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"El saber de mis hijos hará mi grandeza"

Significance of bioactive compounds, therapeutic and agronomic potential of non-commercial parts of the *Coffea tree*

Importancia de los compuestos bioactivos, potencial terapéutico y agronómico de las partes no comerciales del árbol del cafeto

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ABSTRACT

Coffee is one of the most popular and demanded drinks throughout the world; its consumption goes from the ceremonial to the casual, therefore, the plantations destined for its production are valuable. Besides, the coffee tree is perennial, which guarantees leaves supply throughout the year. Additionally to flowers, coffee leaves have been little studied and commercialized, although they represent an important source of phytochemicals. In flowers, different volatile compounds have been detected; while in leaves, bioactive compounds such as chlorogenic acid and mangiferin have been reported as major phenolics. Both compounds are recognized with anti-inflammatory, antioxidant, anti-obesity and anti-carcinogenic effects. These phytochemicals are produced by the plant as a defense mechanism against biotic or abiotic stresses such as pathogens or adverse weather conditions. This review describes the non-conventional applications that aerial parts of the coffee tree could have as therapeutic or agronomic agents, in addition to the uses that have traditionally been linked to the *Coffea* plant.

Keywords: coffee leaves, mangiferin, chlorogenic acid, phenolics, diterpenes

RESUMEN

El café es una de las bebidas más populares y demandadas en todo el mundo, su consumo va desde lo ceremonial a lo casual, por lo tanto, las plantaciones destinadas a su producción son valiosas. Además, el cafeto es perenne, lo que garantiza el suministro de hojas durante todo el año. Adicionalmente a las flores, las hojas de café han sido poco estudiadas y comercializadas, aunque representan una fuente importante de fitoquímicos. En flores, se han detectado diferentes compuestos volátiles; mientras que en las hojas, los compuestos bioactivos como el ácido clorogénico y la mangiferina han sido reportados como los principales compuestos fenólicos. Ambos compuestos son reconocidos con efectos anti-inflamatorios, antioxidantes, antiobesogénicos y anticancerígenos. Estos fitoquímicos son producidos por la planta como un mecanismo de defensa contra el estrés biótico o abiótico, como pueden ser los patógenos o condiciones climáticas adversas. Este artículo de revisión describe las aplicaciones no convencionales que podrían tener las partes aéreas del cafeto como agentes terapéuticos o agronómicos, además de los usos que tradicionalmente se han vinculado a la planta de café.

Palabras clave: hojas de cafeto, mangiferina, ácido clorogénico, fenólicos, diterpenos

INTRODUCTION

Coffee is one of the world's most popular beverages that has grown steadily in commercial importance during the last 150 years (Daglia *et al.*, 2000). Coffee occupies the second place after petrol on the international market. Some authors have reported more than 120 species of *Coffea*. However, *Coffea canephora* and *Coffea arabica* are the most cultivated varieties worldwide, and the latter supplies more than 70% of the coffee distributed internationally (Davis *et al.*, 2011; Patay *et al.*, 2016a; 2016b); in these species lays the importance of the cultivation of coffee trees.

Coffea arabica and *Aloe vera* are amongst the most valuable of all natural products on international markets (Van Wyk, 2015). The global coffee industry is worth over US$50 billion, with key players being over 25 million farmers tending over 3 billion coffee trees (Nair, 2010). Most of these farmers are mainly reliant on coffee as a legal source of income for their livelihoods. Global annual coffee consumption exceeds 7 million tons from over 2 billion coffee cups brewed daily, making coffee one of the most traded agricultural export commodities from developing countries in sub-Saharan Africa, Asia, and Central America (Chemura *et al.*, 2017).

Despite the successful story and positive forecasts of the coffee grain agribusiness, very little has been done and published on the value and utilization of coffee tree aerial parts. Coffee flowers and residual leaves from the tree trimmings represent an important source of phytochemicals that has been partially explored. This raw material might be a potential source of bioactive chemical compounds with impact in the same agricultural field or for providing novel human health nutraceuticals (Figure 1).

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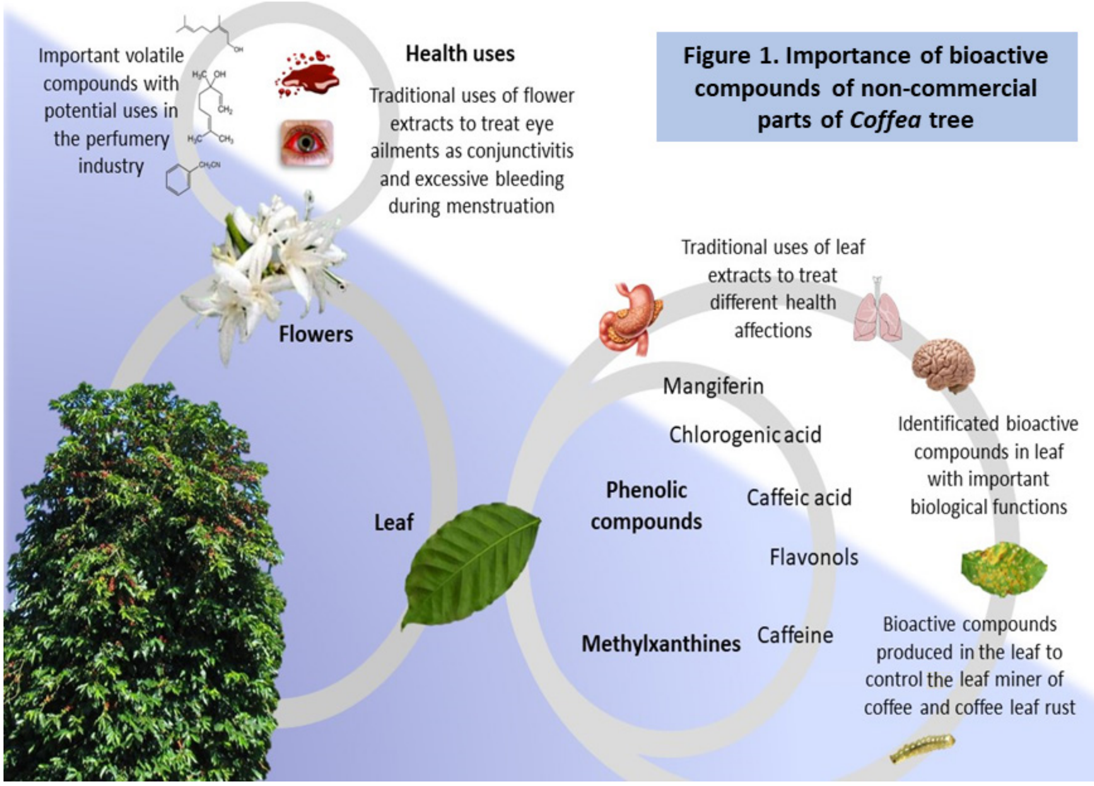

Figure 1. Importance of bioactive compounds of non-commercial pats of *Coffea tree*.
Figura 1. Importancia de los compuestos bioactivos de las partes no comerciales de *Coffea tree*.

METHODOLOGY

An information search was carried out following the key words *Coffea* and coffee leaves, *Coffea* flowers, characterization of *Coffea*, importance of *Coffea*, traditional uses of *Coffea*, chlorogenic acid, mangiferin, therapeutically uses from *Coffea*, in different databases as Scopus, Web of Science and EBSCOhost, and web search engines as Google Scholar. More than 250 significant titles were obtained in the search, which were analyzed and considered for discussion in this publication. The resulting state-of-the-art on the use of aerial parts of the *Coffea* tree is introduced.

Beginning of the uses of *Coffea*

Green coffee beans that are roasted, ground, and brewed to produce the popular beverage known all over the world are actually the seeds contained in fruits from trees and shrubs naturally grown in the shade of the African forests, but also in the Madagascar and Mauritius islands. It is also cultivated in other tropical areas such as equatorial Africa, Java, Sumatra, some islands of the Dutch East Indies, West Indies, India, Arabia, the islands of the Pacific, Mexico, and Central and South America (Ukers 1935; Davis *et al.*, 2007).

Coffea species are generally found in the equatorial region, ranging from 200 to 1200 m in tropical or subtropical zones with temperatures of 18 to 22°C. However, the identified optimum altitude for wild *Coffea* species is between 1300 to 1600 m (Tesfaye *et al.*, 2014).

Coffea flowers

Flowering is the key reproductive phase of *Coffea* plants and from its magnitude depends most of the resulting harvesting (Camayo *et al.*, 2003). Flowers of many plant species emit floral scent to attract, for defense and protection against abiotic stress and herbivores. Such scents are often complex mixtures of various small aliphatic molecules, mostly terpenoid, phenylpropanoid, and benzenoid compounds emitted by flowers into the atmosphere. The relative abundances and interactions between these compounds give the flower its unique, characteristic fragrance. In nature, structure, color, and scent are critical factors in attracting pollinators to flowers (Dudareva & Pichersky, 2006). Knowledge of the chemistry of floral scents is critical in understanding their evolution and biological functions. The study of the chemical composition of the mixtures emitted by flowers is also of commercial importance in the perfumery and flavor industries (Stashenko *et al.*, 2013).

The first investigation of the chemical composition of the flower of *Coffea arabica* was carried out by Emura *et al*. in 1997. The volatile composition was evaluated in hexane extracts of coffee flowers (*Coffea arabica* L.) analyzed by GC-MS and found to comprise a significant number of nitrogen-containing aromatic compounds as well as phenylethane derivatives. In addition to monoterpenoids such as geraniol (16.5% relative peak area, RPA), linalool (14.3% RPA) and nerol (10.5% RPA), N-containing aromatic compounds (e.g., phenyl acetonitrile, 32% RPA) and phenylethane derivatives were found in these extracts analyzed by GC–MS. For example, 2,3-epoxygeraniol and 6,7-epoxygeraniol occurred in low amounts and their optical purity was determined (Emura *et al.*, 1997). More recently, around 150 different chemical substances were isolated by headspace, distillative, solvent and supercritical fluid extractive techniques from *Coffea arabica* flowers (Stashenko *et al.*, 2013). Hydrocarbons (mostly, C_{13}–C_{30} n-paraffins) were the predominant class in all of the sorptive extraction fractions (e.g., HS-SPME, MW-HS-SPME, distillates), followed by terpenoids or oxygenated compounds (depending on the isolation technique).

As part of flower conformation, colleters are secretory structures present in different organs of members in more than 60 angiosperm families, including *Rubiaceae*, *Loganiaceae* and *Apocynaceae*. The colleters in the stipules of *Coffea arabica* are classified as 'standard type'. This type of colleter is formed by a secretory epidermis and the central axis of parenchyma cells, without vascular tissue. The origin of this type of colleter involves the protoderm and the ground meristem, as described for the colleters of *Caryocar brasiliense* Camb. (Lersten, 1974a; 1974b; Thomas & Dave, 1989; de Castro Miguel *et al.*, 2006; Paiva & Machado, 2006).

During development, a viscous exudate of unknown composition covers coffee buds/flowers. The functional role of this secretion has never been proved, but it is argued that it protects the dormant coffee floral bud from dehydration during dry season, as has been suggested for many other plant species. Some investigations found evidence for a functional role of colleters and their exudate in the floration and seed quality (Mayer *et al.*, 2013).

In addition to the volatiles composition in coffee flowers, there are reports of the traditional use of *Coffea* flowers to treat disease conditions. *Coffea benghalensis* flowers are used to treat the excessive bleeding during menstruation in some regions of Nepal (Ghimire & Bastakoti, 2009), and during childbirth, as well as to treat conjunctivitis in West Bengal, India (Bose *et al.*, 2015). *Coffea fragrans* flowers are used to treat eye ailments too in the district of Assam, India (Das and Bordoloi, 2016).

Coffea leaves

Coffea spp. is a perennial plant and evergreen in nature (Murthy & Manonmani, 2008). The coffee tree belongs to the subkingdom of Angiosperms plants, which includes all plants that reproduce by seeds enclosed in a box-like compartment, known as the ovary, at the base of the flower. The *Coffea* genus belongs to the botanical family *Rubiaceae*, which has some 500 genera and over 6000 species. Other members of the family include gardenias. Coffee trees are part of the *Coffea* genus, which is by far the most economically important member of the *Rubiaceae* family (Ukers, 1935).

Originally, coffee may have been a kind of wine made from the coffee fruit. In coffee countries even today, the natives are very fond and eat it freely of the ripe coffee cherries, voiding the seeds. The pulp surrounding the coffee seeds (beans) is pleasant to taste, has a sweetish, aromatic flavor and quickly ferment when allowed to stand (Ukers, 1935). *Coffea arabica* is one of the more frequently reported medicinal plant (Woldeab *et al.*, 2018). However, the use of coffee goes beyond the ultimate use of the grain, and in the present review refers to the use of other parts of the *Coffea* tree, such as leaves and flowers, used for the benefit of human health, in a traditional way and supported by scientific evaluations.

Traditional uses of *Coffea* leaves

Coffea leaves, taken as decoction or infusions, are consumed to treat some affections or health problems as part of the tradition of many people around the world; some common conditions are stomach discomfort, body pain, fever, respiratory problems, etc. (Table 1). However, the acceptability of the drink was not simple, in the 1950's, the distribution of *Coffea arabica* infusions in London markets was not sensorially acceptable by consumers because of its taste (Cramer, 1957). Currently, in the interest and acceptability of functional foods and beverages, these products have become a large market worldwide (Corbo *et al.*, 2014).

Table 1. Traditional uses of *Coffea* leaves around the world.
Tabla 1. Usos tradicionales de las hojas de cafeto en todo el mundo.

<table>
<tr><th>Coffea species</th><th>Use</th><th>Reference</th></tr>
<tr><td>C. arabica</td><td>Topical use of infusion to stop hair loss in Eastern regions of Cuba</td><td>Heredia et al. (2018)</td></tr>
<tr><td>Coffea spp.</td><td>Leaves used in the treatment of TB related diseases or their symptoms</td><td>Sharifi-Rad et al. (2017)</td></tr>
<tr><td>C. liberica</td><td>Tea leaves used as a laxative drug</td><td>Belayneh and Bussa (2014)</td></tr>
<tr><td>C. arabica</td><td>The leaf sap to treat diarrhea and intestinal pain in Africa</td><td>Lamorde et al. (2010)
Belayneh and Bussa (2014)</td></tr>
<tr><td>C. arabica</td><td>Leaves used to manage HIV/AIDS in some districts of Uganda</td><td>Lamorde et al. (2010)</td></tr>
<tr><td>C. arabica</td><td>Leaves both orally or locally to treat migraine in Cuba</td><td rowspan="6">Ross (2007)</td></tr>
<tr><td>C. arabica</td><td>Fresh leaves or infusion onto painful body parts in Cuba</td></tr>
<tr><td>C. arabica</td><td>Decoction coffee leaves for headache and stomach pains in Nicaragua</td></tr>
<tr><td>C. arabica</td><td>Infusion as cough suppressant in Peru</td></tr>
<tr><td>C. arabica</td><td>Infusion to treat fever in Mexico</td></tr>
<tr><td>C. arabica</td><td>Stimulation of prolactin's production in Mexico</td></tr>
<tr><td>C. canephora</td><td>Tea leaves used for bleeding accompanying abortion in Africa</td><td>Neuwinger (2000)</td></tr>
</table>

Phytochemicals compounds reported in *Coffea* leaves

The therapeutic properties reported for *Coffea* leaves are directly related to their phytochemical composition. Some compounds have already been reported in *Coffea* leaves, such as lipids (Delaroza *et al.*, 2014), alkaloids (Zheng and Ashihara, 2004), carbohydrates (Brum *et al.*, 2013; de Lima *et al.*, 2014), some phenolic compounds as caffeic, chlorogenic, p-coumaric, ferulic and sinapic acids, as well as flavonoids including rutin, quercetin, kaempferol and isoquercitrin (Patay *et al.*, 2016c). Dicaffeoylquinic acids, 5-CQA, and feruloylquinic acids have also been detected in the leaves of *C. canephora* (Mondolot *et al.*, 2006) (Figure 2).

Researchers have observed the influence of solar radiation on the composition of leaves (Sanchez *et al.*, 2018), particularly in their phenolic composition, observing cis isomers and higher concentration of chlorogenic acid in leaves exposed directly to the sun with respect to leaves in the shade (Clifford *et al.*, 2008; Delaroza *et al.*, 2014). The presence of compounds such as anthocyanins in *Coffea arabica* var. Purpurascens, prevents degradation of isomers of chlorogenic acid exposed to UV radiation (Domingues Júnior *et al.*, 2012). The hydroxycinnamic acids content in *C. arabica* is higher than in other species such as *Coffea sessilifl* Bridson, *Coffea resinora* Hook. f., *Coffea leroyi* A.P. Davis, and the presence of xanthones as mangiferin has been identified in higher concentration in young leaves (Talamond *et al.*, 2008; Campa *et al.*, 2012). The increase in temperature also affects the leaves carbohydrate composition, observing concentration variations of arabinose, galactose and xylose under heating stress conditions (Lima *et al.*, 2013).

The age of leaves is an important factor for their phytochemical composition (Leitão *et al.*, 2011). Concentrations of caffeine and some phenolics like flavanols (i.e., catechin, epicatechin gallate, catechin gallate and epicatechin) are higher in young leaves respect to mature ones, presenting a caffeine content of 1.8-3.2 mg/g (Ratanamarno & Surbkar, 2017). The mineral composition, specifically the sodium to potassium ratio, also affects the leaves caffeine concentration (Clemente *et al.*, 2015). Total phenolic content is higher in young leaves (174 mg/g) than mature ones (138.9 mg/g). The development of fruits in the plant represents another factor of variation for leaves composition; those plants with fruits have lower phenolic content in leaves respect to plants without formation of fruits (Salgado *et al.*, 2008). Additionally, processing method, age of leaves and time of extraction, may selectively condition the phytochemical and phenolic contents. Consequently, the particular antioxidant and anti-inflammatory responses of the coffee leaves would determine their potential as a suitable source for novel natural health products (Chen et al., 2018).

Phenolic compounds in coffee leaves provides important biological functions; among them chlorogenic acid

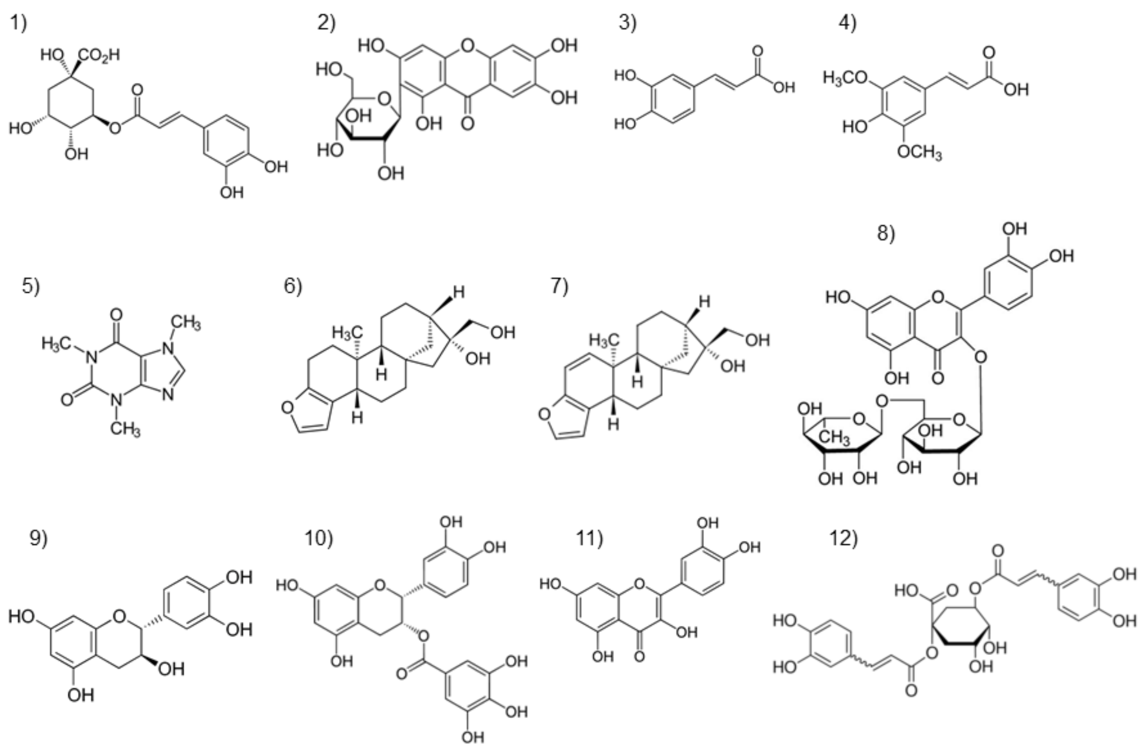

Figure 2. Major phytochemicals associated with aerial parts of *Coffea* species. 1) chlorogenic acid, 2) mangiferin, 3) caffeic acid, 4) sinapic acid, 5) cafein, 6) cafestol, 7) kawheol, 8) rutin, 9) catechin, 10) epicatechin gallate, 11) quercetin, 12) 1,5-dicaffeoylquinic acid.
Figura 2. Fitoquímicos mayoritarios asociados con las partes aéreas de especies de Coffea. 1) ácido clorogénico, 2) mangiferina, 3) ácido cafeico, 4) ácido sináptico, 5) cafeína, 6) cafestol, 7)kawheol, 8) rutina, 9) catequina, 10) galato de epicatequina, 11) quercetina, 12) ácido 1,5-dicafeoilquínico.

exhibits anti-diabetic and anti-lipidemic properties through regulation of the activation pathway of the cellular energy homeostasis enzyme AMPK (Ong *et al.*, 2013). It is an important anti-inflammatory agent able to inhibit the nuclear translocation of NF-κβ and attenuate proinflammatory cytokines such as interleukins1β, 6 and tumor necrosis factor TNFα (Hwang *et al.*, 2014). It also improves liver steatosis, insulin sensitivity and reduces chronic inflammation in obese mice (Ma *et al.*, 2015). Likewise, chlorogenic acid increases antioxidant capacity in liver through the transcription factor Nrf2 signaling pathway (Shi *et al.*, 2016), and exerts an anti-carcinogenic effect that has been reported in different models (Deka *et al.*, 2017; Yan *et al.*, 2017; Sadeghi Ekbatan *et al.*, 2018; Yamagata *et al.*, 2018).

On the other hand, some substances found in coffee leaves could be prejudicial to human health; particularly, cafestol (CAF) and kahweol (KAH) are two anti-nutritional diterpenes unique to coffee. These biologically significant diterpenoids are associated with lipids of coffee and are reported to be responsible for the hypercholesterolemic effects in humans (Sridevi & Giridhar, 2016). Diterpenes CAF and KAH are the major unsaponifiable lipid fraction components in green and roasted coffee beans (Kitzberger *et al.*, 2013; dos Santos Scholz *et al.*, 2016). They also affect beverage quality (Del Terra *et al.*, 2013). In addition, they are commonly associated with anti-inflammatory, anticarcinogenic and antioxidant properties in human health (Chu *et al.*, 2011). In industry, they are used in pharmaceuticals, cosmetic products (e.g., oils and sunscreens) and soluble coffee flavorings. CAF also relates to volatile phenolic compounds released by flowers, which could be responsible for attracting pollinators (Del Terra *et al.*, 2013). However, CAF is also associated with increased cholesterol levels in blood plasma (i.e., hyperlipidemia) at higher ingestion doses, depending on the filter process method used to prepare the coffee drink (Naidoo *et al.*, 2011).

Three diterpenes (i.e., CAF, KAH and 16-O-methylcafestol), which are common ingredients in coffee beans, were also identified in *Coffea* trees leaves. CAF, only traces of KAH and additionally 16-O-methylcafestol were found in leaves of four Arabica varieties (Kölling-Speer & Speer, 1997). Recently, the CAF and KAH profiles were determined by HPLC in leaves, roots, flowers buds, flowers and fruits (i.e., perisperm and endosperm). The identification and quantification of CAF and KAH was possible in roots, flowers buds and flowers, but in the case of *C. arabica* leaves, these diterpenes were not detected particularly in that investigation (Ivamoto *et al.*, 2017).

Novel identification of mangiferin in *Coffea* leaves

Mangiferin (2-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone) is a phenolic compound derived from bark and leaves of the *Anacardiaceae* and *Gentianaceae* families, which may be a unique and underutilized source of potentially therapeutic agents (Yoshimi *et al.*, 2001). Mangiferin has been reported in at least 34 vegetal species (Vyas *et al.*, 2012), including leaves of *Coffea* spp. (Figure 2).

The histochemical observations for the detection of mangiferin in leaves and fruits have been possible on three species: *C. pseudozanguebariae*, *C. arabica* and *C. canephora*, identifying a preferential localization of mangiferin in palisade and spongy (mesophyll) parenchyma of *C. pseudozanguebariae* leaves (Conéjéro *et al.*, 2014). In comparison, the same transverse sections of leaves indicated that mangiferin is absent in *C. canephora*, but present at low concentration in *C. arabica*. In *C. pseudozanguebariae*, *C. eugenioides* and *C. arabica*, mangiferin was present at each development stage, but not detected in *C. canephora* in any case. Irrespective of the developmental stage, the highest mangiferin content was observed in leaves of *C. eugenioides* (Campa *et al., 2012)*. This report is the first in identifying the presence of mangiferin in varieties of *C. arabica*, but others researchers have identified this xanthone in different varieties of *Coffea*.

The concentration of mangiferin and its isomer were quantitated in leaves of five coffee trees species from Brazil and Costa Rica, showing in *Coffea* species a higher concentration of this compound (0.67–4.97 g/kg) (Trevisan *et al.*, 2016). The authors have concluded that consumption of tea brews made of coffee leaves as a natural source of mangiferins, may contribute significantly to a prophylactic intake of these potentially health-promoting phenolic compounds. Mangiferin was initially isolated from leaves, bark, and peel of mango (*Mangifera indica* L.), a well-known plant for its numerous pharmacological properties such as anti-inflammatory, antidiabetic, antihyperlipidemic, and neuroprotective activities, as well as antioxidant and antimicrobial effects in biotic stress conditions (Campa *et al.*, 2012). The anti-inflammatory properties of mangiferin can be attributed, among other mechanisms, to the inhibitory effect on TNFα, as demonstrated in a hyperalgesia model (Rocha *et al.*, 2018), inhibiting NF-κβ activity (Jang *et al.*, 2016).

It was discovered that mangiferin improves cisplatin-induced nephrotoxicity *in vitro* and *in vivo* by attenuating oxidative stress induction and upregulating transcription factors such as Nrf-2, which mediates pro-survival signaling cascades through PI3K activation (Sadhukhan *et al.*, 2018). The promotion in the expression of the intracellular signaling pathway PI3K was also observed in an oxidative stress model in normal cells of kidney epithelium induced by ter-butyl hydroperoxide (tBHP), where mangiferin has shown the potential to maintain normal cellular homeostasis. Thus, mangiferin is situated as a possible candidate for the oxidative stress treatment associated to renal complications thanks to its antioxidant and anti-inflammatory properties (Saha *et al.*, 2016). Other studies have revealed that mangiferin could prevent the secretion of interleukins 6 and 8 (IL-6 and IL-8) induced by cadmium by the endothelial cells of the human glomerulus, modulating the NF-κβ and phospho-JNK phospho-p38 signaling pathways, so that mangiferin could be used to prevent kidney inflammation (Rajendran *et al.*, 2015).

This xanthone is also attributed with neuroprotection properties. Its activity has been evaluated in combination with morin, demonstrating a strong protection against

Aβ-induced mitochondrial dysfunction and neuronal cell death (Alberdi *et al.*, 2018). Therefore, they are promising therapeutic tools for restoring mitochondrial functions and redox homeostasis in Alzheimer's disease. The use of mangiferin in an *in vivo* model demonstrated its anti-inflammatory and anti-arthritic capacity as an inhibitor of NF-κβ and considerably lower levels of the cytokine IL-10, possibly due to the inhibition of the cyclooxygenase-2 (COX-2) enzyme (Pal *et al.*, 2018). Previous works have reported that the mangiferin also impedes COX-2 expression by upregulating TGF-β (García-Rivera *et al.*, 2011; Mahmoud-Awny *et al.*, 2015: Bulugonda *et al.*, 2017). In addition, it has been reported the capacity of mangiferin for inhibiting IL-1β-induced inflammatory response in human osteoarthritis chondrocytes by activating the type II nuclear receptor PPAR-γ (Qu *et al.*, 2017).

It has been suggested that mangiferin could be used for diabetic cardiomyopathy treatment, since it can prevent the release of inflammatory cytokines, inhibit ROS accumulation, avoid production of advanced glycation end products (AGE) and their receptors (RAGE), and promote translocation of NF-κB (Hou *et al.*, 2015). Evidence suggests that mangiferin could be a useful and economical compound not only to maintain and improve health, but also to significantly improve prospects in certain cancers by reducing the likelihood of developing them. It controls the inflammation process by modulating the expression of NF-kβ and PPARγ, thereby regulating the expression of COX-2, Intercellular Adhesion Molecule-1 (ICAM-1), B Cell Lymphoma-2 (bcl-2), IL-6, IL-8, C-X-C Chemokine Receptor type-4 (CXCR4), X linked Inhibitor of Apoptosis Protein (XIAP) and the Vascular Endothelial Growth Factor (VEGF) (Gold-Smith *et al.*, 2016). An anticancer effect of mangiferin has been reported in breast, lung, prostate, gastric, colon and blood cancers (Table 2). Antiobesity effects of mangiferin extracts, capable of regulating blood glucose and lipid levels, have also been reported (Ramírez *et al.*, 2017). A consequent result was also the decrease in body weight gain in an *in vivo* model subjected to a high-calorie diet.

Phytochemicals as defense against leaves pests in *Coffea*

Besides their therapeutic properties, secondary metabolites in Coffea leaves also represent a rich source of bioactive principles that play an important role as plant defense mechanisms to deal with biotic and abiotic factors. Varied microorganisms and pests have been reported to attack the coffee tree with diverse results, sometimes with huge agronomic and economic impacts. As an example, since it was reported in 1867, *Hemileia vastatrix* Berkeley and Broome, a fungus that causes coffee leaf rust, has caused serious affectations to plantations of *Coffea arabica* L. The devastating effects got to the point of eradicating this species from some regions (Várzea & Marques, 2005), including Central and South America, where the plantations loss represented millions of dollars (Avelino *et al.*, 2015).

The ability of the plant to discriminate between its own molecules and those of harmful organisms represents the first essential line of defense of any immune system. Therefore, plants respond to the infection of pathogens using a multilayer immune system (Doehlemann & Hemetsberger, 2013). Particularly, it has been reported the link between phenolic compounds, polysaccharides and cell wall proteins of the plant with the improvement of its protection mechanisms to the digestion by microbial degrading enzymes; therefore, increasing global resistance to the fungi (Bily *et al.*, 2003).

Among the phenolic compounds associated with coffee resistance to *H. vastatrix*, are chlorogenic acids bound to lignin (Silva *et al.*, 2006; Leitão *et al.*, 2011). The benefit of eliciting (i.e., chemical treatment) *Coffea* plants with silicon has been studied to increase the concentration of chlorogenic acid and therefore enhancing their resistance to the fungus; however, no influence of silicon has been found in the expected response (Rodrigues *et al.*, 2011). The content of other phenolics such as proanthocyanidins could be associated with rust resuscitation when higher concentrations of these compounds are observed in *C. canephora* leaves, a rust-resistant species, with respect to the leaves of *C. arabica*, a susceptible species (de Colmenares *et al.*, 1998).

The pesticidal effect of some phytochemical compounds such as methylxanthines, particularly caffeine and phenolic compounds such as chlorogenic acids, has been studied to treat *Leucoptera coffeella* (Lepidoptera: Lyonetiidae) (Magalhaes *et al.*, 2008). It is commonly called the leaf miner of coffee, considered one of the most serious coffee pests in the neotropical regions (Green, 1984). The damage it causes is considerable since its populations reaches the level of plague, when defoliation can be as higher as two thirds of the tree biomass; therefore, production losses can be up to one half of the normal rates (Vega *et al.*, 2006). In this case, the damage to the plant is typically caused by the larva, when piercing the upper part of the leaf epidermis.

Some commercial coffee genotypes (e.g., *Coffea canephora* L. and *Coffea racemosa* Lour. and its hybrids with *Coffea arabica* L.) exhibit high pesticidal activity (i.e., 100% mortality) toward *Leucoptera coffeella*, indicating their antibiosis resistance. The presence of *L. coffeella* correlates actually with a decrease in the foliar content of phenolic acids such as chlorogenic acid, which makes the leaves also vulnerable to other infestations (Magalhães *et al.*, 2010).

CONCLUSIONS

The coffee tree flowers and leaves have been little studied and exploited as byproducts and significant parts of the *Coffea* species. However, their phytochemical composition makes them attractive alternatives for use as source of bioactive nutraceuticals or pesticidal agents. Particularly, leaves contain phenolic compounds such as chlorogenic acid and mangiferin, which have been reported with diverse therapeutic and biological properties. The information gathered in this compilation highlights the potential resource represented by the aerial parts of the *Coffea* plant, in addition to the coffee grain, for their future investigation and industrial utilization.

Table 2. Studies that evaluated the mangiferin anti-cancer property in different models.
Tabla 2. Estudios que evaluaron la propiedad anticancerígena de la mangiferina en diferentes modelos.

Model	Observations	Reference
Androgen receptor positive LnCap The human leukemia Molt-4 cells Estrogen-independent MDA-MB-231 breast cancer cells Colorectal SW-480 adenocarcinoma cells Human lung A-549 carcinoma cells	Different cell lines showed cell growth suppression in a dose-dependent manner when treated with extracts of the mango varieties Ataulfo and Haden rich in mangiferin.	Noratto *et al.*, 2010
Gastric carcinoma cells SGC-7901 and BCG-823	Mangiferin inhibited the proliferation in dose- and time-dependent manners, inhibiting cell growth and inducing apoptosis of gastric cancer cells through inhibition of the PI3K/Akt pathways with relative safety.	Du *et al.*, 2018
Human prostate cancer cells PC3	Mangiferin inhibited proliferation and induced apoptosis in PC3 human prostate cancer cells; this effect was correlated with downregulation of Bcl-2 and upregulation of miR-182.	Li *et al.*, 2016
Breast cancer and colorectal carcinoma MCF-7 and HCT-116 cells	Therapeutic *in vitro* anticancer effect of nanoparticles of mango leaf extracts, rich in mangiferin, were observed in cytotoxicity tests.	Anoop *et al.*, 2018
Human colon adenocarcinoma cell line SW480 Rodent model of colorectal cancer	Antiproliferative and preventive capacity of an aqueous extract of *Mangifera indica* cv. Azúcar was observed on cells SW480 and in a rodent model.	Corrales-Bernal *et al.*, 2014
Proximal tubule cell line HK-2 Caco-2 cell sub-line selected by resistance to vincristine (Caco-2/VCR)	Function inhibition of the MDR-1/P-glycoprotein (P-gp ABCB1) multidrug transporter, leading to potential herb–drug interactions with P-gp activity.	Chieli *et al.*, 2009
Breast cancer Rac1/WAVE2 signalling	Mangiferin delays breast malignancy development and progression by inhibiting different signaling pathways required in mitogenic signaling and metastatic progression.	Deng *et al.*, 2018
Breast cancer cells MCF7 and MDA-MB-231 Non-tumorigenic cells MCF10	Mango leaf extracts showed protective properties against oxidation and cytotoxic effects in breast cancer cell lines, causing minor damage to non-carcinogenic cells, maybe due to synergy of mangiferin and other phenolic compounds in extracts.	Fernández-Ponce *et al.*, 2017
Breast cancer cells MCF-7	Non polar extract (chloroform extract) of fruit peels exhibited capacity to mediate apoptosis via oxidative stress mechanism, which appeared to be due to bio-active phytochemicals such as mangiferin.	Ediriweera *et al*., 2017
Breast cancer cells MCF10A and MCF7	Mangiferin has selectively blocked breast cancer cell growth by inducing apoptosis and arresting cell proliferation through combined action on cholesterol and proteasome pathways, as well inhibiting plasmin-mediated mechanisms of cell migration.	Cuccioloni *et al.*, 2016
Breast cancer cell lines MCF-7 and T47D	Mangiferin inhibits the activation of β-catenin pathway in breast cancer cells, showing clear antitumor effect.	Li *et al.*, 2013
Human HL-60 myeloid leukemia cells and mononuclear human umbilical cord blood cells (MNCs)	Mangiferin as a novel Nrf2 activator reduces oxidative stress and protects normal cells without reducing the sensitivity to etoposide of HL-60 leukemia cells in vitro. Mangiferin may be a potential chemotherapy adjuvant.	Zhang *et al*., 2014
Leukemic cells lines K562	Mangiferin could inhibit telomerase activity of K562 cells in time- and concentration-dependent manners that could induce apoptosis and up-regulate the levels of Fas in K562 cells.	Cheng *et al.*, 2007
Human lung adenocarcinoma cells A549	Mangiferin induced G2/M phase cell cycle arrest via the cdc2-cyclin B1 pathway, and induced cell apoptosis via the PKC-NF-κB pathway.	Shi *et al.*, 2016

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