2011; Simon et al., 2017). Caffeine, known as a central nervous system stimulant, acts as an adenosine A_{2A} receptor antagonist and attenuates the loss of dopamine and dopamine transporter binding sites (Chen et al., 2001). As reported in several studies, adenosine receptor agonists produce decreased locomotor activity (Chen et al., 2001; Chiba, Trevor, & Castagnoli-Junior, 1984; Nehlig, Daval, & Debry, 1992). In addition, the action of coffee against the development of Parkinson's disease may be related to the regulation of excitatory neurotransmission in the brain and the control of movement and behavior (Hamza et al., 2011; Simon et al., 2017).

Another chronic neurodegenerative disorder with high incidence is Alzheimer's disease. It is the most common form of dementia among the elderly, characterized by elevated levels of the amyloid β (Aβ) polypeptide

in the brain. Aβ accumulation results in neurodegenerative processes, including the onset of free radical chain reactions and inflammatory processes, which induce neurotoxic cytokine in brains (Butterfield & Boyd-kimball, 2005; Fiala & Veerhuis, 2010). Epidemiological evidence suggests that coffee caffeine protects Aβ-induced neuronal degeneration and memory impairment, reducing the risk of developing Alzheimer's disease. In addition, acting as an antagonist to adenosine receptors located in the hippocampus and cerebral cortex, caffeine promotes adenosine receptor blockade by increasing extracellular levels of acetylcholine, an important neurotransmitter for cognitive processing (Acquas, Tanda, & Di Chiara, 2002). Additionally, caffeine is associated with reduced neuroinflammation. This effect could be ascribed to the activation of a central antioxidant response factor in the brain (Escartin et al., 2011).

Some evidence shows that habitual coffee consumption reduces the risk of mild cognitive impairment and manifests a protective role in the development of dementia. Dementia is a syndrome caused by a variety of diseases, including Alzheimer's disease. It is characterized by the progressive deterioration of cognitive functions (Finkel, 2001). The concept of cognitive impairment refers to a transitional zone between normal aging and dementia (Petersen et al., 1997). Several meta-analysis and epidemiological studies show that coffee consumption is not associated with different measures of cognitive decline or dementia, but rather with a statistically significant reduction in Alzheimer's disease risk. In addition, as already mentioned, habitual coffee consumption is associated with increased insulin sensitivity and reduced risk of diabetes, which is a strong risk factor for cognitive decline (Vercambre, Berr, Ritchie, & Kang, 2013).

4.3 Protective factors against depression and suicidal behavior

Depression is the most disabling disorder measured in people with some psychical disabilities individual. The mental disorders are the leading global cause of all non-fatal burden disease. The deaths in individuals with mental disorder are grouped to the physical cause of death, i.e., suicide (Whiteford et al., 2013). The suicide is one the main symptom of major depression. Strategies must be adopted to reduce depression and elevate mood in the depressed person. Risk factors involved in depression have implicated a wide range of biological mechanisms. In general, a mental disorder is a dysfunction of the brain caused by a neurotransmitter imbalance, increased neuronal inflammation, defects in neurogenesis and synaptic plasticity,

mitochondrial dysfunction, and impairments of synaptic transmission (Visioli & Burgos-Ramos, 2016).

Recent studies suggest that the neuronal development and physiology and protection of the brain can be affected by the diet and exercise. Coffee caffeine cross the blood-brain barrier, rises the dopamine concentrations and synergizes with noradrenaline, resulting in a reduced fatigue sensation and a stimulated perception. Besides that, coffee consumption has been associated with anti-inflammatory activities due to their phenolic compounds (García-Blanco, Dávalos, & Visioli, 2017).

4.4 Anti-cancer activity

Coffee is the largest contributor of redox-active compounds in the population diet, given its habitual consumption. Coffee antioxidant activity is mainly attributed to phenolic compounds (del Castillo, Ames, & Gordon, 2002). Cancer develops as a result of DNA damage caused by procarcinogens or reactive oxygen species (ROS), which involves several steps including additional mutations in DNA and/or genetic impression—usually involving proto-oncogene activation, suppressor gene inactivation of the tumor and/or inactivation of genomic stability genes. The protection of cells against damage induced by ROS manifests itself as a mechanism against cancer induction. In this context, coffee is seen as a potential anti-carcinogen and may act on the reduction of ROS by a direct antioxidant effect.

Several transcription factors capable of controlling the expression of antioxidant defense and detoxification genes are regulated by the compounds found in coffee. The nuclear factor erythroid 2-related factor 2 (Nrf2), also known as nuclear factor erythroid-derived 2-like 2, consists of a transcription factor that acts by binding to electrophilic response elements and regulating the transcription of a series of defense proteins, thus being involved in redox regulation (Boettler et al., 2011). Cellular oxidative stress initiates Nrf2 translocation to nucleus. Coffee is seen as the most potent transcription inducer regulated by Nrf2 and its activity is increased by coffee consumption (Balstad et al., 2011). Fig. 5 shows the molecular targets within the Nrf2/Keap-1 pathway identified for some of the coffee constituent compounds.

Coffee antioxidant compounds modulate Nrf2-dependent transcription, controlling the production of proteins involved in the detoxification process, antioxidant defense, protein degradation, and inflammation. Diterpene Kahweol induces Nrf2-dependent transcription by signaling in the phosphatidylinositol 3-kinase (PI3K) pathway and protein kinase p38

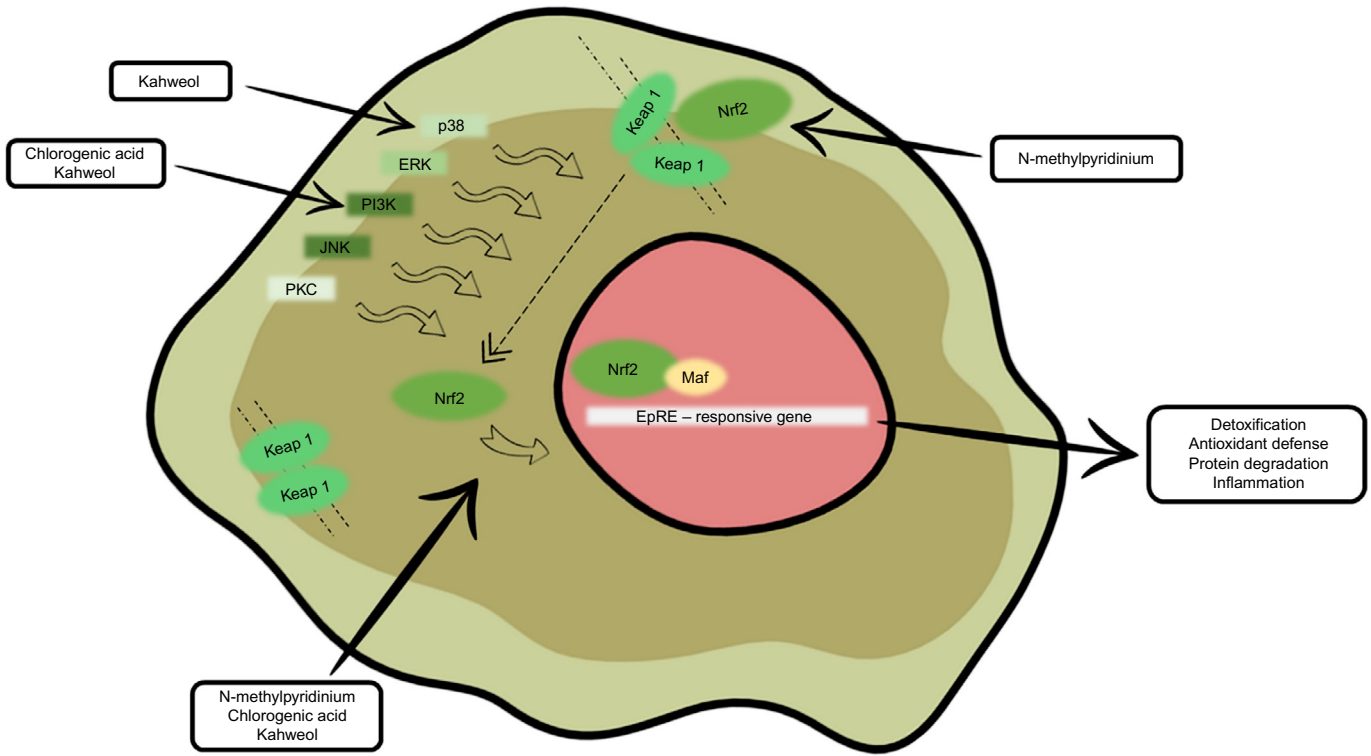

Fig. 5 Molecular targets in the Nrf2 pathway for different coffee compounds.

pathway, as well as by increasing Nrf2 nuclear translocation. Chlorogenic acid increases Nrf2 nuclear translocation through PI3K, while *N*-methylpyridinium compound increases Nrf2 translocation and transcription (Boettler et al., 2011; Feng et al., 2005; Hwang & Jeong, 2008).

As for caffeine, several epidemiological studies highlight its ability to act as an anti-cancer compound. By inhibiting extracellular signal-regulated kinases-1/2 and α-serine/threonine kinases, caffeine suppresses factor-1 expression, matrix-2 metalloproteinase and α-transforming growth factor of cancer-associated fibroblasts, as well as to decrease the concentration of α-actin of the smooth muscle, major markers of myofibroblasts (Niknafs, 2012; Yu, Bao, Zou, & Dong, 2011). Through increased expression of vital tumor suppressor proteins, such as p16, p21, p53 and Cav-1, caffeine plagues the release of various procarcinogenic cytokines (Al-Ansari & Aboussekhra, 2014).

4.5 Hepatic injury and cirrhosis prevention

Evidences suggest the protective effect of coffee consumption on the development and progression of hepatic disease. These effects are related to low levels of liver enzymes (alanine aminotransferase, aspartate aminotransferase and gamma glutamyl transferase) and hepatocellular carcinoma (HCC), in both the presence and absence of chronic hepatitis C virus. Several mechanisms are hepatoprotective assumptions of coffee. For example, coffee and HCC relationship are mediated by an accumulation of oxidized bases without cellular DNA. Oxidative DNA to DNA results in shortening of telomeres, an event called chromosomal instability (Rudolph, Hartmann, & Opitz, 2009). The habitual consumption of coffee induces telomere elongation, stabilizing the chromosomal DNA and preventing neoplastic evolution. Epidemiological studies on food are mediated by caffeine (Lv et al., 2010), the presence of phenolic metabolites (chlorogenic acid) (Gressner, Lahme, Siluschek, & Gressner, 2009), as well as other compounds including diterpenes kahweol and cafestol (Um et al., 2010).

Another assumption mechanism is that caffeine alters liver signaling and inflammatory pathways, leading to lower circulating levels of inflammatory biomarkers such as Interferon-gamma (IFN-γ), CX3CL1-fractalkine, CCL4, FGF-2 and sTNFRII, explaining the inverse association between coffee intake and HCC (Loftfield et al., 2015).

The antifibrotic effects of coffee are also reported. Caffeine shows the ability to decrease the expression of transforming growth factor β and

connective tissue growth factor, favoring the reduction of fibrosis (Arauz, Galicia-Moreno, Cortés-Reynosa, Salazar, & Muriel, 2013). In addition, coffee exposure significantly reduced pro-collagen III levels, a serum marker of fibrosis (Valva et al., 2011). This reduction is due to the caffeine adenosine receptor antagonist activity, since adenosine and its receptors are reported to promote hepatic fibrosis, or even paraxanthine, a caffeine metabolite that suppresses growth factor expression pro-fibrogenic connective tissue (CTGF) (Gressner et al., 2009). Numerous cytokines and growth factors are involved in the development of fibrosis. However, transformation of growth factor-β (TGF-β) is considered the most potent profibrogenic cytokine as it stimulates the differentiation of hepatic stellate cells (HSC's) into myofibroblasts. Caffeine blocks TGF-β expression and reduces mRNA levels of this protein, preventing liver fibrosis (Friedman, 2000).

HSC's are predominant effector cells in the pathogenesis of cirrhosis. The mechanism of caffeine in regulating and/or decreasing caffeine risk is to negatively regulate α-actin protein expression of smooth muscle and procollagen type Ic and induce HSC's apoptosis (Shim et al., 2013).

4.6 Human gut microbiota establishment

The influence of coffee consumption on the gut microbiota is attributed to some components of the beverage (soluble fibers (especially galactomannans and arabinogalactan-proteins)) and chlorogenic acids (phenolic compounds). In addition, alkaloids, minerals, soluble polysaccharides and other phenolic compounds can also influence the establishment of gut microbiota (Cowan et al., 2014; Jaquet, Rochat, Moulin, Cavin, & Bibiloni, 2009).

A study was conducted by Jaquet et al. (2009) to evaluate the effect of coffee consumption on the gut microbiota of 16 healthy adult volunteers. The consumption of three cups of coffee for 3 weeks resulted in the increase of the *Bifidobacterium* spp. population, especially for those volunteers showing the lowest initial levels of this bacterial group. In addition, the study reported that the metabolic activity of *Bifidobacterium* spp., expressed by rRNA extracted from the bacterial cells present in feces, increased in some individuals. The profile of the dominant bacterial groups, however, was not significantly affected.

Cowan et al. (2014) investigated the effect of chronic coffee consumption in the gut microbiota of rats treated with a high-fat diet. The consumption of coffee for a 10-weeks period was able to attenuate the typical increase in the Firmicutes to Bacteroidetes ratio and in the level of *Clostridium* Cluster

XI associated to high-fat diets. An increase in the abundance of Enterobacteriaceae and *Clostridium leptum* was also observed. Different findings, however, were reported by Hegde, Shi, Li, and Shi (2019), that evaluated the effect of coffee administration to rats subjected to normal diet for a period of 3 days. In this case, coffee treatment increased the levels of Firmicutes and decreased the levels of Enterobacteriaceae in the gut.

According to Bhandarkar, Brown, and Panchal (2019), chlorogenic acid treatment decreased Lachnospiraceae and *Oscillospira* levels and increased *Turicibacter* level in male Wistar rats submitted to corn starch-based diet, a treatment to induce metabolic syndrome. Rats fed with high-carbohydrate, high-fat diet had decreases in Bacteroidetes, S24-7, Lachnospiraceae, and *Oscillospira* and an increase in Firmicutes by the consumption of chlorogenic acid. In general, an increase in gut microbiota diversity, represented by the Shannon diversity index, could be correlated to the ingestion of chlorogenic acid.

4.7 Risk factors reduction of cardiovascular disease

Recent studies have demonstrated the beneficial relation between coffee intake and reduction of the risk of cardiovascular disease development. The 2015–2020 Dietary Guidelines for Americans associates the consumption of three to five cups of coffee per day to the reduction in the risk of cardiovascular disease (Chrysant, 2015; Voskoboinik, Koh, & Kistler, 2019).

Many cardiovascular risk factors, such as hypertension and glucose homeostasis (related to diabetes mellitus and metabolic syndrome), can be affected by the long-term consumption of coffee or its components. Coffee increases the secretion of peptides such as the gastric inhibitory polypeptide and reduces the secretion of glucagon-like peptide-1, thus lowering glucose absorption in the small intestine. Regular caffeine intake has been associated with protection from weight gain, by increasing lipid turnover and energy expenditure, and to reduced gut absorption of short chain fatty acids (Voskoboinik et al., 2019).

Among the components of coffee, chlorogenic acid is especially known to present therapeutic properties that promote cardiovascular health. Around one-third of the chlorogenic acid present in coffee is absorbed in the small intestine, while the remaining is metabolized by the gut microbiota in the large intestine (Bhandarkar et al., 2019; Chrysant, 2015).

The beneficial effects of chlorogenic acid include the modulation of glucose and lipid metabolism through the increased mRNA expression of

specific receptors, the inhibition of the activity of glucose-6-phosphatase, thus reducing glucose release in the liver, the reduction of the expression of sodium-dependent glucose transporters in the small intestine, thus reducing glucose absorption, and finally its antioxidant and anti-inflammatory properties. Such therapeutic effects result in many cardiovascular health benefits that include the decrease in triglyceride concentration and increase in high-density lipoprotein (HDL) cholesterol concentration, increased fat oxidation, and in the reduction of risk of developing metabolic syndrome and type 2 diabetes (Bhandarkar et al., 2019).

4.8 Positive effects on the gastrointestinal tract

Coffee ingestion has been often associated, empirically, with activated intestinal function, heartburn and dyspepsia. Scientific studies have elucidated some mechanisms by which coffee avoids constipation, which occurs in part by the stimulation of the central nervous system by caffeine, and heartburn is a symptom reported by some individuals after coffee intake. However, no proved correlation with dyspepsia was found (Boekema, Samsom, Henegouwen, & Smout, 1999).

Caffeine is known to inhibit the activity of phosphodiesterase, which results in increased concentrations of cyclic nucleotides such as cyclic adenosine monophosphate (cAMP). Some effects related to cAMP concentration are stimulation of gastric acid secretion, intestinal secretion and relaxation of the lower esophageal sphincter (Turnberg, 1978), so these activities are expected to be associated with coffee intake. However, since coffee is a complex mixture of almost 1000 compounds (Bhandarkar et al., 2019), it is important to investigate the effect of the whole beverage and of different preparation modes on the functions of the gastrointestinal tract.

Hegde et al. (2019) demonstrated, in vitro and in vivo, that coffee treatment stimulated the contractility of the ileal and colonic smooth muscle, in a dose-dependent and caffeine-independent manner, since decaffeinated coffee presented similar effect. Promotion of gastro-esophageal reflux, gastrin release, gastric acid secretion, prolongment of the adaptive relaxation of the proximal stomach, induction of cholecystokinin release, colonic motion and gallbladder contraction have also been demonstrated scientifically (Boekema et al., 1999).

Recently, Eamudomkarn et al. (2018) developed a systematic review and meta-analysis to evaluate the benefits of coffee consumption after abdominal surgery. The results demonstrated that postoperative coffee intake is

effective and safe for enhancing the recovery and stimulating the gastrointestinal function, even by reducing the length of hospital stay, and with no adverse events reported.

5. Coffee by-products for functional food development

Coffee seeds correspond to 50% of total coffee fruit, while the other 50% are coffee pulp and husk, parchment, silverskin, and spent coffee grounds (Campos-Vega et al., 2015; Murthy & Naidu, 2012b). These by-products account for over 6 million tonnes of residual waste per year. Disposal of coffee by-products usually causes difficulties due to the volume and recalcitrant structure that characterize it (Mussatto et al., 2011). A serious example of this inappropriate practice occurred between 1930 and 1943, where 77 million bags (60 kg) of green coffee were incinerated and discarded in Brazilian sea and landfill due to low exportation during the World War II (Cunha, 1992).

Animal feed (Mazzafera, 2002), fertilizer development (Hachicha et al., 2012) and biotechnological transformation (biofuels, enzymes and aroma compounds production) are alternatives for the reuse of coffee by-products (Cerda, Gea, Vargas-García, & Sánchez, 2017; Hachicha et al., 2012; Karmee, 2018; Mazzafera, 2002; Soares, Christen, Pandey, & Soccol, 2000). However, the chemical composition of coffee residues often offers limits to their reuse. For instance, caffeine is a purine alkaloid present in all coffee constituents, which shows cytotoxic effect in microorganisms for biotechnological transformation and physiological disturbances on the central nervous systems of cattle and fish (Rallis, Codlin, & Bähler, 2013; Rodriguez, Haugen, Rueber, & Huang, 2014), while chlorogenic acids interfere in seed germination and growth (Janissen & Huynh, 2018). Thus, additional detoxification steps are generally necessary for the reuse of coffee waste. It includes pre-treatment with filamentous fungi capable of degrade caffeine (Brand, Pandey, Roussos, & Soccol, 2000; Gokulakrishnan, Chandraraj, & Gummadi, 2005) or chemical extraction, such as supercritical fluid and solvent extraction (Tello, Viguera, & Calvo, 2011).

The use of coffee by-products as functional ingredients has been an emerging sector in the food industry. This is because of the high concentration of antioxidant compounds and the non-toxic nature for human consumption (Iriondo-DeHond et al., 2019). The coffee pulp and husk has been mainly applied as an enriched substrate for the cultivation of edible

mushrooms (Alemu, 2015; da Silva et al., 2012; Leifa, Pandey, & Soccol, 2001) and as a source of phytochemicals, dietary fiber and caffeine for beverage supplementation (Esquivel & Jiménez, 2012; Heeger, Kosinska-Cagnazzo, Cantergiani, & Andlauer, 2017; Murthy & Naidu, 2012a; Velissariou, Laudano, Edwards, Stimpson, & Jeffries, 2010). Coffee pulp and husk can also be used as natural food colorants due to the presence of anthocyanins (Murthy, Manjunatha, Sulochannama, & Naidu, 2012). Moreover, the high content of pectin (3.83% of dry weight) in coffee pulp and husk could be explored as a gelling agent, thickener, texturizer, emulsifier, stabilizer, and sugar or fat replacer in low-calorie foods (Menezes et al., 2013; Thakur et al., 1997).

Several bioactive compounds have been described in coffee pulp, such as phenolic compounds (5-caffeoylquinic acid, 3,5-dicaffeoylquinic acid, 5-feruloylquinic acid, epicatechin, catechin, rutin, and ferulic acid), anthocyanins (cyanidin-3-rutinoside, cyanidin-3-glucoside) and flavanols (Esquivel & Jiménez, 2012; Mullen, Nemzer, Stalmach, Ali, & Combet, 2013; Murthy et al., 2012). Although there are no applications using coffee pulp in the food industry to date, it has been suggested as a source of bioactive ingredients for the formulation of foods (Murthy et al., 2012).

Coffee parchment is the thin, paper-like, polysaccharide layer warping both hemispheres of the coffee beans with rich composition of insoluble dietary fiber (cellulose (40–49%), hemicellulose (25–32%), and lignin (33–35%)), caffeine (58.2 mg/g), and phenolic and flavonoids content (68.2 and 6 μmol chlorogenic acid eq/g, respectively) (Bekalo & Reinhardt, 2010; Iriondo-DeHond et al., 2019). To date, the application of coffee parchment is focused as a source of antioxidant dietary fiber with hypolipidemic and hypoglycemic properties (Benitez et al., 2019). These physiological benefits are associated with the formation of a coating around lipid droplets, which hinders the action of lipases, and the adsorption of amylase on the hemicellulosic and cellulosic polysaccharides surface (Benitez et al., 2019; Dhital, Warren, Butterworth, Ellis, & Gidley, 2017).

Coffee silverskin presents a constitution with high contents of insoluble dietary fiber (45–66%) and total proteins (10.9–19%), low amounts of reducing sugar (0.2%) and fat (2.2%), and marked antioxidant activity (Ballesteros, Teixeira, & Mussatto, 2014; Iriondo-DeHond et al., 2019; Narita & Inouye, 2014). The coffee silverskin can be used as replacer of fat and wheat flour in the formulation of bread, cakes and biscuits, and formulation of blend beverages destined to weight control (Ateş & Elmaci, 2018a, 2018b; Garcia-Serna, Martinez-Saez, Mesias, Morales, & del

Castillo, 2014; Martinez-Saez et al., 2014; Pourfarzad, Mahdavian-Mehr, & Sedaghat, 2013; Ribeiro, Leitão, Ramalho, & Lindon, 2014).

A spent coffee ground is the major residual waste of instant coffee and espresso beverages. The low content of free glucose (0.04 mg/100 g), in conjecture to the high amounts of total proteins (11.2%), total dietary fibers (47.30%) and antioxidants, turns it a viable option of food ingredient to low glycemic index diets (Martinez-Saez et al., 2017). Moreover, the presence of 5-caffeoylquinic acid has been associated to the preservation of food lipids (Jully, Toto, & Were, 2016; Junior & Morand, 2016; Panzella et al., 2016). Finally, the extraction of melanoids, a polymeric high molecular weight compounds derived from Maillard reactions, from spent coffee grounds showed potential to be used as prebiotic due to supporting the growth of *Bifidobacteria* (Mesías & Delgado-Andrade, 2017).

6. Conclusions

Many cups of coffee are consumed each day by adults. This consumption has been increasing every year due to the proven health actions of coffee. This includes the prevention of various diseases, including type 2 diabetes, depression and suicidal behavior, cancer, hepatic injury and cirrhosis, and neurological and cardiovascular diseases. Coffee consumption is also associated with positive effects on the gastrointestinal tract and gut microbiota.

The progressive increase in coffee consumption reflects directly on the generation of coffee by-products during on-farm and industrial processing. Application of coffee by-products in the food sector offers effective tools and solutions for managing residues from coffee crops, which tend to minimize the accumulation of large amounts of these residues in the environment. Coffee pulp and husk, silverskin, parchment and spent coffee ground can be used in the formulation of food products, as source of prebiotic and caffeine for beverage supplementation. The advancement of studies, creation of strong research networks and development of industrial applications are appropriate strategies to boost progress and add value to the coffee production chain.

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