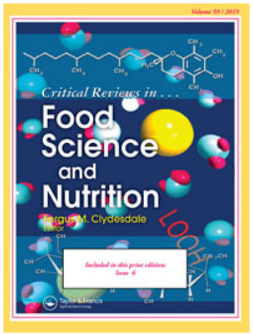

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Xiumin Chen (2019) A review on coffee leaves: Phytochemicals, bioactivities and applications, Critical Reviews in Food Science and Nutrition, 59:6, 1008-1025, DOI: 10.1080/10408398.2018.1546667

To link to this article: https://doi.org/10.1080/10408398.2018.1546667

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2019, VOL. 59, NO. 6, 1008–1025
https://doi.org/10.1080/10408398.2018.1546667

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REVIEW

A review on coffee leaves: Phytochemicals, bioactivities and applications

Xiumin Chen

Department of Food Science and Engineering, School of Food and Biological Engineering, Jiangsu University, Jingkou District, Zhenjiang, Jiangsu, P.R. China

ABSTRACT

Coffee leaves have a long history for use as ethnomedicine and tea beverage by locals from countries where coffee plants grow. Recently, attentions have been paid to their health benefits to human beings because of abundant bioactive components in coffee leaves. However, the researches related to the bioactivities, applications, and the impacts of processing methods on the phytochemical composition and activities of coffee leaves are scarce. The reviews specific to coffee leaves in these aspects are rare too. Due to the growing interests to coffee leaves, in this review, the chemical compositions in coffee leaves and the influence of environmental conditions and processing methods on them were summarized. Furthermore, various applications of coffee leaves, including ethnomedicine, coffee leaf tea, therapeutic agent, packaging material, tobacco substitute, organic fungicide, personal hygienic products, and animal feed et al. were presented. The future prospects of coffee leaves are also discussed. In conclusion, coffee leaf is a very promising resource in the areas of food and industry, especially, in the beverage industry. The researches in understanding impacts of the processing methods on the phytochemicals, enzymes, bioactivities, and flavor of coffee leaves are highly needed.

KEYWORDS

Bioactive components; coffee leaf tea; ethnomedicine; function; industrial application

Introduction

The genus *Coffea*, belonging to the *Rubiaceae* family, comprises 124 species, among which *Coffea arabica*, *Coffea canephora (C. robusta)* and *Coffea liberica* are three of species that are used to make coffee beverage (Davis et al. 2011). *C. arabica* and *C. canephora* account for 75–80% and ~20% of the world's coffee production, respectively. Coffee, the second most traded commodity, is produced widely in tropical or subtropical regions such as central and South American, Africa, and South Asia (Wintgens 2004). Coffee leaf has been traditionally used as ethnomedicine to ameliorate various diseases or disorders by locals in the coffee plant growing countries (Ross 2005; Campa and Petitvallet 2017; Patay, Bencsik, and Papp 2016). In Ethiopia, South Sudan, Indonesia, Jamaica, India, Java, Sumatra, coffee leaves have been consumed as tea since 1800s (Campa and Petitvallet 2017; Ross 2005; Chen, Ma, and Kitts 2018). However, it was not until 2012 when France and British researchers published a paper in which the bioactive components of 23 coffee leaves were determined, the health benefits of coffee leaves to human were recognized by public worldwide (Campa et al. 2012). Numerous researches focus on the chemical and biological activities of *C. arabica* and *C. canephora* beans, whereas, the studies related to the phytochemicals and bioactivities of coffee leaves are scarce. Due to the presence of beneficial phytochemicals in coffee leaves, there are growing interests in application of coffee leaves as tea like beverage, functional food supplements, and ethnomedicines.

The ethnopharmacological application of coffee leaves are mainly due to the fact that coffee leaves contain various bioactive phytochemicals such as alkaloids, flavonoids, terpenes, tannins, xanthonoids, phenolic acids, flavonoids, phytosterol, amino acid, and carotenoids, which contribute to the antioxidant, anti-inflammatory, anti-hypertensive, anti-bacterial, anti-fungi activities (Campa et al. 2012; Patay et al. 2016; Ross 2005; Campa and Petitvallet 2017; Jyotshna, Khare, and Shanker 2016; Luczkiewicz et al. 2014; Upadhyay and Mohan Rao 2013). Although there are very few researches related to the bioactivities of coffee leaves, their applications have been patented as coffee leaf tea or beverage, therapeutic agents, tobacco substitute, proliferating agent, facial cleanser, packaging material, absorbent pad, animal feed, organic fungicide, et al. The phytochemical profile of coffee leaves varied according to the plant species, cultivars, growing region, climate, developing stage, et al. and processing methods affected both phytochemical compositions and bioactivities of coffee leaves (Chen, Ma, and Kitts 2018).

Compared to the other two popular beverages, coffee and tea, the significances of coffee leaves to human health and to

CONTACT Xiumin Chen xmchen@ujs.edu.cn School of Food and Biological Engineering, Jiangsu University, 301 Xuefu Road, Jingkou District, Zhenjiang, Jiangsu 212013, P.R. China.

Supplemental data for this article can be accessed https://doi.org/10.1080/10408398.2018.1546667.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.
This article is part of the supplemental issue '3rd International Symposium on Phytochemicals in Medicine and Food (3-ISPMF, August 25-29 2018, Kunming, China)' in Volume 59.

economics are underestimated for centuries. Coffee leaves are rich in chlorogenic acids and mangiferin, which have been proved to have various health benefits. The roasting process in coffee bean production causes the loss of majority chlorogenic acids in the roasted coffee beans, whereas, the production procedures for coffee leaf tea enable chlorogenic acids to be largely retained. Mangiferin, a phytochemical with various bioactivities, was found in the leaves of *C. Arabica*, whereas, it was not detected in the beans, suggesting that coffee leaves have greater health benefits. Coffee leaves are also considered as a better antioxidant source than tea. Moreover, compared to 3–4 months coffee bean harvest season, the year-round harvest of coffee leaves can not only increase the income for the coffee farm owners, but also create more jobs for coffee farm workers, thus reduces migration due to the shortage of jobs and provides a new economic model for coffee plant growing countries and regions (Campa and Petitvallet 2017; Bacon et al. 2014). Considering the promising benefits of coffee leaves on human health and economics and the increasing interests in the applications of coffee leaves, it is necessary to understand the bioactive components, activities, health benefits of coffee leaves as well as the impact factors that influence the phytochemical compositions. To this purpose, this paper reviews the phytochemical composition, bioactivities, ethnomedicinal and novel applications of coffee leaves. The literature overview was based on Web of Science, PubMed, Google Scholar and Google Patent.

The leaf of coffee

Coffee leaves are shiny and waxy light or dark green or bronze in color depending on the development stages and the origin of the plants. They grow on the sides of the main stem and branches in opposite pairs (Wintgens 2004). The life span of *C. canephora* leaves is about 7–10 months and *C. arabica* is about 8 months. Coffee leaves can be categorized into the following three types according to the development stages: buds and young leaves, which are recently emerged with a fresh weight of around 25 mg and a size about 20 mm long and 7 mm wide; mature leaves, which are fully expand second and third leaves located below the apex with a weight of ~1.2 g; aged leaves, which are dark green leaves located near the base of the shoot with a weight of ~1.3 g. The size of mature and aged leaves range from 10 to 15 cm long and ~6 cm width (Ashihara et al. 1996).

Chemical composition of coffee leaf

The chemical compositions of coffee leaves are summarized in Table 1 and some chemical structures are shown in Figure 1. The proximate compositions of mature *C. arabica* coffee leaves from different regions of Ethiopia are as follow: 5.5–7.8% moisture, 8.8–12.4% ash, 14.4–19.0% protein, 4.5–12.5% fat, 17.1–20.0% fiber, 51.0–63.9% carbohydrate (Woldesenebet 2005). Ca, Mg, and Fe are three major minerals whose amount varied depending on the growing region. Mineral content in Ethiopia coffee leaves (8.8–12.4% ash) is much higher than that of coffee bean (3.9–4.4%) and conventional tea (≈4.8%). Martins et al. (2014) detected 63 primary metabolites in the leaves of *C. arabica* plant grown in South-Eastern Brazil. These primary metabolites include amino acids, organic acids, sugars, sugar alcohols and polyamines. More recently, the untargeted metabolomic technique was applied to investigate the metabolite fingerprint of coffee leaves from 9 *Coffea* species and several key metabolites such as caffeine, ent-kaurane diterpenoid, theobromine and theophylline were selected as biomarkers to discriminate between species (Souard et al. 2018). The phytochemical contents in coffee leaves are affected by various factors, including the geography region, environmental conditions, species, cultivar, the age of plant, leaf developing stage, and collecting season et al. For example, leaves harvested in November contain less metabolites compared with those harvested in other seasons (Souard et al. 2018). Total phenolic content (TPC) was greater in production stage and young coffee leaves compared with fruit formation stage and mature leaves, respectively (Salgado et al. 2008). Sanchez-Gomez et al (2018) found that compared with conventional drying method, high temperature short time drying did not influence TPC. Phytochemicals such as alkaloids, hydroxycinnamic acids, xanthonoids, and flavonoids contents followed a descending order in juvenile, growing and mature leaves (Campa et al. 2017). The literature related to the chemical composition of coffee leaves focus on the impact of light intensity, nitrogen concentration, growing region, and species, cultivar, and the age of leaves on the phytochemical profiles.

Carbohydrates

The carbohydrates that were detected in coffee leaves include monosaccharides (glucose, fructose, galactose and rhamnose), oligosaccharides (sucrose, maltose and raffinose), polyols (threitol, sorbitol and galactinol), and starch (Martins et al. 2014). Starch accounts for around 2.1% of the dry weight of leaves exposed to low light, whereas its content reaches 2.9% under high light condition. Except for sucrose, the rest of carbohydrates are more abundant in the coffee leaves exposed to more light (Martins et al. 2014).

Amino acids and proteins

Except for the 20 common amino acids, β-alanine, homoserine, 4-OH-proline, cystine, and γ-aminobutyric acid (GABA) were detected in coffee leaves. Light intensity influences amino acids differently and the content of total amino acids were higher in the leaves received more sun light, which is associated with lower nitrogen concentration (Martins et al. 2014). Glutamate and aspartate contents are lower under higher light intensity, whereas, the other amino acids are similar or more abundant when exposed to full sunlight with histidine increasing 10 times. Pompelli et al. (2010) also found that under low nitrogen condition, amino acid content was lower when coffee leaves exposed to lower sunlight, whereas, in the case of high nitrogen supply, the results vice versa. For protein contents, higher sunlight and

Table 1. Chemical compositions of coffee leaf.

Group	Chemicals	References
Carbohydrate		
Monosaccharide	glucose, fructose, galactose and rhamnose	Martins et al. 2014
Oligosaccharide	sucrose, maltose and raffinose	Martins et al. 2014
Polyols	threitol, sorbitol and galactinol, alkan-1-ols (C28–C36)	Martins et al. 2014; Holloway, Deas, and Kabaara 1972
Amino acid and Protein		
Amino acid	GABA, β-alanine, homoserine, 4-OH-proline, cystine, and 20 common amino acids	Martins et al. 2014
Polyamines	ornithine, putrescine, spermine, threonine, triethanolamine, tyramine	Martins et al. 2014
Organic acid		
In cuticle	monobasic acid (C16-C34), monohydroxytetradecenoic acids (7-,8-,9-,10-OH), monohydroxypentadecanoic acids (7-,8-,9-,10-OH), 16-hydroxyhexadecanoic acid (16-OH), monohydroxyhexadecane-1,16-dioic acids (7(10)-, 8(9)-OH), dihydroxypentadecanoic acids (7,15-, 8,15-, 9,15-, 10,15-OH), dihydroxyhexadecanoic acids (7,16-, 8,16-, 9,16-, 10,16-OH), 9,10,18-trihydroxyoctadecanoic acid	Holloway, Deas, and Kabaara 1972
In Epidermis and mesophyll	lactate, glycolate, 2-oxoglutarate, 5-amino-valerate, aconitate, ascorbate, citrate, dehydroascorbate, fumarate, galactonic acid, glutarate, glycerate, isocitrate, malate, nicotinate, pyroglutamate, pyruvate, quinate shikimate, Pipecolic acid	Martins et al. 2014, Chaves et al. 2008
Alkaloid	caffeine, trigonelline, theobromine, and theophylline	Chen, Ma, and Kitts 2018, Fujimori and Ashihara 1994, Ky et al. 2001, Souard et al. 2018
Phenolic compound		
Phenolic acid	caftaric acid, gentisic acid, caffeic acid, p-coumaric acid, ferulic acid, benzoic acid, 3-OH-benzoic acid, sinapic acid, protocatechuic acid, chlorogenic acids (3-CQA, 4-CQA, 5-CQA, 3,4-diCQA, 3,5-diCQA, 4,5-diCQA), feruloylquinic acids (3-FQA, 4-FQA, and 5-FQA)	Chaves et al. 2008, Martins et al. 2014, Patay, Bencsik, and Papp 2016, Patay et al. 2016
Flavonoid	catechins (catechin, EC, EGCG, ECG); anthocyanin (delphinidin 3,5-diglucoside and Delphinidin 3-(6''-malonyl-glucoside)); myricetin, fisetin, patuletin, luteolin, apigenin, quercetin and its glycosides (quercitrin, isoquercitrin, hyperoside, rutin, quercetin-3-Glc-Hex-DeHex, quercetin-3-glucuronide), kaempferol and its glycosides (kaempferol-3-Glc-Hex-DeHex, kaempferol-3-Glc-Hex, kaempferol-3-Glc-6''-Rha, kaempferol-3-Glc),	Martins et al. 2014, Patay et al. 2016, Ratanamarno and Surbkar 2017, Domingues et al. 2012
Xanthone	mangiferin and isomangiferin	Chen, Ma, and Kitts 2018; Campa et al. 2012; Conejero et al. 2014; Martins et al. 2014; Talamond et al. 2008; Trevisan et al. 2016
Terpene	ent-kaurane diterpenoid, 16-O-methylcafestol, cafestol, kahweol, ursolic acid	Souard et al. 2018; Ross 2005
Carotenoid		
Carotene	α-carotene, β-carotene	Pompelli et al. 2010
Xanthophyll	neoxanthin, lutein, violaxanthin, antheraxanthin, zeaxanthin	Pompelli et al. 2010
Phytosterol	Sitosterol	Maurel 1995a b; Maurel et al. 1996
Flavor compound		
Aldehyde	isobutyraldehyde, isovaleraldehyde, valeraldehyde, octanal, nonanal, decanal	Furukawa et al. 1991b
Alcohol	Hexanol, 1-penten-3-ol, Cis-2- penten-1-ol, cis-3-hexen-1-ol, amyl alcohol, butanol, L-menthol	Furukawa et al. 1991b
Ketone	geranylacetone, 2-methyl-2-heptene-6-one	Furukawa et al. 1991b
Ester	ethyl acetate	Furukawa et al. 1991b

nitrogen conditions resulted in the greater total proteins in *C. arabica* leaves. However, the activity of antioxidant enzymes decreased under high nitrogen condition (Reis et al. 2015). Polyamines including ornithine, putrescine, spermine, threonine, triethanolamine, tyramine were also detected in *C. arabica* coffee leaves and five of them except spermine exist higher amount in high light exposure leaves (Martins et al. 2014). Using proteomic technique, Guerra-Guimaraes et al. (2015) identified 116 proteins that belong to 23 diverse superfamilies in the apoplastic fluid of *C. arabica* leaves. The functional categories of these proteins include protein degradation, cell wall metabolism, stress/defense, miscellaneous enzyme families, minor carbohydrates metabolism, secondary metabolism, and redox. Chitinase, pectin methylesterase, serine carboxypeptidase, reticuline oxidase, and subtilase are considered as putative biomarkers for the coffee leaves to resist *H.vastatrix* infection. Antioxidative enzymes including superoxide dismutase, ascorbate peroxidase, catalase, and glutathione reductase were found to be affected by the light conditions and nitrogen supply. Low nitrogen and sunlight condition cause the low activity of ascorbate peroxidase and glutamine synthetase, however catalase activity was lower

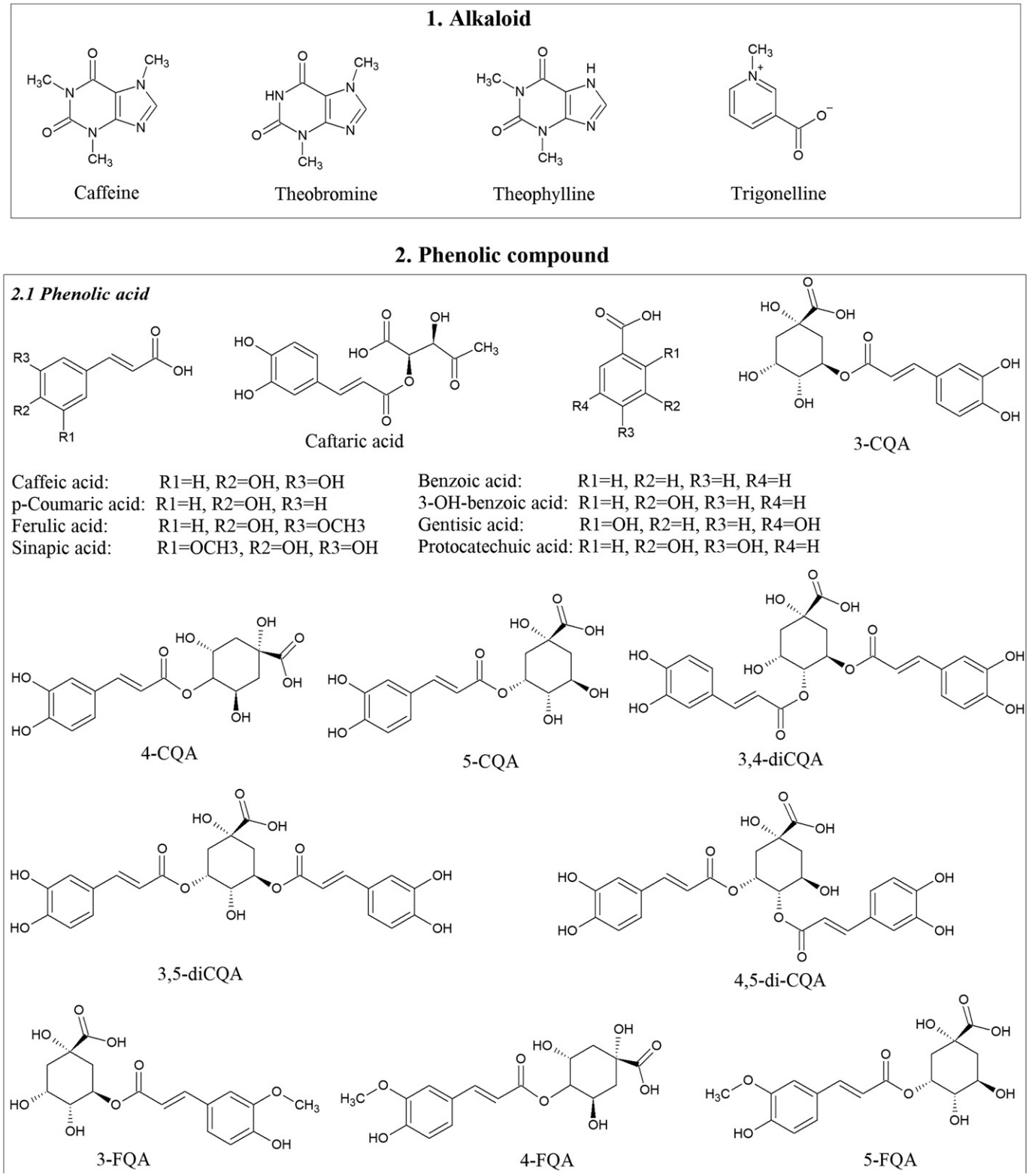

Figure 1. Chemical structures of coffee leaf components.

in the plant grown in the shaded condition, but not influenced by the nitrogen supply (Pompelli et al. 2010).

GABA, an ubiquitous nonprotein amino acid that exist in mammal, bacteria, and plants, is one of the most promising amino acids found in coffee leaves (Zhao et al. 2015). It is one of the major inhibitory neurotransmitters in the sympathetic nervous system and has been found to improve brain function (Huang et al. 2014), prevent hypertension (Di Lorenzo et al. 2016), control pancreatic secretion (Bansal et al. 2011), regulate cardiovascular function (Cherng et al. 2014), inhibit metastasis of cancer cells (Joseph et al. 2002), promote sleep (Zhao et al. 2015). GABA is produced

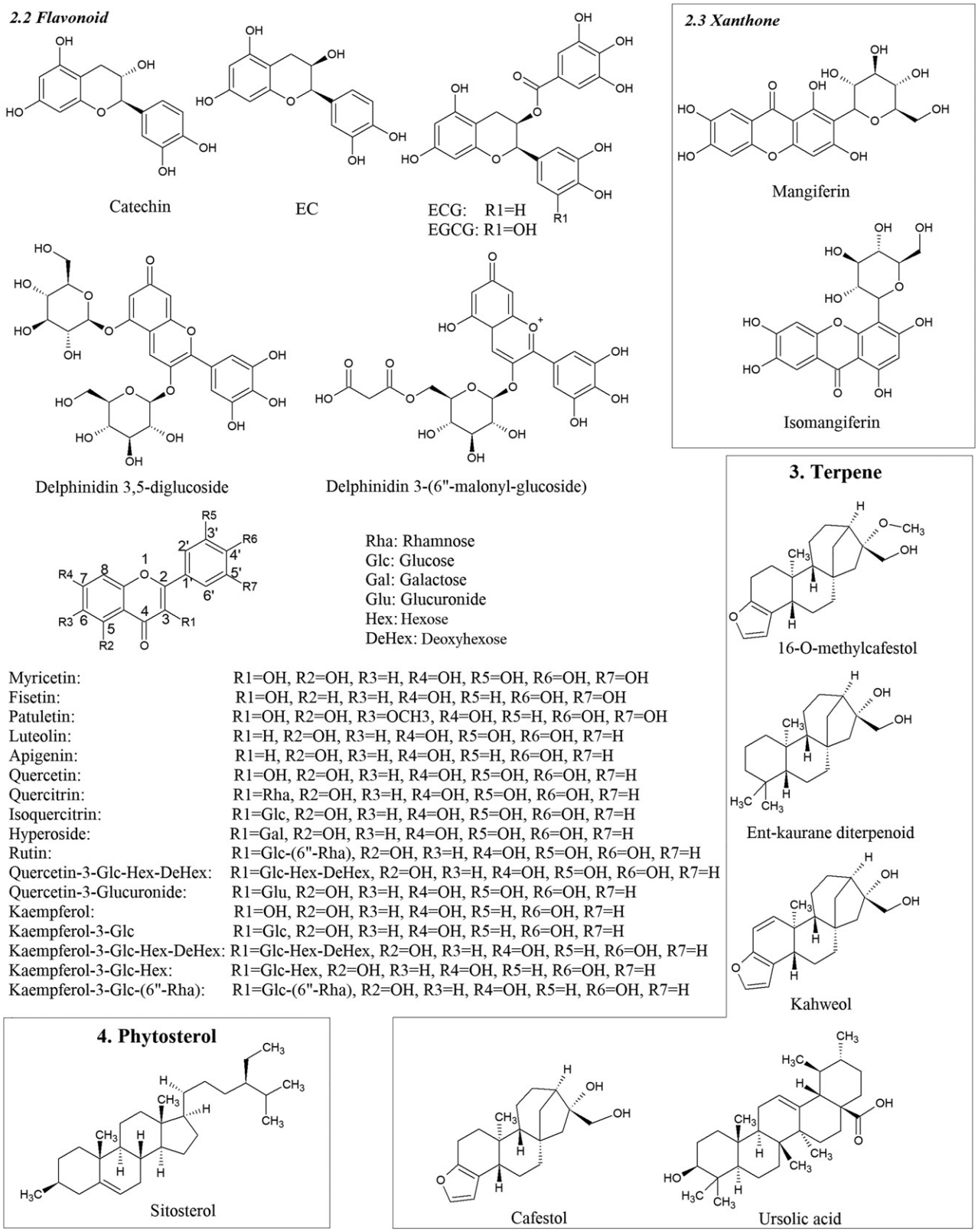

Figure 1. Continued.

through glutamate decarboxylase catalyzed enzymatic conversion of glutamic acid under anaerobic condition (Deewatthanawong, Rowell, and Watkins 2010). Untreated coffee leaves contain 4 mg/100 g, 24 mg/100 g, 35 mg/100 g of GABA, respectively in sprout, growing, and mature leaves, indicating that GABA content increases during the ageing process. After anaerobic treatment, GABA increases to 44 mg/100 g, 41 mg/100 g, and 63 mg/100 g, respectively in the corresponding coffee leaves (Inoue 1994). The fact that the percentage increase of GABA in leaves followed a

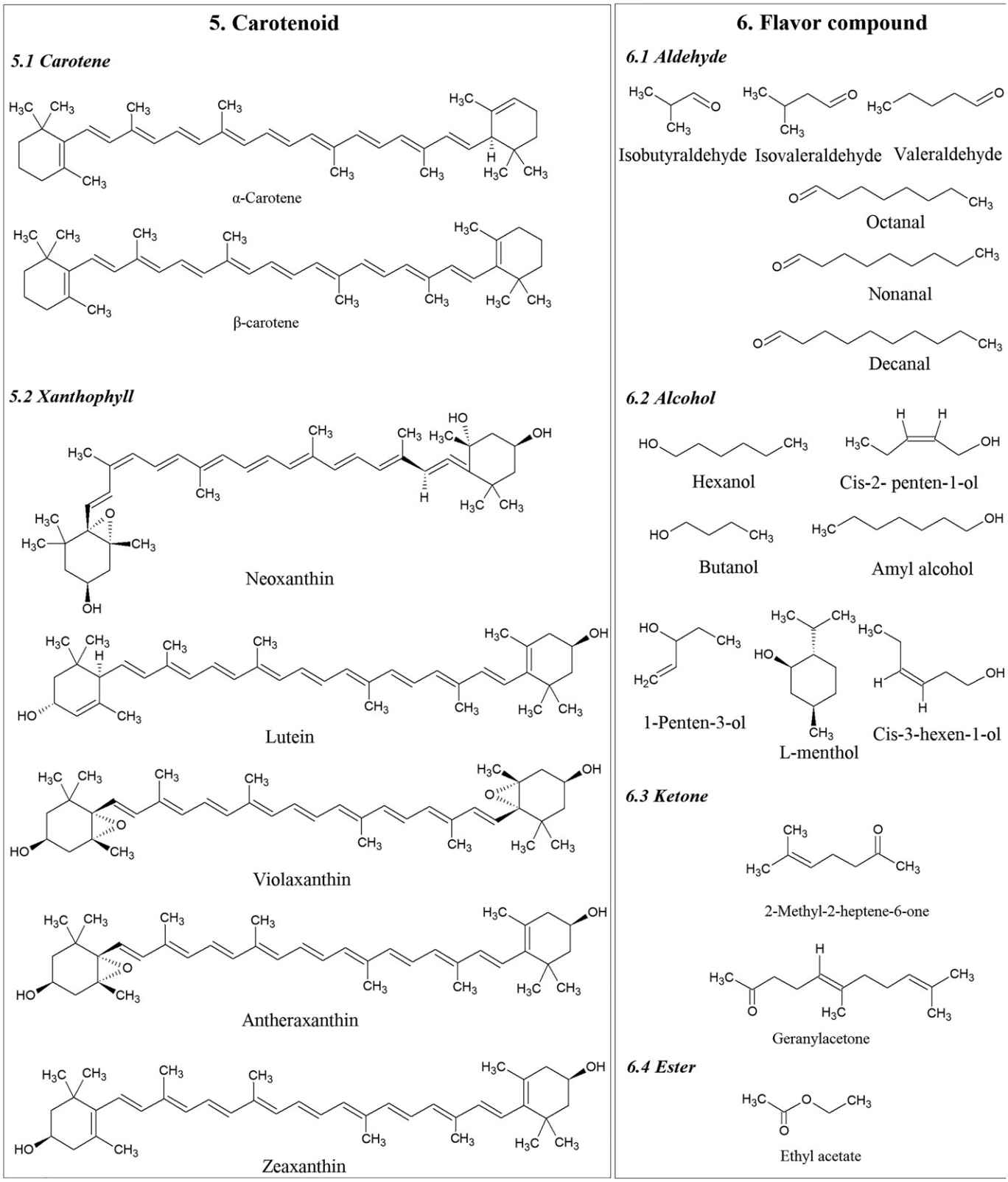

Figure 1. Continued.

descending order as the age of leaves increase is possible due to the decrease of glutamate decarboxylase activities. Anaerobic treating time also affect the content of GABA evidenced by GABA content increasing from 41mg/100 g to 66 mg/100 g when the treating time extend from 3 to 9 h (Inoue 1994). Activation of CsGAD1 enzymatic activity by calmodulin and accumulation of high levels of CsGAD2 mRNA are dual mechanisms for regulating the accumulation of GABA in tea under stress (Mei et al. 2016). Great interests are focused on the production and health impact of

GABA tea. Although no research paper published relative to GABA in coffee leaves, three patents about preparation of GABA enrich coffee leaf tea has been reported (Inoue 1994; Takagaki and Tsuzaki 2000; Toshimitsu Hattori and Takagaki 1999). Therefore, investigations of synthetic pathways and control factors for GABA accumulation in coffee leaves to produce GABA enrich coffee leaf tea that can be used to decrease blood pressure and promote sleep quality are promising research fields in future.

Organic acids

Martins et al. (2014) detected over 20 organic acids including lactic acid, ascorbic acid, citric acid, pyruvic acid, quinic acid, et al. in coffee leaves. The response of organic acids to the light intensity varied according to the type of organic acids. For example, leaves exposed to low light contain greater amounts of pyruvate, malate, fumarate, citrate, aconitate and 2-oxoglutarate compared with the leaves under high light, whereas, the result of isocitrate, lactate, nicotinate, and pyroglutamate vice versa. Ascorbate was detected in *C. arabica* leaves and it is more abundant when the plants receive more sun light (Chaves et al. 2008). The organic acids, including C16-C34 monobasic acids, C14 and C15 monohydroxymonobasic acids, C16 ω-hydroxymonobasic acid, C16 monohydroxydibasic acids, C15 and C16 dihydroxymonobasic acids, and C18 trihydroxymonobasic acid in the cuticle of young and mature coffee leaves were compared by Holloway, Deas, and Kabaara (1972). Dihydroxyhexadecanoic acids accounts for over 60% of the total acids and the composition of acids in cuticle of leaf surface were not significantly affected by the leaf developing stages and the side of the surface.

Alkaloids

Caffeine, trigonelline, theobromine, and theophylline are four kinds of alkaloids that are detected in coffee leaves and the first two compounds are predominant in coffee bean and leaves. Caffeine, a adenosine receptor antagonist and a phosphodiesterase 3 inhibitor, was discovered in coffee and tea (*Camellia sinensis*) in 1820s (Ashihara and Crozier 2001). Coffee, tea and coffee leaves contain 60–80, ~27 and ~12 mg/cup caffeine, respectively, indicating that coffee leaves possess much lower caffeine compared with coffee and tea (Lelo et al. 1986, Chen, Ma, and Kitts 2018, Martinko 2015). The amount of caffeine in coffee leaves is affected by the plant variety and age, growing season and region, environment, field condition, soil nutrients, rainfall, stress by pests, the position of the leaves on the plant (Ratanamarno and Surbkar 2017). Ratanamarno and Surbkar (2017) reported that caffeine content in dry *C. arabica* leaves ranged from 1.8 to 3.2 mg/g and young leaves (3–4 weeks old) contain greater amount of caffeine than mature leaves (5-6 weeks). Fermentation or anaerobic treatment process did not affect caffeine content significantly (Chen, Ma, and Kitts 2018, Takagaki and Tsuzaki 2000). Caffeine content in *C. arabica* leaves was 800 times higher than in the leaves of *C. canephora* (Souard et al. 2018). The biosynthesis of caffeine in coffee leaves starts at the very early stages of the leaf development and reaches a maximum in the fully open leaves (Patay et al. 2017). The accumulated caffeine in the mature leaves translocates to the seed and reach the final quantity in 8 months after flowering. Another reason for the accumulation of caffeine is because that it is catabolized into theophylline at a extremely slow rate in *C. arabica* (Ashihara and Crozier 1999). In plant, caffeine prevents the invasion of inset and germination of other seeds (Ashihara and Crozier 2001).

In human body, caffeine is metabolized into theobromine, theophylline, and paraxantine (Patay, Bencsik, and Papp 2016) and has both beneficial and harmful effects. The biomedical impacts of caffeine and its analogs have been reviewed by Daly (2007). The bioactivities include antioxidant (Chu et al. 2012), anti-inflammatory (Horrigan, Kelly, and Connor 2004), anti-cancer (Yang et al. 2005), anti-Alzheimer's disease (Maia and de Mendonca 2002), anti-diabetics (Petrie et al. 2004), diuretic (Rieg et al. 2004), anti-Parkinson's disease (Xu, Bastia, and Schwarzschild 2005), and increasing alertness (Smith 2002). Caffeine inhibits LPS-induced inflammatory responses such as nitric oxide, iNOS, COX-2, IL-3, IL-6, and IL-12 through regulating NF-κB activation and p38 MAPK in Raw 264.7 cells (Hwang et al. 2016). Caffeine and its metabolites theobromine and xanthine prevent lipid oxidation through inhibiting the production of free radicals including hydroxyl radical, peroxyl radical and singlet oxygen (Azam et al. 2003). The adverse effects of over consumption of caffeine include gastrointestinal disturbance, anxiety, hypertension, palpitations, insomnia, tremor, numbness, muscle spasms, headache, abortion, et al. (Ashihara and Crozier 2001, Patay et al. 2017). It may also cause bone related problem such as osteoporosis and iron deficiency anemia (Chen and Whitford 1999, Massey 2001).

Trigonelline, synthesized from nicotinic acid, is another alkaloid that present abundantly in coffee beans and leaves. In plant, the functions of trigonelline including nutrient source, compatible solute, nyctinasty substance, cell cycle regulator, signal transductor, were summarized by Ashihara et al. (2015). In coffee bean, trigonelline together with sucrose are aroma precursors that produce furans, pyrazine, alkyl-pyridines and pyrroles in the Maillard reaction and Strecker's degradation during roasting, thus attribute to the pleasant flavor and aroma of coffee. The higher concentration of trigonelline (1.2% vs 1.0%) and sucrose (9.3% vs 5.5%) in *C. arabica* vs C. *canephora* explains the better flavor of the former coffee (Ky et al. 2001). The biological activities of trigonelline include neuroprotective, anti-apoptotic, anti-cancer, anti-bacterial, anti-invasive, anti-cariogenic, hypoglycemic, estrogenic activities (Ashihara et al. 2015). The neuroprotective and anti-apoptotic effects of trigonelline in 6-hydroxydopamine induced Parkinson's rat model are due to restoring substantia nigra par compacta neurons and inhibiting malondialdehyde level and rotations (Mirzaie et al. 2016). Trigonelline is also a source of vitamin B3 since it is demethylated to nicotinic acid during roasting

(Ashihara et al. 2015). Trigonelline content in coffee leaves depends on the age and processing methods. Stages I and II young coffee leaves contain 27–28 μmol/g fresh weight trigonelline which is decreased during aging (Zheng, Nagai, and Ashihara 2004). Our previous study found that *C. arabica* leaves contain 3.9–6.8 mg/g trigonelline and both age and processing method influence its content (Chen, Ma, and Kitts 2018). Oolong-tea-process young coffee leaves have lower trigonelline compared with mature leaves, whereas, the results vice versa for the other tea processing method processed coffee leaves (Fujimori and Ashihara 1994).

Theobromine contents in the freshly emerged and young expanded *C. arabica* leaves were 36.8 and 42.6 μmol/g wet mass basis (wmb), respectively, whereas, theophylline was not detected in those leaves (Fujimori and Ashihara 1994). Souard et al. (2018) found similar results, which is partially due to the extremely slow catabolism of caffeine to theophylline (Ashihara and Crozier 1999).

Phenolic compounds

Phenolic compounds are abundant secondary antioxidative metabolites that are synthesized in plant cells to form a defense system to meliorate cellular oxidative stress that is caused by abiotic or biotic stress from environment (Campa and Petitvallet 2017). Except for the protective effects of phenolic compounds to the plants, phenolics have various health benefits to human. TPC in *C. arabica var. Purpurascens* and *C. arabica* L cv. Obatã IAC 1669-20 were equivalent to 372 mg 5-CQA/g leaves (Domingues et al. 2012) and 118–205 mg tannic acid/g leaves (Salgado et al. 2008), respectively. TPC in different developing stage leaves of *C. arabica* that are processed by 5 tea processing methods equivalented to 13.4–59.1 mg gallic acid/g leaves (Chen, Ma, and Kitts 2018). The diverse TPC is due to the different standard, coffee leaf variety, and extraction method used. Phenolics in leaves decreased during grain expansion and formation stages, whereas, they remained constant in leaves of developing coffee trees (Salgado et al. 2008). Different phenolic compounds including phenolic acids, flavonoids, and xanthones et al. are found in coffee leaves. Coffee leaves' processing method also influences TPC. Fermented coffee leaves have lower phenolics compared with non-fermented leaves (Ratanamarno and Surbkar 2017, Chen, Ma, and Kitts 2018).

Phenolic acids

Phenolic acids that were detected in coffee leaves include benzoic, 3-OH-benzoic, caffeic, p-coumaric, ferulic, sinapic, protocatechuic, and chlorogenic acids (CGAs) (Martins et al. 2014, Patay, Bencsik, and Papp 2016, Patay et al. 2016). CGAs include two main subgroups, caffeoylquinic acids (CQAs) and feruloylquinic acids (FQAs), which are esters of hydroxycinnamic acid or ferulic acid with quinic acid, respectively. CQAs, including 3-CQA, 4-CQA, 5-CQA, 3,4-diCQA, 3,5-diCQA, 4,5-diCQA, are a group of most accumulated phenolic compounds in coffee leaves with 5-CQA accounting for 80-94% of CQAs in most of *Coffea* species (Chen, Ma, and Kitts 2018), except for *C. augagneuri* Dubard, in which 4-CQA is predominant (Campa et al. 2012). The histochemical analysis found that CQAs first appear in chloroplasts in juvenile leaves, then accumulate in the specific chlorenchymatous bundle sheath cells, last exist in phloem sclerenchyma cells during ageing (Mondolot et al. 2006). The location of CQAs in chloroplasts suggests that CQAs function as protectors for light damage.

CGAs contribute to the bitter flavor of coffee due to their degradation into phenol derivatives during roasting. CQAs accumulated more in leaves of *C. arabica* compared with *C. canephora* (3.9 and 2.4% of dry leaf, respectively), however, in the case of coffee bean, the results vice versa (Campa et al. 2012). CGAs contents in *C. arabica* and *C. canephora* beans are 4.1 and 11.3%, respectively (Ky et al. 2001). Therefore, consumers favor *C. arabica* coffee beans since they are less bitter. CQAs are predominant in commercial coffee plants, whereas, in the wild type *C. pseudozanguebariae*, FQAs exist more abundantly. CQAs contents range from 0.66 to 0.99% dry matter basis (dmb), while FQAs contents are 2.08–12.5% dmb in *C. pseudozanguebariae leaves* with developing stages from 3 to 1 (Bertrand et al. 2003). Patay et al. (2016) also found that leaf of *C. arabica* contains greater amount of chlorogenic, ferulic, p-coumaric and sinapic acids compared with *C. benghalensis*. In the leaves of coffee plants from Africa and Madagascan, CQAs varied from 0.85 to 3.96% dmb in mature leaves and they are accumulated more abundantly in African species than in Madagascan species (Campa et al. 2012). This phenomenon can be explained by the monophyletic lineage and low DNA sequence diversity of Madagascan species within *Coffea* (Anthony et al. 2010).

CGAs content decrease as leaves grow older (Campa et al. 2012; Mondolot et al. 2006; Campa et al. 2017) and undergoing the fermentation process (Chen, Ma, and Kitts 2018). Our previous study showed that boiled coffee leaves contained greater CQAs compared with leaves processed by pan fired and oxidation significantly decreased CGAs (Chen, Ma, and Kitts 2018). The impact of sun light intensity on the CQAs varied according to their chemical structures.

Flavonoids

Different groups of flavonoids including catechins (catechin, epicatechin (EC), epigallocatechin gallate (EGCG), epicatechin gallate (ECG)); anthocynin (delphinidin 3,5-diglucoside and delphinidin 3-(6″-malonyl-glucoside)); myricetin, fisetin, patuletin, luteolin, apigenin, quercetin and its glycosides (quercitrin, isoquercitrin, hyperoside, rutin, quercetin-3-Glc-Hex-DeHex, quercetin-3-Glu), kaempferol and its glycosides (kaempferol-3-Glc-Hex-DeHex, kaempferol-3-Glc-Hex, kaempferol-3-Glc-6″-Rha, kaempferol-3-Glc) are found in coffee leaves (Martins et al. 2014; Patay et al. 2016; Ratanamarno and Surbkar 2017; Domingues et al. 2012).

Catechins belong to the subgroup of flavanols and the reports of catechins in coffee leaves are scant. Ratanamarno and Surbkar (2017) found that the amount of EGCG, ECG, EC, and catechin in fresh *C. arabica* coffee leaves

followed a descending order: 5.5–16.4 mg/g; 0.26–0.48 mg/g, 0.27–0.40 mg/g, 0.05–0.18 mg/g, respectively, however, we could not detect catechins in our coffee leaf samples. Except for catechin, dry young coffee leaves contain greater amount of EGCG, ECG, and EC than that of mature leaves, which is different from the result of fresh coffee leaves. This is possible due to the impacts of processing steps such as rolling and fermentation. Fermentation process significantly decreased catechins' contents in young coffee leaves, however, its impact on mature leaves is different in the case of ECG. This result indicated that processing method affected phytochemicals differently based on the nature of phytochemicals and the age of leaves, which was also confirmed by our previous study (Chen, Ma, and Kitts 2018).

Anthocyanins are another flavonoid subgroup that are rarely reported in coffee leaves. Delphinidin 3,5-diglucoside and delphinidin 3-(6"-malonyl-glucoside) were identified in the young leaves of *C. arabica* var. Purpurascens but not in the mature leaves. Anthocyanins are mainly located along the adaxial epidermis and partly in the mesophyll. In other plant, anthocyanins can change photosynthesis, but they did not have such impact in *C. arabica* var. Purpurascens although they influenced the light quality and the optical properties of the leaves. It was suggested that anthocyanins prevented the decrease of CQAs in the young leaves due to their protective effects against UV-B light (Domingues et al. 2012).

Xanthones

Mangiferin is one kind of xanthones that was first identified in *Coffea pseudozanguebariae* leaves by Talamond et al. (2008). The amount of mangiferin in coffee leaves varied in different coffee species and its content is much greater than its isomer isomangiferin. Campa et al. (2012) found that *C. sessilifl ora* and *C. salvatrix* contain 0.026 and 16.3% (dmb) of mangiferin in coffee leaves, respectively, and its content decreased with ageing. Mangiferin content was also affected by the species grown in different geography regions. For example, all of the nine coffee species from Madagascar and Africa do not contain mangiferin (Campa et al. 2012). This is partially due to the response of these low altitude species and clades to the environmental condition. *C. arabica* leaves grown in Brazil and Costa Rica contain 0.067 to 0.497% (dmb) mangiferin (Trevisan et al. 2016), however, it was not detectable in the leaves of *C. canephora* (Campa et al. 2012). Our previous study found that mangiferin content in *C. arabica* coffee leaves varied from 0.04 to 0.78% based on the processing method and age of the leaves (Chen, Ma, and Kitts 2018). Mangiferin content also influenced by the light intensity for that its content is higher in the leaves grown under the full-sun than in the shaded conditions (Martins et al. 2014).

In coffee plant, mangiferin is considered to involve in the stress response. The histochemical results showed that mangiferin localize in the palisade, spongy parenchyma and cuticle of coffee leaves and the exocarp and the external layers of mesocarp of young fruits, but disappeared from the seeds and endocarp, all of which hypothesized that mangiferin is involved in preventing *Coffea* plant from UV-radiation (Campa et al. 2012, Conejero et al. 2014). The bioactivities of mangiferin including anti-allergic, anti-bacterial, anti-viral, anti-inflammatory, antioxidant, anti-obesity, anti-hyperuricemia, anti-nociceptive, anti-diabetic, anti-hyperlipidemic, anti-cancer, anti-rheumatoid arthritis, cardioprotective, hepatoprotective, and neuroprotective activities have been reviewed in several papers (Telang et al. 2013; Luczkiewicz et al. 2014; Imran et al. 2017; Jyotshna, Khare, and Shanker 2016; Rajendran et al. 2015). The high antioxidant activities of mangiferin are due to formation of stable phenoxyl radicals through donation of phenolic hydrogen atoms from four of them in mangiferin structure (Mendoza-Sarmiento et al. 2016).

Terpenes

Diterpenes including cafestol, kahweol, and 16-O-methylcafestol generally found in the lipid fraction of coffee bean, are also detected in the coffee leaves (Kölling-Speer and Speer 1997). Ivamoto et al. (2017) detected cafestol and kahweol in *C. arabica* roots, flower buds, and fruits, however neither of them was detected in coffee leaves. More recently, Souard et al. (2018) used LC-HRMS based metabolomics fingerprint to find ent-kaurane diterpenoid in coffee leaves. Waller et al. (1991) identified ursolic acid, a pentacyclic triterpenoid, in the *C. arabica* leaves. The impacts of diterpenes on human health are being debated. Cafestol and kahweol are found to have anti-inflammatory, anticarcinogenic, and antioxidant properties (Chu et al. 2011), however, high cafestol coffee can also cause the increase of cholesterol levels in the blood plasma (Naidoo et al. 2011). Therefore, attention should be paid to this group of chemicals when choose specific species and cultivar of coffee plant to make coffee leaf tea as beverage that will be consumed daily.

Pigments

α/β-Carotenes and xanthophylls including neoxanthin, lutein, violaxanthin, antheraxanthin and zeaxanthin were found in mature leaves of *C. arabica*. Low nitrogen supplement decreases chlorophylls and total carotenoids, therefore, nitrogen fertilization can prevent coffee plant from photodamage (Pompelli et al. 2010). The pigments in coffee leaves were found to have photoprotective and antioxidative functions. The reactive oxygen species (ROS) produced by the excessive excitation energy obtained from photosynthesis can cause the oxidation of pigments and proteins that involved in the photosynthesis. Plants use the strategy of lowering chlorophyll contents to avoid absorption of sun light, thus prevent oxidative stress (Adams et al. 2004). The increase of xanthophylls (antheraxanthin and zeaxanthin) at high light dissipating the heat of the absorbed light also contributes to the protective effects (Pompelli et al. 2010). Moreover, carotenoids are also antioxidants that can quench ROS effectively.

Phytosterols

Sitosterol is alcohol-soluble phytosterols present in coffee leaves. The presence of sitosterol in coffee bean was detected by Nagasampag et al. (1971), however, the report of sitosterol in coffee leaves are scarce. Maurel et al. (1995a, b) found that coffee leaves contain 9.914 g sitosterol per kg leaves and 51% of which is free sitosterol. Due to its structural similarity to cholesterol, it was found to be able to reduce blood cholesterol levels (Rudkowska et al. 2008) and benign prostatic hyperplasia (Kim et al. 2012). Therefore, coffee leave extract was formulated with other active components to produce organometallic complexes that can be used to prevent cardiovascular diseases and diabetes (Maurel et al. 1996, Maurel et al. 1995a, b).

Aroma compounds

Aroma compounds in coffee leaf tea were reported by (Furukawa et al. 1991b) and they are varied based on the processing method. In the non-fermented (mimic green tea processing method) coffee leaves tea, isobutyraldehyde, isovaleraldehyde, valeraldehyde, hexanol, 1-pentene -3-ol, 3-penten-1-ol, cis-2-penten-1-ol, cis-3-hexen-1-ol and geranylacetone were detected. However, in the semi-fermented (mimic oolong tea processing method) coffee leaf tea, ethyl acetate, butanol, 1-pentene-3-ol, amyl alcohol, octanal, 2-methyl-2-heptene-6-one, nonanal, decanal, and L-menthol were detected.

Ethnomedicinal application of coffee leaf

Ethnomedicine plays a very important role in the health care, especially in the developing countries such as Africa, Asia, and Latin America due to its affordability, accessibility, and effectiveness. For example, around 80% of human and 90% of livestock use plant source as traditional medicine for primary health care in Ethiopia (Belayneh and Bussa 2014). *C. arabica* was one of the commercially important medicinal plants in Africa (Van Wyk 2015) and the ethnopharmacological usage of coffee leaves has been summarized by Ross (2005) and Patay, Bencsik, and Papp (2016). They are used to treat anemia, edema, asthenia and rage in Haiti; cure diarrhea, intestinal pain, bleeding caused by abortion in Africa (Neuwinger 2000); control HIV/AIDS (Lamorde et al. 2010) and tuberculosis in Uganda (Tabuti, Kukunda, and Waako 2010); treat and relieve the pain of migraine in Cuba; relieve cough associated with flu and lung ailments in Peru; relieve fever and stimulate prolactin production in Mexico (Ross, 2005); mitigate headache, diarrhea, and nausea through drinking coffee leaf beverage named "hoja" in Ethiopia (Patay, Bencsik, and Papp 2016). In Nicaragua,

Table 2. Applications of coffee leaves.

Application	Characteristics/Function	References
Coffee leaf tea, extract or beverage	Anti-ageing; nourish stomach; clean liver capillaries, lower blood pressure; improve the immunity; GABA enriched coffee leaf tea with anti-hypertensive activity; mixed with green, oolong, or black tea to make novel flavor beverage; high polyphenol extract	(Huang 2014; Shan 2015; Ryu 1991; Steffan, Duffin-Maxwell, and Bradbury 2006; Matsuo and Mito 1991; Ito 1993; Kamiya 2016; Hirose, Yoshimura, and Yamamoto 2011; Iwai and Nakabayashi 2000; Zhang et al. 2016; Zhang et al. 2014; Takagaki and Tsuzaki 2000; Toshimitsu Hattori and Takagaki 1999; Inoue 1994; Furukawa et al. 1991a, b; Kim 2014; Furukawa 1992a; Tanaka 1992; Hizaki, Tanaka, and Yamauchi 1992)
Genome DNA extract	Used for coffee leaf molecular biology research such as gene cloning, hybridization, and gene library construction.	(Li et al. 2015)
Therapeutic agents	Promote hepatocytes proliferation or prevent disease-induced nerve growth factor; enhance alertness, attention, concentration and memory of a person; treat or prevent hypercholesterolaemia, hypertriglyceridaemia, and diabetes; deliver drugs; inhibit helicobacter pylori and gastrointestinal inflammation including gastritis, and gastric and duodenal ulcer; selectively inhibit harmful bacteria without influencing beneficial bacteria; treat asthma; improve blood flow, prevent and/or treat cerebral and myocardial infarction; inhibit pancreatic lipase; external dermatological product to treat various skin diseases	(Sagawa et al. 2000; Rio et al. 2016; Maurel 2004; Maurel et al. 1996; Maurel 1995a b; Inami et al. 2002; Murata and Yasuda 1997; Nakagawa, Ono, and Yamamoto 2003; Wang 2017a)
Lactobacillus/bifidobacteria proliferating agent	Stimulate lactobacterial and bifidobacterial proliferation and resistant to contamination	(Furukawa et al. 1992b; Hizaki and Yamauchi 1992)
Packaging material	Plant based wrapping paper with specific flavor	(Ragot et al. 2014)
Absorbent pad	Odor reducing absorbent pad with anti-bacterial, anti-allergic and anti-inflammatory activities	(Kim et al. 2015)
Deodoriser	Remove ammonia odor of hospital bed	(Ucc Ueshima Kohi 1997)
Vehicle perfume	Prevent sleepy	(Wang 2017b)
Facial cleanser	Coagulate dead skin cells' protein and shrink skin pores	(Madya and Sutriyo 2015)
Tobacco substitute	Contain no detectable amount of nicotine or nicotine related compounds; coffee flavor cigarette with the potential to alleviate fatigue and refresh sedative	(Teruel 2006; Xu 2003)
Organic fungicide and bactericide	Control fungal disease in plants; control pathogen	(Berquist 2000; Sudantha 2011)
Animal feed	Promote growth and development of broilers	(Ye 2014)

coffee leaves are applied on the forehead to treat headache and the drink is also used to treat stomach pains (Barrett 1994).

Industrial applications and bioactivities of coffee leaf

Although there are scarce research articles study the bioactivities of coffee leaves, around 50 patents are found to relate to the industrial application of coffee leaves (Table 2, supplement Table 1 and Figure 2). We search google patent, web of science and PubMed databases with the keyword "coffee leaf" or "coffee leaves" and 1,464 patents were found. After screening, 45 patents are related to the application of coffee leaves in the area of therapeutic agents, animal feed, coffee leaf tea or beverage, tea extract, Genome DNA extract, packaging material, absorbent pad, Lactobacillus proliferating agent, tobacco substitute, organic fungicide, facial cleanser, vehicle perfume, and deodoriser. Coffee leaf tea or beverage and tea extract that has enrich GABA or polyphenol are the most popular applications of coffee leaves followed by using as therapeutic agents to treat or prevent various diseases or disorders. Japan and China are two of countries own most coffee leaves related patents.

Coffee leaf tea or beverage or tea extract

Making coffee leaves into tea is the most popular application of coffee leaves. The report of coffee leaf tea can be dated back to 1873 in New York times and a patent about the preparation of coffee leaf tea was issued to Dr. Gardner of Ceylon in 1850s (Campa and Petitvallet 2017). Coffee leaf tea is traditionally consumed in coffee plant growing countries such as Indonesia, India, Jamaica, Java, Sumatra, Ethiopia. For example, a tea prepared from *C. arabica* or *C. canephora* leaves is called "copi daon" in Indonesia, "giser" in Yemen, "kuti, jeno, or jenuai" in Ethiopia (Patay,

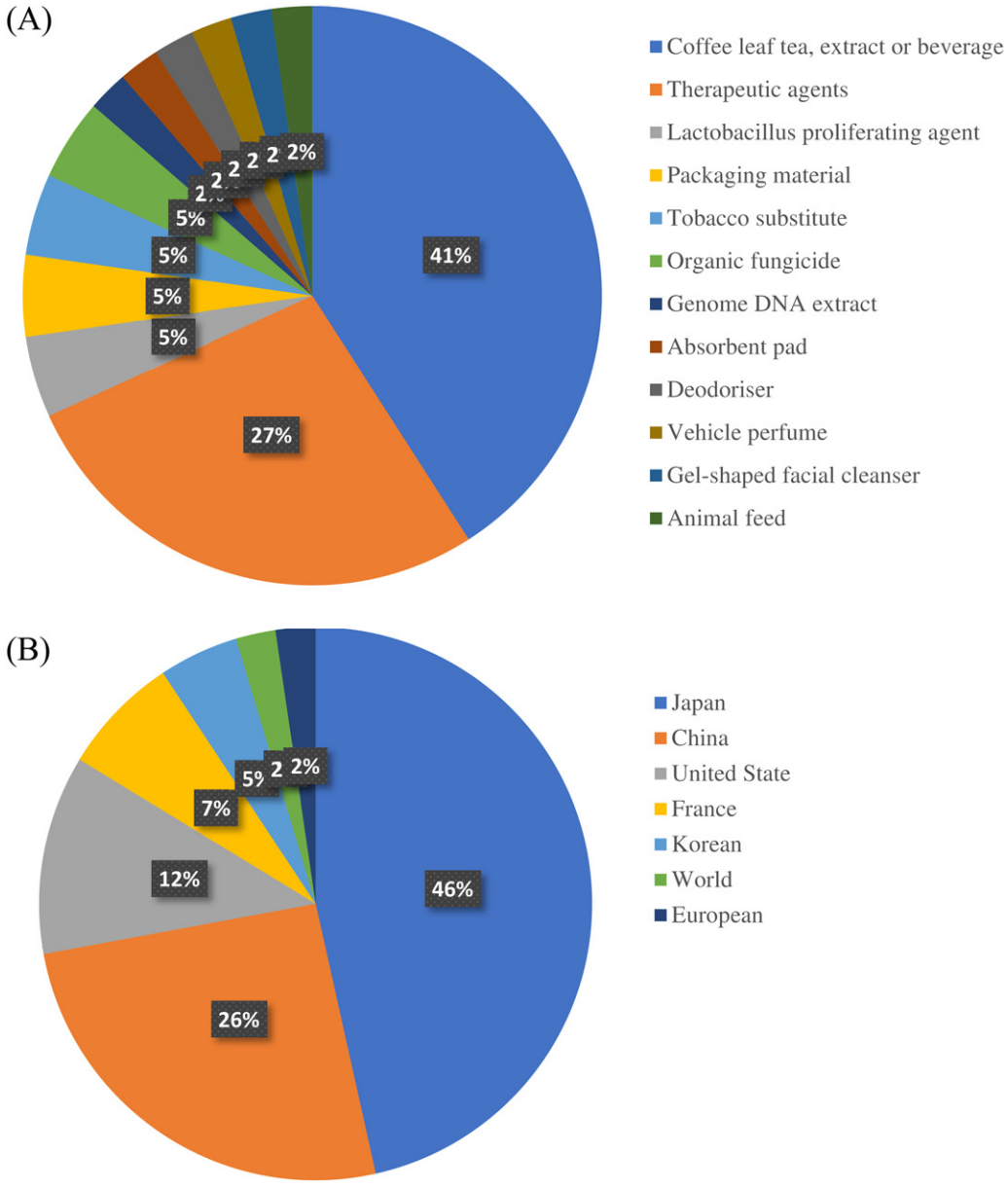

Figure 2. Patents related to coffee leaves. (A) Percentage distribution of patents in terms of application; (B) Percentage distribution of patents in terms of countries.

Bencsik, and Papp 2016). Attempt was made to market coffee leaf tea in UK during 1800s, however, it was not succeeded due to lack of consumer acceptance (Davis et al. 2006). Coffee leaf tea has been successfully commercialized by a Canadian company since 2014 and it was gradually accepted by consumers, especially in North American. Similar to the more popularity of coffee made from *C. arabica* compared with *C. canephora*, most of coffee leaf teas are made from *C. arabica* as well. Weather it is due to the same reason as the quality and flavor of coffee beans between these two species, or the presence of mangiferin in *C. aribica* influencing its flavor and beneficial effects need further discovery.

The production methods for the coffee leaf tea varied by different inventors. For example, Shan (2015) prepared coffee leaf tea with anti-ageing activities through treating coffee leaves with inert gas, steaming, rolling, and drying. Similar method was used to make granular coffee leaf tea under normal air condition (Zhang et al. 2014). A fermented coffee leaf tea that was claimed for nourishing stomach was prepared by fermenting coffee leaf with Pu'er tea bag (Zhang et al. 2016). Other inventors produce tea like beverage by mixing coffee leaves with other plant sources. For example, a burnt wolfberry leaf tea was made by mixing wolfberry leaves, coffee leaves, custard apple tree leaves, dried tangerine peel, rice vinegar, meldar juice, et al. It was claim to be able to clean liver capillaries, lower blood pressure and improve the immunity (Huang 2014).

High GABA coffee leaf tea was prepared under anaerobic condition by addition of N_2 or CO_2 gas (Inoue 1994; Takagaki and Tsuzaki 2000; Toshimitsu Hattori and Takagaki 1999) and the products have anti-hypertensive activity. Inert gas can also prevent oxidation of phenolic compounds (Ito 1993). Another method that was used to prepare coffee leaf tea as health beverage included steaming, drying and roasting coffee leaves until reaching L-value between 20 and 35. This processing method can prevent the loss of chlorogenic acid (Iwai and Nakabayashi 2000). Coffee leaf tea was also prepared under reducing atmosphere followed by roasted in 250-500 °C overheat steam (Hirose, Yoshimura, and Yamamoto 2011). Coffee leaves were extracted by water to make beverage (Kamiya 2016) or extracted by aqueous solvents in addition of sugars, salts, alcohol, emulsifier, stabilizer, flavoring and coloring agents, and acids such as citric acid, ascorbic acid, or acidic acid until pH 4-5 to reduce turbidity. Mixing coffee leaf tea with green and black tea in the tea bag produced a tea beverage with new taste (Ryu 1991). A combination of sunlight and hot air drying was used to process young coffee leaves to have unique taste and flavor due to the presence of isobutylaldehyde, isovaleraldehyde, valeraldehyde, hexanol, 1-penten-3-ol, 3-penten-1-ol, cis-2- penten-1-ol, cis-3-hexen-1-ol and geranylacetone (Takagaki and Tsuzaki 2000). Polyphenols enriched coffee leaf extract was also prepared by extracting with a mixture of water and organic solvents such as ethanol and acetone (Steffan et al. 2006).

Except for extracting phenolic bioactive components from coffee leaves, a high-quality genome DNA extraction method was developed by Li et al. (2015) who effectively remove polysaccharides, terpenes, phenolics, and pigments to produce pure genomic DNA for coffee leaf molecular biology research such as gene cloning, hybridization, and gene library construction.

It is plausible that processing method affects the flavor, taste, color, and consumer acceptance of the coffee leaf tea since it influences the chemical composition, thus changes the organoleptic properties of coffee leaf tea. Our previous study had shown that coffee leaves processed by different tea processing methods (white, green, oolong, and black tea) have distinct phytochemical profiles. However, how these chemical changes link to the sensory attributes of the coffee leaf tea needs further investigation. It is known that during the preparation of "*kuti*" in Ethiopia, grounding the fresh coffee leaves to small size using mortar and pestle before drying is a key step to make the acceptable coffee leaf tea (Woldesenebet 2005). The well ground coffee leaf tea has preferable red color, appropriate thickness and mouth feel, whereas, the not well ground or simply cut counterparts result in the thin and watery tea with grassy taste and unacceptable color. This is possible because that oxidation happens during the grounding process which changes the chemical compositions of coffee leaf tea. In addition, grinding causes the chemical constituents infusing into the boiling water easily due to the small size and the disrupted cell structure. However, to my knowledge, there are no papers reported the mechanisms underlining the association of chemical changes with the organoleptic properties and the sensory attributes of coffee leaf tea.

Therapeutic agents

Plant extract including coffee leaf has been used to produce growth factor production enhancing composition which can be used to make therapeutic agents to prevent or treat diseases or used in food, beverage or feed for enhancing good health. This enhancing composition was found to promote hepatocytes proliferation or prevent disease-induced nerve growth factor (Sagawa et al. 2000). Composition containing mangiferin enrich coffee leaf extract was used to enhance brain activities including alertness, attention, concentration and memory (Rio et al. 2016). Coffee leaves contain high level of free sitosterol, therefore, their extract combining with diglyceride and metal can be used as pharmaceutical products to treat or prevent hypercholesterolaemia, hypertriglyceridaemia, and diabetes (Maurel et al. 1996, Maurel 1995a, b). Reverse micelles comprising phytosterols and acylglycerols were produced to deliver drugs (Maurel 2004). An anti-helicobacter pylori agent containing pepermint oil, spearmint oil, and natural material extracts such as Alpiniae Katsumadai Semer, coffee leaves, saffron, et al. can inhibit gastrointestinal inflammation including gastritis, and gastric and duodenal ulcer (Murata and Yasuda 1997). Furukawa et al. (1991a) used coffee leaves extract to formulate an antibacterial agent that selectively inhibits harmful bacteria with no adverse impact on beneficial bacteria. Aqueous extract of dried Solanum auriculatum leaves and dried *C. canephora* leaves was used to treat asthma (Fidele 1990). Coffee leaf

extract containing GABA improves blood flow, thus can be used to prevent or treat cerebral and myocardial infarction (Inami et al. 2002). Since coffee leaves contain caffeic acid, their extract together with extracts containing 3,4-dihydroxyphenyl carboxylic acid, gallic acid, or their salts were used to make lipase inhibitor which inhibits pancreatic or bacterial lipases thus prevents obesity, acne, and dermatitis (Nakagawa, Ono, and Yamamoto 2003). An external dermatological product containing coffee leaf extract was made to treat various skin diseases including red and swollen skins, erosion, psoriasis, whelks, acnes, et al. (Wang 2017a).

Lactobacillus/bifidobacteria proliferating agent

Coffee leaf extract was used to make lactic acid bacteria proliferating agent which is free of unpleasant odor and promote the proliferation of lactobacillus and bifidobacteria (Furukawa et al. 1992b).Enteric-coated lactobacillus granule containing lactobacillus, coffee leaves or extract, fatty oil, vehicle, and aqueous alcohol-soluble protein is an excellent lactobacterial proliferation agent due to its insoluble in mouth and stomach but soluble in intestine (Hizaki and Yamauchi 1992).

Packaging material, deodoriser, and absorbent pad

A coffee leaf-based wrapping paper was prepared to wrap foods which contains specific and improved flavor (Ragot et al. 2014). Coffee leave or tea waste can also be made as deodoriser to remove ammonia odor of hospital bed (Ucc Ueshima Kohi 1997). Absorbent pad containing coffee leaves can reduce the odor and have anti-bacterial, anti-allergic and anti-inflammatory activities (Kim et al. 2015).

Vehicle perfume and facial cleanser

The aqueous extract of coffee leaves and Laggera pterodonta was mixed with floral extract, citric acid, folic acid, sodium chloride, ethanol, and other ingredients to make a vehicle perfume which is used to prevent sleepy (Wang 2017b). A gel-shaped product containing coffee leaf powder was make to coagulate dead skin cells' protein and shrink skin pores. This product can be used to make facial cleanser (Madya and Sutriyo 2015).

Tobacco substitute

Compared to tobacco leaves, coffee leaves contain no detectable amount of nicotine or nicotine related compounds, therefore, it is a good candidate of tobacco substitute. Coffee leaf was used to make smoking products such as cigarettes, cigars and pipe material, chewable tobacco-like products which are useful for reducing or quitting tobacco products (Teruel 2006). Cigarette with coffee flavor containing 40–60% coffee leaves has the potential to ameliorate fatigue and refresh sedative (Xu 2003).

Organic fungicide and bactericide

A biofungicide tablet formulated with coffee leaves, clay, and fungus isolates was used to control pathogens (Sudantha 2011). Berquist (2000) also produced a fungicidal solution comprising of organic solution that was made from tea leaves, coffee leaves, et al. and fermented solution containing alcohol and grape juice to control fungal disease in plants. Coffee-leaf aqueous extract was found to prevent *Xanthomonas vesicatoria* caused tomato leaves' bacterial spot through transcriptionally upregulating defense-related genes encoding chitinases, glucanases and peroxidases and the activity of corresponding enzymes, which were reported to have the potential against pathogens (Medeiros et al. 2009). Its bactericidal effects were equivalent to a commercial fungicide, acibenzolar-S-methyl (Bion®). The aqueous extract of coffee leaf infected by *Hemileia vastatrix* was also resistant to *Phoma costarricensis* (Barguil et al. 2005). However, there were no information about what phytochemicals in coffee leaves contribute to the fungicidal and bactericidal effects. Although caffeic and chlorogenic acids are reported to have pestistatic or pesticidal activity, Magalhaes et al. (2010) showed that caffeine, 7-methylxanthine, xanthine, theobromine are not corelated with the resistance of coffee leaves to *Leucoptera. coffeella*.

Animal feed

Coffee leaves were used as ingredients of animal feed which can promote growth and development of broilers, increase the weight of the broilers, shorten the growth cycle and reduce the diseases and the death rate, through regulating the metabolism of body cells and increasing appetite, digestive absorption capacity, and feed intake (Ye 2014).

Structure-function relationships of major phytochemicals (chlorogenic acids) in coffee leaves

Chlorogenic acids are a group of most abundant phytochemicals that have known beneficial effects. The different structures of CQA and di-CQA isomers contribute to their varied bioactivities. CQAs are phenolic acids formed by esterification of quinic acid and caffeic acid. Mono-CQAs (3-CQA, 4-CQA, and 5-CQA) contain only one molecule of caffeic acid, whereas, di-CQAs contain two molecules of caffeic acids, which cause the greater antioxidant and anti-inflammatory activities of di-CQAs compared with mono-CQAs (Chen, Mu, and Kitts 2019, Iwai et al. 2004). The superoxide scavenging activity of CGAs showed a descending order as followed: di-CQA > caffeic acid > mono-CQAs >5-FQA (Iwai et al. 2004). The fact that the reducing power, ferrous ion chelating ability, and DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) scavenging capacity of 4,5-di-CQA were greater than 3,4-di-CQA and 3,5-di-CQA was due to the position of caffeic acid on the quinic moiety (Xu, Hu and Liu 2012). The closer location of two caffeic acid moieties may cause a steric hindrance effects, thus enhance the chemical bonding energy, reduce stability and increase activity (Xu, Hu and Liu 2012).

Impact of processing method on the bioactivity of coffee leaf

The literature about the processing method on the bioactivity of coffee leaves are rare. Our previous study showed that coffee leaves processed by white, green, oolong, and black tea processing methods have distinct phytochemical composition and antioxidant and anti-inflammatory activities. The processes that use boiling water to kill green and without fermentation produced coffee leaf with greatest ABTS, DPPH, AAPH (2,2′-azobis(2-amidinopropane) dihydrochloride) free radical scavenging capacity and anti-inflammatory activities through inhibiting IL-1α (interlukin-1 alpha), IL-6. GM-CSF (granulocyte macrophage colony-stimulating factor), nitric oxide (NO), and iNOS (inducible nitric oxide synthase) in IFN-γ and LPS induced Raw 264.7 cells. Whereas, mature coffee leaves underwent 48h fermentation produced products that has lowest of antioxidant and anti-inflammatory activities. More interestingly, this type of coffee leaf tea (BTP-M) induced NO, iNOS, COX-2 (cyclooxygenase 2), pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, GM-CSF, G-CSF (granulocyte-colony stimulating factor), and TNF-α (tumor necrosis factor-alpha), as well as anti-inflammatory cytokine, IL-10 under basal condition (Chen, Ma, and Kitts 2018). We further elucidated that the known bioactive components including caffeine, chlorogenic acids, mangiferin, and rutin are not the major components that attribute to the anti-inflammatory activities of coffee leaves and the high polarity compounds contribute to the pro-inflammatory effects (Chen, Mu, and Kitts 2019).

Conclusion and future prospects

Due to the existence of abundant bioactive phytochemicals in coffee leaves, increasing interests have been paid to research and consume coffee leaves as a health beverage by scientists and public, respectively. Except for consumption as a tea like beverage, coffee leaves have a long history to be used as ethnomedicines and more recently as therapeutic agents to ameliorate diseases and disorders. However, the mechanisms underline the health benefits of coffee leaves and the structure-relationships between the phytochemicals and their bioactivities, and how the processing methods affect the bioactivities need further research. More novel applications of coffee leaves including vehicle perfume, facial cleanser, tobacco substitute, animal feed, lactobacillus proliferating agent, absorbance pad, deodoriser, organic fungicide indicate that coffee leaves not only can be used in pharmaceuticals and beverage, but also in various industrial areas.

In order to prepare high quality and consumer preference coffee leaf tea, researchers need to discover the impacts of different species and cultivars, environmental conditions, age of plant, leaf developing stages, harvest seasons et al. on the aroma, flavor, and other organoleptic characteristics of coffee leaf tea. Elucidation of chemical changes behind each step of coffee leaf tea processing, such as kill-green, rolling, fermentation, and drying processes is another key point to produce high quality coffee leaf tea. Understanding the relationship between the chemical and bioactivity changes during coffee leaf tea processing is crucial for producing coffee leaf product with best health benefits. Producing GABA enrich coffee leaf tea to mitigate hypertension is a promising application of coffee leaves. Therefore, further researches need to focus on how different processing methods including anaerobic condition, reduced pressure, spraying glutamic acid before or after harvesting, socking fresh leaves in the glutamate solution, adjusting pH, fermentation with Lactobacillus, and microwave, infrared, ultrasound, and other physical treatment affect the production of GABA and the activities of important enzymes (glutamate decarboxylase, GABA transaminase, diamine oxidase and polyamine oxidase) involved in the conversion and metabolisms of GABA in coffee leaves. Due to the much higher mineral content in coffee leaf, it is a very good source for mineral supplement as well.

In conclusion, coffee leaf is a valuable resource to produce value added coffee leaf tea, food, medicine, therapeutic agents, personal hygiene products and other industrial products. Thus, coffee leaf R&D will also help increase the income of coffee plant growing countries which mainly locate in developing countries from Africa, central and South American, and South Asia.

Abbreviation

AAPH	2,2′-azobis(2-amidinopropane) dihydrochloride
ABTS	2,2-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid
CGAs	chlorogenic acids
3-CQA	3-caffeoylquinic acid
4-CQA	3-caffeoylquinic acid
5-CQA	5-caffeoylquinic acid
3,4-diCQA	3,4-dicaffeoylquinic acid
3,5-diCQA	3,5-dicaffeoylquinic acid
4,5-diCQA	4,5-dicaffeoylquinic acid
COX-2	cyclooxygenase 2
DeHex	deoxyhexosese
DPPH	2,2-diphenyl-1-picrylhydrazyl
EC	epicatechin
ECG	epicatechin gallate
EGCG	epigallocatechin gallate
FQAs	feruloylquinic acids
GABA	γ-aminobutyric acid
Gal	galactose
G-CSF	granulocyte-colony stimulating factor
Glc	glucose
Glu	glucuronide
Hex	hexose
GM-CSF	granulocyte macrophage colony-stimulating factor
IFN-γ	interferon γ
IL-1α	interleukin 1 alpha
iNOS	inducible nitric oxide synthase
LPS	lipopolysaccharide
MAPK	Mitogen-activated protein kinases
NF-κB	nuclear factor kappa B
NO	nitric oxide
Rha	rhammose
TFA	trifluoroacetic acid
TNF-α	tumor necrosis factor-alpha
TPC	total phenolic content

Disclosure statement

The author has no conflicts of interest to declare.

Funding

This paper was supported by Jiangsu University senior talent startup fund (No.4111360002) to Xiumin Chen.

ORCID

Xiumin Chen http://orcid.org/0000-0003-2622-1824

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