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Ethnopharmacological study of the genus *Coffea* and compounds of biological importance

Estudio etnofarmacológico del género *Coffea* y compuestos de importancia biológica

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Abstract
The present review is focused to know the origin of the coffee drink, its agroindustrial position in Mexico and the world, and the importance of its biological effects on human health. Coffee is native of Ethiopia and it was used in Arab countries as food and as a fermented beverage due to its stimulating effect. Over the years the "*Moka*" infusion of green and/or roasted beans became popular in Europe. The genus *Coffea* (Rubiaceae) comprises more than 100 species of which the best known are *C. arabica* and *C. canephora* and their hybrids Colombia, Oro Azteca and Costa Rica 95, which are resistant to the rust fungus. The predominant commercial production (70%) and infusion drinking is of *C. arabica* due to its cup quality, low caffeine content and fine aroma, on its part *C. canephora* is mainly used as a base for instant coffee. The main consumers are the United States and countries of the European Union, while the main producers are Brazil and Vietnam. Mexico is the tenth largest producer, with Chiapas being the major producer and Guerrero standing out for its organic and specialty coffee by indigenous communities. Coffee beans are rich in phenolic compounds such as chlorogenic acids (CGAs) and alkaloids like caffeine and trigonelline, their contents are reduced after the beans are roasted. Trigonelline and CGAs confer aroma, bitterness and astringency to coffee. The main biological effects of CGAs are antioxidant, anti-inflammatory and antidiabetic, and caffeine is a neurostimulator.
Keywords: chlorogenic acid, anti-inflammatory, antidiabetic, coffee, caffeine, *Coffea*.

Resumen
La presente revisión fue enfocada en conocer el origen de la bebida de café, su importancia agroindustrial en México y en el mundo, y la importancia de sus efectos biológicos sobre la salud del humano. El café es originario de Etiopia y se empleó en países árabes como alimento y como bebida fermentada debido a su efecto estimulante. Con el tiempo la infusión "*Moka*" de granos verdes y/o tostados fue popular en Europa. El género *Coffea* (Rubiaceae) comprende más de 100 especies, las más conocidas son *C. arabica* y *C. canephora* y sus híbridos Colombia, Oro Azteca y Costa Rica 95 resistentes al hongo de la roya. La producción comercial predominante (70%) e infusión de consumo es de *C. arabica* por su calidad en taza, bajo contenido de cafeína y fino aroma, en cambio *C. canephora* se utiliza principalmente como base para el café instantáneo. Los principales consumidores son Estado Unidos y la Unión Europea, en tanto que los principales productores son Brasil y Vietnam. México está en décimo lugar como productor, siendo Chiapas el mayor productor y Guerrero se destaca por el café orgánico y de especialidad en comunidades indígenas. Los granos de café son ricos en compuestos fenólicos como los ácidos clorogénicos (CGAs) y alcaloides como cafeína y trigonelina, cuyo contenido se reduce posterior al tostado del grano. Los CGAs y la trigonelina le confieren el aroma, amargor y astringencia al café. Las principales actividades biológicas de CGAs son antioxidante, anti-inflamatoria y antidiabética, y la cafeína es un neuro-estimulante.
Palabras clave: ácido clorogénico, antiinflamatorio, antidiabético, café, cafeína, *Coffea*.

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1 Introduction

In ancient times, coffee beverage and plant were used by travelers and to feed slaves due to their stimulant effect (Clifford & Willson, 1985; ICO, n.d.). The attributes of infusion of roasted coffee beans were discovered in Ethiopia; coffee infusion was named *qahwah* in Arabia and Khave in Turkey, and later was known as coffee in Europe. Currently, there are different techniques for obtaining infusion from beans of *Coffea arabica* and *C. canephora* to prepare cold and hot coffee beverages throughout the world. Nevertheless, there are regional species of *Coffea* used for the preparation of infusions in countries of Africa and Asia (Clifford & Willson, 1985; Herrera & Lambot, 2017).

The coffee belongs to the Rubiaceae family, the Ixoroideae subfamily with 15 tribes, including the Coffeeae and 11 genera together with the *Psilanthus* and *Coffea* genera, with more than 103 species (Anthony *et al*., 2011; Davis *et al*., 2007). Coffee plants grow in countries with hot and humid climates of Asia, Africa and America between the Tropics of Cancer and Capricorn, forming the well-known coffee belt (Bobadilla Landey, 2013).

The production and marketing of coffee are related to its cup quality, caffeine content and aroma (Philippe *et al*., 2009); Mexico is known as a coffee producer.

Nowadays, there has been a growing interest in the research of *Coffea* species around the world to take advantage of their potential to prepare coffee drinks for the main consumer countries. The consumption of coffee beverages is based on their ethnopharmacological uses and biological properties attributed to their chemical components. In the *Coffea* species, the concentrations of chemical components vary among species and cultivation places; besides, some compounds are degraded during the roasting process, and some of them can be toxic pollutants (Farah & Donangelo, 2006; Ruiz-Palomino *et al*., 2019; Castaldo *et al*., 2020; Várady *et al*., 2021).

2 Methodology

In this review, published articles addressing the *Coffea* genus were searched for in scientific search engines such as NCBI, ScienceDirect, Web of Science and Google Scholar based on their titles and abstracts then analyzed and compiled. The systematic review of studies covering the species of the genus *Coffea* was subject to the following criteria: the study (1) was published in English; (2) addressed the traditional or popular practices of consuming coffee beverages; (3) considered the description and taxonomy of the genus *Coffea*; (4) and addressed the production and marketing of coffee. Furthermore, to meet the study criteria, the articles must have integrated into tables results of (5) the isolation of secondary metabolites and identification techniques used; (6) the biological activity evaluated and the models used for analyzing infusions/extracts, phenolic compounds and alkaloids including authorship. The chemical structures were drawn using ChemDraw Pro 8.0 software, and the PubChem database was used to verify the IUPAC names of the major compounds reported in species of the genus *Coffea*.

3 Species explored for the preparation of coffee

In ancient times, ground coffee beans mixed with other plants and animal fat were used as food by travelers. Similarly, the beans or the fruit were fermented to obtain a drink similar to wine, a liquor that became popular in Arab countries. There is also evidence of the leaves and pulp being used to prepare infusions. The consumption of coffee spread from Ethiopia to the Arabian Peninsula by merchants and slave traders due to its stimulating effects, for that the origin of the coffee drink is attributed to Arabia. In this region, it was forbidden for travelers to visit the crops, and they were not allowed to take the beans unless they were roasted or boiled; later, coffee was cultivated in other Muslim countries and in India. It has been established that the domestication of coffee began in the high mountains of Ethiopia in the 7th century (Anthony *et al*., 2011; Reich, 2010). There is a record that in the province of Kaffa, now Ethiopia, the attributes of the roasted coffee bean were discovered. The cultivation of plants and distribution of beans from Kaffa spread to Sudan and later to Yemen, where the drink was named "*Moka*", referring to the city where it was grown (Mocha-Yemen). The "*Moka*" drink became popular due to the diffusion of its consumption by the local authorities, thus reducing the consumption of the "kat" shrub, whose leaves and buds were chewed to obtain stimulating effects (ICO, n.d.-b).

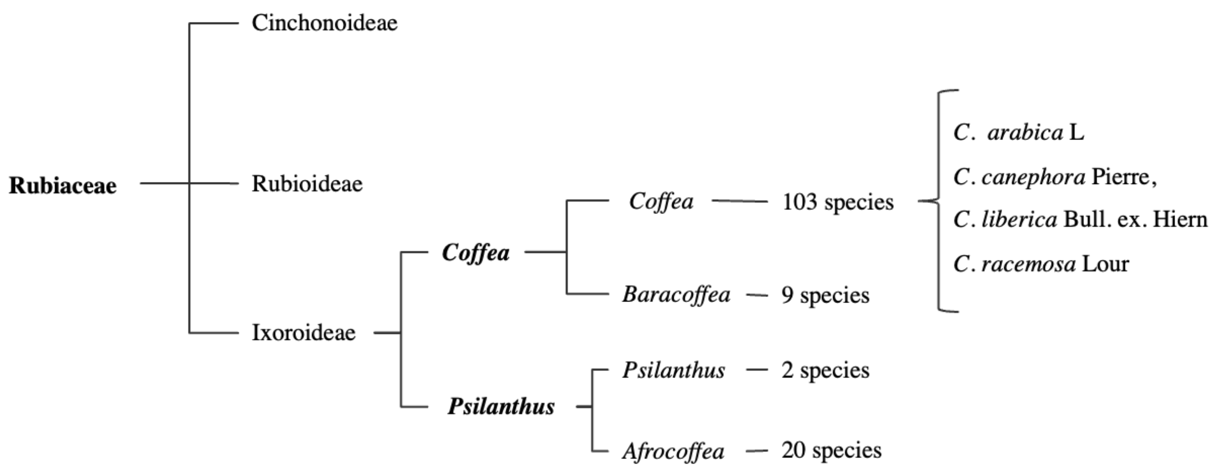


Figure 1. Diagram of taxonomic classification of coffee plants. Authors elaborated this diagram based on Anthony *et al*., 2011 and Davis *et al*., 2007.

The word coffee has an Arabic origin, "*qahwah*", which means exciting; the Turks named it "*kahve*", referring to the fruit of the coffee plant, and this term spread throughout Europe until it was known as "coffee" (Clifford & Willson, 1985; Smith, 1985).

According to the "*Book of coffee*", in the sixteenth century, during the movement of travelers from Arabia to Europe (currently Istanbul), the first establishments for selling coffee drinks were introduced. By the seventeenth century, this drink was consumed and marketed in Cairo; since that time, coffee shops have been present in European countries. The development of the printing press and the light bulb caused cafeterias to gain prominence, as they were used as centers for social and political meetings (Reich, 2010). Currently, cold and hot coffee beverages made from beans of *C. arabica* and *C. canephora* are common in various forms throughout the world. However, there are other little-known species used for the preparation of infusions that are produced and consumed locally in countries of Africa, Indonesia and the Philippines, including *C. liberica*, *C. racemosa*, *C. stenophylla* and *C. humblotiana*. The species *C. liberica* is native to Liberia and is cultivated in West Africa and Malaysia. Despite being very aromatic in markets, it is rarely accepted by consumers. In Sarawak and Borneo, beans of this species are mixed with beans of *C. canephora* to create an infusion, to which condensed milk and sugar are added; sometimes, the beans are roasted with margarine and sugar. The species *C. excelsa* was identified at the beginning of 1900 in Africa. This species is very similar to *C. liberica*, and it is rarely found in markets, although its beans are very aromatic (Clifford & Willson, 1985; Herrera & Lambot, 2017). *C. racemosa* is a lesser known species; it is cultivated in Mozambique and in northern South Africa; the caffeine content of *C. racemosa* is lower than that of *C. arabica*, and it is characterized by a bitter taste, highlighting the flavors of mint and wood (Davis *et al*., 2021). The species *C. stenophylla* is found in West Africa, where it is endemic to the Comoros Archipelago, and is characterized by a mild flavor similar to that of Arabica coffee. However, it is an unprofitable species because its growth in culture is slow, so it is considered an endangered species. *C. humblotiana*, endemic to the Comoros Archipelago, is a different species from others described within the genus *Coffea* since it does not produce caffeine; therefore, this species produces a naturally decaffeinated coffee product, and its metabolic pathways are currently under study (Raharimalala *et al*., 2021).

4 Coffee taxonomy

Coffee belongs to the Rubiaceae family, which is divided into three subfamilies: Cinchonoideae, Rubioideae and Ixoroideae (Figure 1); the latter comprises about a fifth of the family. The subfamily Ixoroideae is made up of 15 tribes, including the Coffeeae DC tribe, made up of 11 genera including the *Psilanthus* and *Coffea* genera, which have beans with similar morphological characteristics and only differ in flower morphology. Both genera are subdivided into subgenera, *Psilanthus* includes the subgenera *Psilanthus* with 2 species and *Afro Coffea* with 20 species, while the genus *Coffea* includes the subgenera *Coffea* of which there is a report of 103 species, and *Bara Coffea* with 9 species. In the subgenus *Coffea*, the species of *Coffea arabica* L., *Coffea canephora* Pierre, *C. liberica* Bull stand out. ex. Hiern and *C. racemosa* Lour (Anthony *et al*., 2011; Davis *et al*., 2007). The first species of coffee taxonomically identified by Carlos Linnaeus in 1750 in the Republic of Yemen was *Coffea arabica* L.

5 Botanical description of the most important species of the genus *Coffea*

The genus *Coffea* is composed of shrubs and trees over 10 m high, with a vertical stem (orthotropic) with horizontal primary, secondary and tertiary branches (plagiotropic), white flowers and red or yellow fruits (Bobadilla Landey, 2013; ICO, n.d.-a). *C. arabica* (Arabica) is a shrub that can reach a height of 5 m with open branches (Figure 2a). It has large, oval, dark green leaves. This species is self-pollinated, its fruit is oval, and fruit maturation occurs within 7 to 9 months of formation. The fruit contain two crushed seeds, and sometimes the fruit can have a single seed known as snail (Clifford & Willson, 1985; Lim, 2013b). *C. canephora* (Robusta) is a coffee tree taller than Arabica; it measures up to 10 m in height and gives it a robust appearance due to the type of branching that presents (Figure 2b). Its leaves are large, broad, and green. The fruit is round and takes up to 11 months to mature, so the harvest time is longer; usually, the fruit contains two ovoid seeds of variable size that are smaller than those of Arabica (Clifford & Willson, 1985; Lim, 2013a).

Figure 2. Photographs of the main species of coffee cultivated in the world were provided by the coffee producers L. Gonzalez and M. Fadanelli-Figueroa: (a) *Coffea arabica* in “El Encino farm" at Tierra Colorada-Malinaltepec, Guerrero between 1,100 masl, and (b) *Coffea canephora* in “El Rancho el Molino" at Potrero-Zentla, Veracruz between 780 masl.

6 Geographical distribution and cultivation of coffee in the world

Coffee is grown in countries with hot and humid climates that are located in Asia, Africa and America between the Tropics of Cancer and Capricorn, forming the well-known coffee belt (Figure 3), which covers a range of altitudes of 4,000 km (Bobadilla Landey, 2013). The Arabica species grows between 1,200 and 2,000 m above sea level in areas with cool and slightly humid climates and temperatures that range between 15 and 25 °C. It requires soils rich in organic matter with slight acidity or alkalinity and is grown mainly under the shade of trees. Currently, several varieties are cultivated in coffee-growing regions; Typica and Bourbon were the first varieties cultivated and continue to be the most popular in many countries (ICO, n.d.-a; Lim, 2013b).

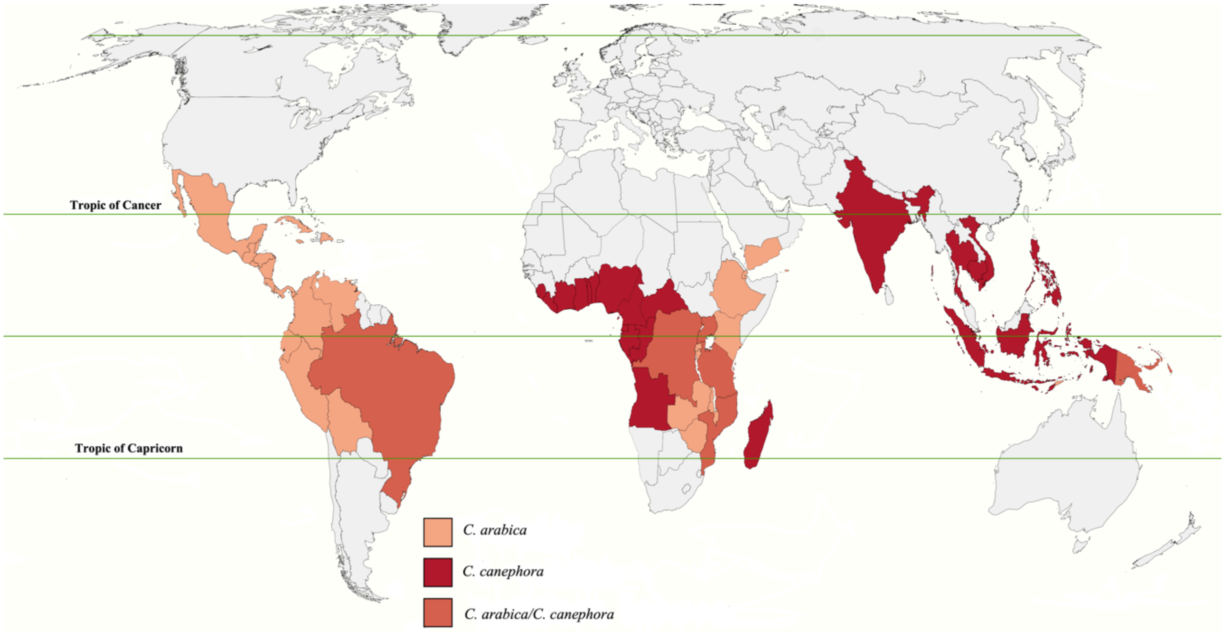


Figure 3. Producing countries of the main coffee species *Coffea arabica* and *Coffea canephora* are located between the Tropic of Cancer and the Tropic of Capricorn. Authors elaborated this map based on ICO, 2021.

The species that produces Robusta coffee is more tolerant of a range of climate and soil conditions; it can be grown as low as 800 m.a.s.l. and in areas with a temperature between 18 and 36 °C. It is mainly cultivated in open fields and adapts easily to different types of soils with greater acidity or alkalinity (ICO, n.d.-a; Lim, 2013a). The species *C. liberica*, *C. racemosa*, *C. stenophylla* and *C. humblotia* can be found in some countries of Africa and Asia at altitudes below 1,000 m.a.s.l. (Davis *et al*., 2020).

7 Generation of hybrid varieties

Within the species *C. canephora* and *C. liberica*, relevant traits and the identification of the carrier genes that can be used in artificial interspecific hybridization processes have been sought. During hybridization procedures, two individuals of the same genus are crossed to create crops with beneficial qualities, for examples the hybrids of *C. arabica* with resistance to orange rust (*Hemileia vastatrix*), the coffee berry borer (*Hypothenemus hampei*) and the leafminer (*Leucoptera coffeella*), which are the main pests affecting coffee plants (Anthony *et al*., 2011; Davis *et al*., 2007). The Typica and Bourbon varieties have served as the genetic basis for the generation of other varieties, such as Mundo Novo (Brazil), Tico (Central America), San Ramon enano (Costa Rica), Jamaican Blue Mountain (Jamaica) and Caturra, a natural mutant of the Bourbon variety identified in Brazil (ICO, n.d.-a). The best-known is the Timor hybrid which arose naturally from a cross between *C. arabica* and *C. canephora*, which is resistant to rust. The Arabusta and Icatu varieties were obtained from crosses between *C. arabica*, which provides high-quality attributes, and *C. canephora*, which offers resistance to pests. Crosses of *C. racemosa* with Arabian varieties have been reported, generating hybrids such as *C. aramosa*, with resistance to *L. coffeella* and drought and low caffeine content. Similarly, hybrids have been obtained from a cross between *C. canephora* and *C. congensis* with drought tolerance (Barrera, 2017; Davis *et al*., 2021). The species *C. liberica* and *C. excelsa* express greater resistance than other species to *H. hampei* because their fruits have a thicker pericarp that hinders the entry of microorganism; although no hybrid species have been reported in the market with resistance to this insect, these coffee species could be an alternative to meet the demands of farmers (Barrera, 2017).

Figure 4. Regions of Mexico from different sheds recognized as the main coffee beans producers. Authors elaborated this map based on Flores Vichi, 2015.

8 Production, marketing and consumption of coffee

Commercial coffee production is mainly based on two species, *C. arabica* (Arabica) and *C. canephora* (Robusta). The Arabica species is predominant in cultivation, accounting for 70% of global production due to its cup quality, low caffeine content and fine aroma. The cultivation of the Robusta species is lower due to its strong flavor and high caffeine content compared to those of *C. arabica*; it is widely cultivated in Vietnam, Brazil and Indonesia and is used essentially as a base for instant coffee (Philippe *et al*., 2009). According to the International Coffee Organization (ICO), total coffee production in 2020 was 175.3 million 60 kg bags; Brazil was the main producer with 59.3 million bags, followed by Vietnam with 31.3, Colombia with 13.8, Indonesia with 10.7, Ethiopia with 7.45, Honduras 5.6 with, India with 4.89, Peru with 4.45, Uganda with 4.25 and Mexico with 3.7 (ICO, 2021). For the 2020-2021 cycle, based on reports from the United States Department of Agriculture (USDA), the main countries that imported green coffee beans, roasted and soluble, were those that make up the European Union with 30% of the total production, followed by the United States with 19% and Japan with 5%, with the main coffee consumers being the European Union, the United States and Brazil (USDA, 2021).

9 Coffee production in Mexico

Mexico ranks 11th as coffee producer worldwide and represents 0.66% of agricultural GDP and 1.34% of the agro-industrial production. In Mexico (Figure 4), coffee is cultivated in 4 main regions: 1) the Gulf of Mexico slope, which includes the States of San Luis Potosi, Queretaro, Hidalgo, Puebla, Veracruz, part of Oaxaca and Tabasco; 2) the Pacific Ocean slope, including Colima, Guerrero, Jalisco, Nayarit and part of Oaxaca; 3) the Soconusco Region, which includes part of the state of Chiapas; and 4) the north central region of Chiapas (Figure 4) (Flores Vichi, 2015). In 2020, a total production of 953,682.90 t of coffee was recorded, the State of Chiapas was the main producer, with 378,000 t, followed by Veracruz (235,000 t), Puebla (160,000 t), Oaxaca (86,000 t) and Guerrero (38,000 t) (SIAP, n.d.). Mexico stands out for its production of organic coffee, ranking second after Peru. Organic coffee is exported to countries in Europe and the United States. Data from the Ministry of Agriculture and Rural Development (SADER) indicate that 3.24% of the total cultivation area is allocated to organic coffee cultivation, with 8% of the producers included in the national census participating (Otero & Elms, 2021).

The participation of 500 thousand coffee producers has been reported, with production distributed in 15 states and 480 municipalities; entire families of men, women and children participate in the production process. The majority of these families belong to indigenous communities (85%) dedicated to the production of specialty coffee and whose cultivation area does not exceed 3 ha (Contreras-Medina *et al*., 2020; SADER, 2018). One of the main characteristics of coffee cultivation in Mexico, compared to other countries, is that cultivation areas can be found in forests with high, medium and low altitudes and in mesophilic forests and in pine-oak forests, which is called shade cultivation. According to the ADESUR (Strategic Alliance for the Development of the South Pacific Region) and based on agricultural censuses in land where coffee is cultivated at the national level, 33% of cultivation areas are found in coniferous forest, 21% are found in cloud-covered mountain forest, 14% are found in evergreen forest, 9% are found in oak forest, 7% are found in low deciduous forest and 6% are found in mid-altitude deciduous forest (ADESUR, 2020). The Agricultural and Fisheries Information Service (Servicio de Información Agroalimentaria y Pesquera - SIAP) reports that 85% of national production is based on Arabica coffee and, to a lesser extent, Robusta coffee. Thirty-five percent of coffee plant crops are found at altitudes greater than 900 m.a.s.l., which is considered high-altitude coffee, and the rest of the crops are distributed between 600 and 900 m.a.s.l (Otero & Elms, 2021).

Considering the problems presented by Mexican coffee due to pests, old plantations and low yields, government institutions have created programs for 10 years to strengthening the increase of national production and consumption by people, granting certified genetic material, certified nurseries, technological packages, training and specialized advice support for payment of external inspection for organic certification, Rain Forest Alliance, 4C, UTZ, Fair Trade among others (CEDRSSA, 2018; SAGARPA, 2017). Coffee producers have organized themselves into cooperatives to seek certifications such as USDA Organic, Fair Trade, Shade Grown, Rainforest Alliance, and Small Producer, which allows them to enter new markets and offer their products. In Mexico, there is a record of 600 units, called cooperatives, 400 of them are located in the state of Chiapas. These cooperatives obtain financing from government banks and private banks, and technical support from government institutions (Otero & Elms, 2021). Although production in Mexico has been reduced by environmental factors such as droughts, plagues and floods, worldwide production has had a considerable increase.

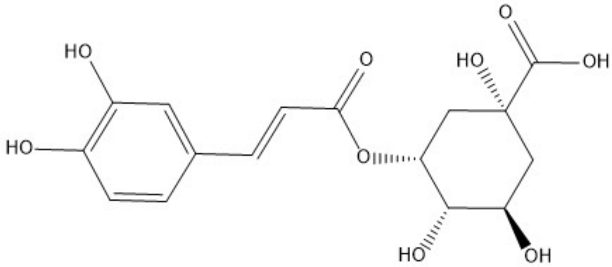
Due to the Mexican population drinks mainly the soluble coffee imported from Brazil and the roasted coffee consumption is low (1.4 kg per person), the government has implemented diffusion strategies to encourage the population to consume roasted coffee. Since then there has been an increase in the production of specialty coffees and new coffee outlets have been created (CEDRSSA, 2018; SAGARPA, 2017). In the state of Guerrero, the 80% of the coffee production cover a plantation of 45,000 ha distributed into two areas (SIAP, n.d.): the area of Costa Grande in the municipalities of Atoyac de Alvarez, Coyuca de Benitez and Tecpan de Galeana, followed by the area of La Montaña in the municipalities of Malinaltepec, Iliatenco and San Luis Acatlan. In mountainous areas, coffee is produced by people from the Mixtec and Tlapaneco ethnic groups. Coffee production occurs in polyculture incorporated into plantations of beans, squash, chili, soursop fruit trees, avocado, banana, pineapple, and some timber trees (Tablas González *et al*., 2021). These populations are mainly dedicated to the cultivation of the species *C. arabica* of the varieties Typica, Mundo Novo, Bourbon, Caturra and Garnica (Hidalgo-Espinosa, 2020).

In Mexico, the processing of coffee fruit is carried out mainly by the wet method, the 90% of the coffee that is marketed is washed. A small amount of honey coffee is also produced. Natural coffee is obtained by the dry method, which is simpler and requires little machinery (Hidalgo-Espinosa, 2020). In mountainous regions, coffee processing is mainly performed by a dry process, where ripe cherries are cut and dried in the sun for 15 to 20 days until capulin coffee (coffee with husk) is obtained. This coffee is sold in bulk to intermediaries such as the ARIC (Rural Association of Collective Interest RL and CV), CAFECO Agroindustrial del Pacifico S.A. de C.V. and the Union of Ejidos and Communities Luz de La Montaña, A.C. (Delgado-Alvarado, 2018; Hidalgo-Espinosa, 2020; Tablas González *et al*., 2021). Coffee that is not sold to marketing organizations is roasted at the producer's homes for self-consumption or sale locally. Producers have organized to obtain seedlings of coffee varieties that are resistant to pests; these varieties include Colombia, Oro Azteca, Marsellesa, Costa Rica 95, and Sarchimor, among others and have replaced varieties susceptible to damage from pests and varieties that ceased to be productive (Delgado-Alvarado, 2018; Hidalgo-Espinosa, 2020; Tablas González *et al*., 2021).

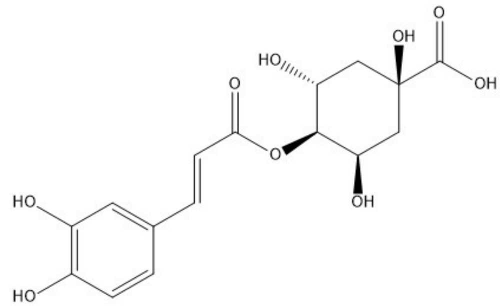
10 Coffee-based beverages

The oldest form of preparation is the Turkish coffee; for this, coffee powder is added to a container with boiling water, and it is kept over a fire. The drink produces a foamy layer, and the beans settle. This technique is used mainly at home. In Mexico, the most common method for preparing the Turkish coffee involves using a clay container, with cinnamon and brown sugar added to the product (Mestdagh *et al*., 2017). Another widely used preparation process is drip filtration or percolation. For this process, a coffee maker and medium-ground beans are placed in a paper filter inside a container located at the top of the coffee maker, through which hot water passes, and the filtered drink is collected in a glass jug. The most common drink made with this method is American coffee, which can be found in restaurants and self-service stores (Caprioli *et al*., 2015). For the preparation of coffee by immersion or by the French press, a coarse grain mill is used, and a filter is attached to a plunger at the upper end of a glass container. The ground beans are mixed with boiling water and left to rest for 2 to 5 min. After that time, pressure is applied by pressing the plunger down, and the filter removes the coffee residues; the liquid that remains in the container is consumed. This type of coffee is mainly consumed at home due to its preparation method (Stanek *et al*., 2021). For espresso coffee, a compact fine-ground grain in the form of a tablet is used, and hot water (150 mL) is applied to the grain under pressure for 25 to 30 s. Espresso is a very strong drink and is one of the most widely consumed drinks after the American coffee. Another method that uses a pressurized technique is the Italian coffee or the espresso *Moka*. For this type of coffee, a coffee maker with a closed system divided into 3 sections is used: the coffee is placed in the middle section on a metal filter, water is added to the first section, and the coffee maker is heated, causing boiling water to pass through the coffee; the drink is then collected at the top of the coffee maker (Caprioli *et al*., 2015; Mestdagh *et al*., 2017). Another way of consuming coffee is in cold preparations. These preparations use some of the previously described techniques and can be performed with water or cold milk; flavoring, creams and other ingredients can be added to the drink for embellishment. Cold coffee preparations are one of the drinks of choice among young populations (Mestdagh *et al*., 2017). Soluble coffee is made by the infusion process, with beverages obtained from dried and pulverized coffee by different methods. In one process, hot air is applied to evaporate remaining water in coffee beans, leaving a fine coffee powder. In another method, frozen infusions are lyophilized at -40 °C and subjected to vacuum pressure to evaporate remaining water to obtain dry coffee crystals. Soluble coffee is one of the most widely consumed types of coffee due to its practicality, since only hot water is needed to rehydrate the coffee powder and obtain a beverage (Caprioli *et al*., 2015; Mestdagh *et al*., 2017).

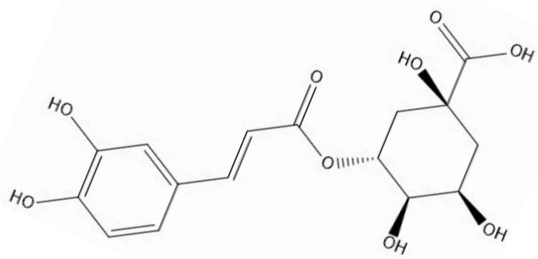
The quality of coffee depends on the physical and organoleptic properties of the beverage, such as flavor, aroma, acidity, body and balance. The storage of the beans is essential to preserve their physical and organoleptic characteristics since they are kept in jute sacks and in many cases there is no humidity control, which allows the development of microorganisms that can contaminate the beans, one option is to control of relative humidity and use of atmosphere packaging preserving the properties of green coffee beans for one year (Trujillo-Carretero *et al*., 2022).The quality of the drink is also associated with the contents of its chemical compounds, mainly chlorogenic acids (CGAs); caffeine; trigonelline; volatile compounds such as furans, pyridines, pyrazines, and pyrroles; hydroxybenzoic acids such as vanillic; and hydroxycinnamic acids such as cinnamic (Farah & Donangelo, 2006).



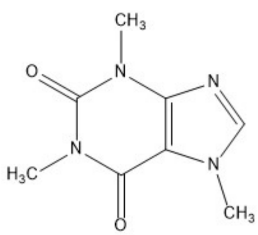
a) 3-*O*-caffeoylquinic acid

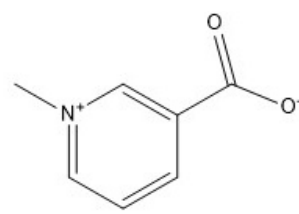


b) 4-*O*-caffeoylquinic acid



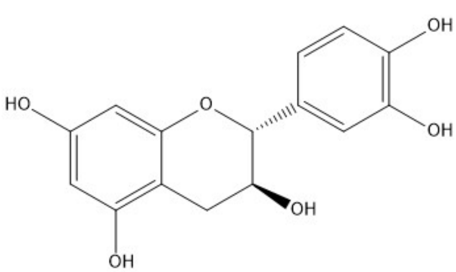
c) 5-*O*-caffeoylquinic acid

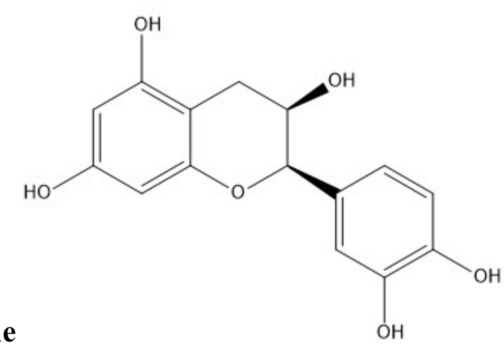




d) 1,3,7-trimethylxanthine

e) N-methylnicotinic acid





f) (−)-*trans*-3,3′,4′,5,7-pentahydroxyflavane

g) (−)-*cis*-3,3′,4′,5,7-pentahydroxyflavane

Figure 5. Chemical structures of main compounds identified in the beans of *Coffea arabica* and *Coffea canephora* species.

Table 1. Chemical compounds and biological activity reported for infusions of roasted beans from *Coffea arabica* species.

Analysis method	Compounds	Biological activity	Reference
Colorimetric and high-performance liquid chromatographic (HPLC)	Total polyphenols Chlorogenic acid Caffeine	Antioxidant - DPPH, ABTS and FRAP	Duangjai *et al*., 2021
	Total phenolics Total flavonoids Chlorogenic acid Caffeine	Antioxidant - DPPH and FRAP	Jung *et al*., 2021
	Total polyphenols Caffeine Flavonoids	Antioxidant - DPPH, ABTS, FRAP, PFRAP and CUPRAC	Muzykiewicz-Szymańska *et al*., 2021
	Acrylamide Total polyphenols Flavonoids	Antioxidant - DPPH and FRAP	Endeshaw & Belay, 2020
	Total phenolic content Caffeic acid Caffeine Chlorogenic acid	Antioxidant - ABTS Antiplatelet - Measurement of platelet aggregation Cyclooxygenase (COX) inhibitors	Hutachok *et al*., 2020
	Total phenolic Ascorbic acid *P*-coumaric Caffeic acid Chlorogenic acid Caffeic acid Catechin	Antioxidant - ABTS Antidiabetic - α-glucosidase inhibition	Vázquez-Sánchez *et al*., 2018
HPLC	Total phenolics Phenolic acids Flavonoids	Not reported	Król *et al*., 2020
	Caffeic acid Caffeine Chlorogenic acid Ferulic acid Gallic acid Hydroxybenzoic acid Protocatechuic acid Sinapic acid Vanillic acid	Apoptotic - Expression of Bcl-2, Bax, caspase 3 and VEGF. Anti-inflammatory - Determination of inflammatory markers TNF-α, IL-1β, NF-κB and BDNF. Neuroprotective - Expression of biomarkers of oxidative stress in a model of injury induced by cerebral ischemia in rats.	Rizk *et al*., 2021
	Caffeic acid Caffeine Chlorogenic acid	Antioxidant - ABTS	Lazcano-Sánchez *et al*., 2015
Not reported	Not reported	Antioxidant - GHS measurement Anti-inflammatory - Expression of TNF-α, IL-6, iNOS, IL-1β and COX-2 levels in a mouse model with septic shock induced by lipopolysaccharide (LPS).	Choi *et al*., 2018

Table 2. Chemical compounds and biological activity reported for infusions of green beans from *Coffea arabica* species.

Analysis method	Compounds	Biological activity	Reference
HPLC	Total polyphenols Caffeine Flavonoids	Antioxidant - DPPH, ABTS, FRAP, PFRAP and CUPRAC	Muzykiewicz-Szymańska *et al*., 2021
	Caffeic acid Caffeine Chlorogenic acid Ferulic acid Gallic acid Hydroxybenzoic acid Protocatechuic acid Sinapic acid Vanillic acid	Apoptotic expression of Bcl-2, Bax, caspase 3 and VEGF. Anti-inflammatory - Determination of inflammatory markers TNF-α, IL-1β, NF-κB and BDNF. Neuroprotective - Expression of biomarkers of oxidative stress, in a model of injury induced by cerebral ischemia in rats.	Rizk *et al*., 2021
	Caffeic acid Caffeine Chlorogenic acid	Antioxidant - ABTS	Lazcano-Sánchez *et al*., 2015
Colorimetric and spectrophotometry	Total polyphenols Total flavonoids Caffeine Tannins	Antioxidant - ABTS Antimicrobial in a simulated stomach model in the presence of *E. coli* F4 and *Streptococcus suis*. Anti-tyrosinase activity - Optimized inhibition of the enzyme tyrosinase	Prandi *et al*., 2021
Colorimetric	Total phenolic Total flavonoids	Antioxidant - Enzymatic regulation of oxidative stress. Anti-inflammatory - Pro-inflammatory cytokines in a diabetic rat model	Al-Megrin *et al*., 2020

11 Active compounds identified in the beans of *Coffea* species

The chemical composition of *C. arabica* is the most well-studied, followed by that of *C. canephora* and other coffee species. Spectroscopic analyses show that the main components in green and roasted beans are phenolic compounds, highlighting phenolic acids such as chlorogenic (CGAs) (Figure 5a, b, c), caffeic, ferulic, p-coumaric, vanillic and sinapic acids, as well as the flavonoids quercetin, isoquercitrin, rutin, epicatechin and catechin and tannins (Tables 1 and 2). These compounds have been quantified by determining the total phenolic compounds and total flavonoids using colorimetric techniques. Infusions of coffee beans, both green and roasted, have been chemically analyzed because the infusion process is generally used in the preparation of beverages commonly known as coffee (Tables 1 and 2). The chemical analyses by spectrophotometry carried out in different studies have shown that the predominant compounds in the beans of both Arabica and Robusta are CGA and caffeine; in addition to these compounds, many important associated biological activities have been identified. The CGA content varies between 6% and 12% of the dry weight of green beans and gives astringency to the beverage (Farah & Donangelo, 2006; Górnaś *et al*., 2016; Mengistu *et al*., 2020). Another group of compounds identified in the coffee bean are the alkaloids caffeine and trigonelline (Tables 1 and 2, Figure 5 d, e); these compounds are responsible for bitterness and aroma in the final beverage. The concentration of trigonelline in seeds ranges between 0.39% and 1.77%, while that of caffeine ranges between 0.5% and 4% (Mengistu *et al*., 2020). Higher concentrations of trigonelline are found in *C. arabica* than in *C. canephora*, and 90% of this compound is degraded during roasting, forming mainly niacin, pyridines and some pyrroles (Hutachok *et al*., 2020; Mengistu *et al*., 2020). In Arabica and Robusta coffee beans, procyanidins, anthocyanins, mangiferin, tannins, lignans, catechin and epicatechin have been reported as minor compounds (Hutachok *et al*., 2020; Khochapong *et al*., 2021; Ontawong *et al*., 2019). The content of phenolic compounds and caffeine is related to the species of coffee, the soil where plants are grown, the harvesting process and the processing of the beans. In the species *C. arabica*, a higher content of CGAs (6.0-11.5%) was found, while in *C. canephora*, it was between 4.0 and 8.0%. Caffeine is found in greater quantities in the species Robusta between 1.7 and 4.0%, while in Arabica, its content is lower, ranging between 0.8 and 1.4% (Babova *et al*. 2016). The CGA content and the quality of beans depend on the altitude where plants are grown, which determines the time needed for the fruit to form and mature (Babova *et al*., 2016; Mengistu *et al*., 2020). *C. arabica* plants of the Typica and Bourbon varieties fertilized with nitrogen have higher caffeine contents (57.9 mg) than plants grown organically (48.1 mg of caffeine). On the other hand, the contents of polyphenols and phenolic acids are higher in organic crops (Table 3) because they act as a natural protection for plants (Górecki & Hallmann, 2020; Król *et al*., 2020). The content of chemical compounds in coffee beans also depends on the processing and storage of the beans, the time and level of roasting of the beans, and the type of preparation and extraction used to create beverages (Hutachok *et al*., 2020; Jeszka-Skowron *et al*., 2016; Várady *et al*., 2021). During the roasting of coffee beans, some of the chemical components in the beans are degraded; for example, the decrease in the content of phenolic compounds is correlated with the roasting temperature and time, and it has been reported that the CGA content is lower than 6%. The content of caffeine can vary between 1.2% and 2.4% (Hutachok *et al*., 2020; Mengistu *et al*., 2020). The compounds identified in the different varieties of *C. arabica*, such as Typica, Bourbon, Mundo Novo and Caturra, are the phenolic acids, flavonoids and caffeine, and their content depends on the crop area and type (Table 3). For chemical analyses, aqueous extractions of the beans have been performed, resulting in chlorogenic acids, caffeine, nicotinic acid, soluble melanoidins and hydrophilic volatile compounds. Chemical analyses of other components of coffee plants, such as peel, pulp and leaves have also been performed using organic solvents, such as methanol and ethanol, for the extraction of the compounds (Table 4). Compounds such as caffeine and ferulic, caffeic and CGA acids have also been found in the beans. Another species studied due to its importance and high demand in the market and widespread consumption is *C. canephora*; both green and roasted beans of this species as well as soluble coffee have been studied, highlighting the presence of CGAs and caffeine (Table 5).

Table 3. Chemical compounds and biological activity reported for infusions of beans from *Coffea arabica* varieties.

Variety	Extraction	Analysis method	Compounds	Biological activity	Reference
Typica-Bourbon	Infusion of roasted beans	HPLC	Total poliphenols Total phenolics acids Caffeic acid Chlorogenic acid Gallic acid Salicylic acid	Antioxidant - ABTS	Górecki & Hallmann, 2020
Catuai/Vermelho-amarelo	Infusion of green and roasted beans	Colorimetric and HPLC/PDA	Total phenolic Caffeic acid Caffeine Chlorogenic acid	Antioxidant - DPPH, FRAP, ABTS and ORA Antiproliferative in prostate cancer cell lines (PC-3 and DU-145)	Souza *et al*., 2020
Typica, Bourbon, Mundo Novo and Caturra	Infusion of roasted and ground beans	Colorimetric	Total phenolic Total flavonoids	Antioxidant - DPPH and ABTS	Ozuna *et al*., 2020

Table 4. Chemical compounds and biological activity reported in cherry, peel and leaves from *Coffea arabica* species.

Extraction	**Analysis method**	**Compounds**	**Biological activity**	**Reference**
Beans roasted with methanol 80%	Ultra-high resolution mass spectrometry (UHRMS)	Total polyphenolics Acrylamide Caffeine Heavy metals	Not reported	Várady *et al*., 2021
Hydroalcoholic (70%) of cherries	HPLC/UV	Caffeine Chlorogenic acid Trigonelline	Antioxidant - DPPH, FRAP, ORAC, HORAC; NORAC, SORAC and SOAC. Enzymatic inhibition of α-glucosidase, α-amylase and AChE activity	Nemzer *et al*., 2021
Ultrasound-assisted extraction with water, ethanol or water/ethanol from hulls	HPLC-UV/VIS	Total phenolic Total Flavonoids Condensed tannins	Antioxidant activity - ABTS, DPPH and FRAP	Silva *et al*., 2020
Silver film infusion of roasted beans	Ultra-High Performance Liquid Chromatography and Orbitrap High Resolution Mass Spectrometry Analysis (UHPLC-Q-Orbitrap)	Total phenolic Caffeine Chlorogenic acids Theobromine Theophylline Trigonelline Melanoidins	Antioxidant - ABTS, DPPH and FRAP	Castaldo *et al*., 2020
Extraction with methanol 70% of fresh and dry leaves	Colorimetric and HPLC-mass spectrometry (HPLC/MS)	Total phenolic content Total procyanidins Caffeine Chlorogenic acids	Antioxidant - DPPH	Ngamsuk *et al*., 2019
Leaves with methanol	HPLC/DAD and UV-spectrophotometry	Total phenolic content Total flavonoids Chlorogenic acid Mangiferin	Antioxidant-DPPH and FRAP and β-carotene/linoleic acid assays. Anti-inflammatory-Immediate-type hypersensitivity reaction in a histamine-induced ear edema model	Segheto *et al*., 2018
Pulp fermentation	Colorimetric	Total phenolic	Enzymatic activity-Expression of cellulolytic and xylanolytic enzymes	Peña-Maravilla *et al*., 2017

12 Compounds generated by roasting the beans

For the roasting of coffee beans, temperatures between 200 and 250 °C are applied for 5 to 20 min; these temperatures stimulate the Maillard reaction, Strecker degradation, pyrolysis and caramelization. The change in the color of the beans during roasting from blue-green to yellow, orange, brown and black is an indicator of the degree of roasting. Many acids are degraded in this stage, but high molecular weight compounds are also formed. The Maillard reaction is a nonenzymatic reaction between the amino groups of free amino acids such as asparagine, glutamic acid

Table 5. Chemical compounds and biological activity reported for beans from *Coffea* species.

Species	**Extraction**	**Analysis method**	**Compounds**	**Biological activity**	**Reference**
Coffea canephora	Aqueous due to overpressure of roasted beans	HPLC/MS	Mono-chlorogenic acids Di-chlorogenic acids	Antioxidant - DPPH Regulation of oxidative stress in βTC3 cell lines. Accumulation of lipids in 3T3L1 adipocyte lines	Budryn *et al.*, 2017
Coffea arabica and *Coffea canephora*	Green beans infusion	HPLC-DAD	Total phenolic Caffeine Chlorogenic acid	Antioxidant - CUPRAC	Jeszka-Skowron *et al.*, 2016
Coffea arabica and *Coffea canephora*	Infusion of roasted beans	HPLC and Colorimetric	Total phenolic acids	Antioxidant - FCR, MCA, DPPH, FRAP and TRAP	Górnaś *et al.*, 2016
Coffea arabica and *Coffea canephora*	Green beans/ethanol-water	HPLC/MS	Caffeine Chlorogenic acids	Antioxidant - DPPH	Babova *et al.*, 2016

Table 6. Chemical compounds and biological activity reported in the pulp of fruits of *Coffea arabica*.

Extraction	**Analysis method**	**Compounds**	**Biological activity**	**Reference**
Aqueous pulp	Spectrophotometry UV/vis	Total phenolic Anthocyanins Caffeine Chlorogenic acid	Antioxidant activity - DPPH and FRAP. Antimicrobial - test by disk diffusion method in *Escherichia coli* TISTR 780 and Staphylococcus aureus TISTR 1466.	Khochapong *et al.*, 2021
Pulp infusion	Colorimetric	Total phenolic content	Renoprotectors - Renal organic cation and anion transporter function in a rat model of DM2	Boonphang *et al.*, 2021
Pulp infusion	Colorimetric and liquid chromatographic-mass spectrometry (LC/MS)	Total phenolic content Caffeine Chlorogenic acid	Antioxidant - ABTS and DPPH Antibacterial - Determination of the minimum inhibitory concentration and the minimum bactericidal concentration in Gram-negative and Gram-positive bacteria	Duangjai *et al.*, 2016
Ethanolic extraction by sonication of pulp and husk	Colorimetric and HPLC	Total phenolic Caffeic acid Chlorogenic acid Total flavonoids Total tannins	Antioxidant - DPPH, ABTS and FRAP. Antifungal - *in vitro* and *in vivo* antifungal assays	Alvarado-Ambriz *et al.*, 2020
Pulp in 80% methanol, 80% acetone and 80% ethanol	Colorimetric	Total phenolic content	Antioxidant - DPPH	Geremu *et al.*, 2016
Methanolic fraction of a dichloromethane extract (95%) of pulp	HPLC - quadrupole-time of flight mass spectrometry (QTOF)	Total phenolic content Caffeic acid Caffeine Epigallocatechin gallate *p*-coumaric acid Total flavonoids	Antioxidant - ABTS and DPPH Antifungal against *Alternaria brassicicola*, *Pestalotiopsis sp.* and *Paramyrothecium breviseta*.	Sangta *et al.*, 2021

and aspartic acid and the carbonyl groups of reducing sugars such as glucose and fructose, giving rise to compounds such as melanoidins and acrylamides (Endeshaw & Belay, 2020; Várady *et al*., 2021). Melanoidins give the beans a brown pigment and flavor and color to the beverage. In addition, these compounds are associated with antioxidant activity that is enhanced by simple phenolic compounds such as caffeic, ferulic and chlorogenic acids binding to their structure. Acrylamides are considered toxic pollutants since they can be carcinogenic or genotoxic (Castaldo *et al*., 2020; Várady *et al*., 2021).

13 Agroindustrial residues or coffee by products

During the cultivation and processing of coffee fruits, products such as leaves, pulp, silver skin and peel are discarded and are considered agro-industrial waste. These byproducts have been used to generate compost or organic fertilizer used to fertilize crops; some of the compounds reported in beans, such as CGA and caffeine, as well as other compounds, such as epicatechin, catechin and anthocyanins, have been found in these residues (Table 6). (Boonphang *et al*., 2021). These compounds, which have repellent and antifungal or allelopathic effects, can act as a defense against insects and pathogens in cultivated plants (Li *et al*., 2022). In aqueous extracts of *C. arabica* pulp, the contents of epicatechin (0.18 mg) and catechin (0.26 mg) per gram of pulp were determined (Ontawong *et al*., 2019); in leaves of *C. arabica* extracted with 70% methanol, the content of catechin and epicatechin was 2.24 mg/g of leaves (Ngamsuk *et al*., 2019). The theobromine (0.3 mg/g) and theophylline (0.1 mg/g) contents in the silver skin of *C. arabica* were reported; these alkaloid compounds serve as ingredients in energy drinks (Castaldo *et al*., 2020).

14 Biological activities of coffee

Naturally, the phenolic compounds in the leaves of *Coffea* (Table 7) are not only active during various phenological stages and plant growth but also act as a defense mechanism against external factors such as infection by pathogens or pests (Segheto *et al*., 2018). The main biological properties reported for coffee infusions are associated with antioxidant, anti-inflammatory, antidiabetic, antibacterial, and anticancer activities, among others (Jeszka-Skowron *et al*., 2016; Khochapong *et al*., 2021). Oxidative stress is a trigger for chronic degenerative diseases such as diabetes, cancer, aging, inflammatory diseases and cardiovascular diseases (Nemzer *et al*., 2021). The antioxidative properties of coffee infusions have been studied using classical and widely used *in vitro* techniques; these properties are mainly attributed to CGA and caffeine, although other compounds that influence antioxidative properties, such as epicatechin, catechin and anthocyanins, have also been reported (Hutachok *et al*., 2020; Nemzer *et al*., 2021).

Table 7. Biological activity of the main compounds of *Coffea* species.

Compounds	**Biological activity**	**Reference**
Chlorogenic acid	In plants, it acts as a defender against microorganisms and protects against UV rays Improves glucose and lipid metabolism Antioxidant Anti-inflammatory	Bhandarkar *et al*., 2019; Stefanello *et al*., 2019; Vázquez-Sánchez *et al*., 2018
Caffeine	CNS stimulant Improves glucose and lipid metabolism	Ludwig *et al*., 2014; Nuhu, 2014
Melanoidins	Antioxidant	de La Cruz *et al*., 2019
Trigonelline	Anticancer Anti-hyperglucemic Analgesic	Nuhu, 2014
Catechin and epicatechin	Naturally, they act as a defense against insects and pathogens in crops, showing antifungal and repellent actions Antioxidant Antimicrobial properties	Li *et al*., 2022

The anti-hyperglucemic effect of coffee cherry extract and roasted bean waste of *C. arabica* has been attributed to the inhibitory activity of the enzymes α-glucosidase and α-amylase (Nemzer *et al*., 2021; Vázquez-Sánchez *et al*., 2018). Likewise, glucose regulation by CGA is mediated by the inhibition of glucose-6-phosphatase activity to reduce glucose production in the liver. Another regulatory pathway is the decrease in the expression of sodium-dependent glucose transporters to reduce their absorption in the small intestine (Bhandarkar *et al*., 2019). The apoptotic, anti-inflammatory and neuroprotective potential of aqueous extracts of green and roasted coffee was demonstrated in a rat ischemia model; the administration of these extracts reduced serum glucose levels after ischemia/perfusion surgery. The pro-apoptotic markers Bax and caspase-3 decreased due to the intake of coffee extracts; simultaneously, the anti-apoptotic protein was overexpressed. Both extracts improved neuronal function and survival; improvements were associated with reductions in oxidative stress by measuring the levels of NO, a marker of neuropathy and the marker of lipoperoxidation, malondialdehyde. The extracts also increased the levels of the antioxidant enzymes catalase and superoxide dismutase (SOD) and reduced the levels of the pro-inflammatory cytokines nuclear factor kappa B (NF-κB) and tumor necrosis factor-alpha (TNF-α) (Rizk *et al*., 2021). The effect of green coffee of the species *C. arabica* on testicular damage was evaluated in a diabetic rat model. The levels of testosterone, luteinizing hormone and follicle-stimulating hormone were reduced in diabetic rats and increased after the administration of the green coffee infusion. The levels of the antioxidant markers glutathione, SOD, catalase, glutathione peroxidase and glutathione reductase increased, while the levels of NO and malondialdehyde decreased. The levels of anti-inflammatory markers (IL-1β and TNF-α) and apoptotic markers (Bax and caspase-3) also decreased, which reduced testicular damage (Al-Megrin *et al*., 2020). In studies conducted with the pulp of *C. arabica*, CGA, catechin, and polyphenols were the main compounds found. The aqueous extract of the pulp of this species was evaluated in a diabetic rat model; the extract reduced the levels of glucose and triglycerides in plasma and improved insulin resistance. Likewise, it reduced renal damage by offering a renoprotective effect by modulating the function of transport proteins that reduce the accumulation of triglycerides in the kidney and lipid peroxidation and oxidative stress in renal epithelial cells through the modification of the mRNA expression of antioxidant enzyme genes, specifically catalase and Cu-Zn-dependent SOD (Boonphang *et al*., 2021). The extracts of different infusions of roasted *C. arabica* beans inhibited the platelet aggregation induced by adenosine diphosphate (ADP), collagen, epinephrine and arachidonic acid in a dose-dependent manner. Likewise, they showed a greater inhibition in the activity of the cyclooxygenase (COX) enzymes COX-1 and COX-2 than CGA and caffeine standards, indicating that the CGA and caffeine present in the extract can act synergistically in anti-inflammatory and antioxidant processes (Hutachok *et al*., 2020). In a study using the aqueous extract of the pulp of *C. arabica* fruits, the antimicrobial and antioxidant evaluation of the extract was carried out before and after being subjected to an *in vitro* digestion model. The extract inhibited the growth of *Escherichia coli* TISTR 780 and *Staphylococcus aureus* TISTR 1466 bacteria; the evaluation with the digested extract reduced the antimicrobial activity against *E. coli* and *S. aureus*, however, for *Lactobacillus acidophilus* TISTR 1338 showed no effect before and after digestion. The antioxidant activity of the extract was reduced after the digestion process. The biological activity is related to the number of compounds present in the extract since their content decreased in the digested extract (Khochapong *et al*., 2021). Methanolic extracts of *C. arabica* pulp showed fungicidal activity against *Alternaria brassicicola* (IC_{50}=0.09 g/mL), *Pestalotiopsis sp* (IC_{50}=0.31 g/mL) and *Paramyrothecium breviseta* (IC_{50}=0.14 g/mL). Similarly, ethanolic extracts of pulp and peel (1.0-2.0 mg/mL) of *C. arabica* inhibited ~80%) the growth of *Aspergillus niger*, *Botryris cinerea* and *Rhizopus stolonifer*. In the *in vivo* assay using strawberries as substrate (0.4 and 2.0 mg/mL), the ethanolic extract inhibited the development of fungi in a similar way to carbendazim (methyl benzimidazole-2-yl carbamate), a systemic fungicide. Methanolic and ethanolic extracts from coffee residues are an alternative for fungal control in various crops, including coffee (Alvarado-Ambriz *et al*., 2020; Sangta *et al*., 2021). Trigonelline reduced the blood glucose levels in a rata model of diabetes mellitus and it also shown beneficial effects in rats displaying peripheral neuropathy. This compound induces apoptosis as an inhibitor of Nrf2 gene transcription in pancreatic cancer (Nuhu, 2014).

It has a proven antidiabetic effect; its administration to model rats suffering from diabetes mellitus has resulted in reduced blood glucose levels in oral glucose tolerance test. It has also shown beneficial effects in rats displaying peripheral neuropathy, a condition for which there is no effective drug for its treatment. Its function as an inhibitor of Nrf2 gene transcription has caused pancreatic cancer cells to be more susceptible to cell death through apoptosis (Nuhu, 2014).

15 Chlorogenic acid and caffeine as the main components of coffee

Caffeine and CGA are the main chemical components within the genus *Coffea* (Figure 5). The CGA compounds are formed by esterification of *trans*-cinnamic acids (caffeic acid or ferulic acid) with quinic acid, from which subclasses of caffeoylquinic (CQA), feruloylquinic (FQA) and dicafeoylquinic (diCQA) acids are formed (Babova *et al*., 2016). Chlorogenic acid (5-CQA) is found in high concentrations (6-12% of the dry weight) in green coffee beans (*C. arabica*) and degrades during the roasting process; the content of 5-CQA depends on the roasting temperature (Ruiz-Palomino *et al*., 2019). In green beans *C. canephora* from Uganda, 3 CGAs were identified and quantified: acid 3-*O*-cafeoylquinic (3-*O*-CQA), 4-*O*-caffeoylquinic (4-*O*-CQA) and 5-*O*-caffeoylquinic (5-*O*-CQA). The predominant CGAs were 5-*O*-CQA, with a 77% of the total content and 4-*O*-CQA with a 13%, while 3-*O*-CQA a 10% of the total content. These CGAs were found in very similar proportions in Arabica coffee from Brazil (Jeszka-Skowron *et al*., 2016). During the process of coffee roasting, CGA can be isomerized, hydrolyzed or degraded into low molecular weight compounds (Farah & Donangelo, 2006). For Robusta coffee, the total content of CGAs (monochlorogenic and dichlorogenic) in a green bean extract was 54.35%; in beans roasted at 230 °C for 12 min, the CGA content was reduced by 24% (Budryn *et al*., 2017). Depending on the species, the form of extraction and the roasting process, between 70 and 350 mg of CGA can be ingested in a 200 mL cup of coffee, 30% of which is absorbed in the small intestine; the rest reaches the colon, where it can be hydrolyzed by the intestinal microflora to obtain caffeic acid and quinic acid, compounds with antioxidant properties (Godos *et al*., 2014). It has been determined that the antioxidative properties of caffeine are related to increased levels of reduced glutathione (GSH) due to greater absorption of cysteine in the presence of caffeine and its ability to eliminate reactive oxygen species (ROS), particularly the hydroxyl radical (-OH), it is the main target being the adenosine receptors involved in the regulation of ROS production (Stefanello *et al*., 2019). In *in vivo* tests, antioxidant activity has been determined based on the actions of regulatory enzymes that protect against oxidative damage, such as SOD and GHS reductase (Al-Megrin *et al*., 2020; Choi *et al*., 2018; Kwak *et al*., 2018; Nemzer *et al*., 2021). Other functions associated with CGA are anti-inflammatory activity and the regulation of glucose and lipid metabolism (Bhandarkar *et al*., 2019). In metabolic syndrome conditions, CGA has beneficial effects on glucose and lipid metabolism. In the case of lipids, it reduces serum and hepatic levels of cholesterol and triglycerides, inhibits fat absorption and activates fat metabolism in the liver (Sarriá *et al*., 2018). The effect of the inhibition of glucose-6-phosphate by CGA has helped in the regulation of blood glucose, its absorption in the small intestine, and the degradation of glycogen, making it a potential agent for the treatment of diabetes. In skeletal muscle, CGA is an important activator of the AMP-activated kinase (AMPK) pathway, increasing the gene expression of glucose transporters (GLUT-4) and therefore reducing blood glucose levels (Naveed *et al*., 2018). *in vitro* studies were used to assess the inhibition of α-glucosidase and α-amylase using an extract of the coffee cherry (*C. arabica*), CGA and acarbose, a drug used in diabetic patients. The treatments inhibited both enzymes, presenting mean inhibitory concentrations (IC_{50}) in the α-glucosidase test of 33 mg/mL, 2.1 mg/mL and 1.25 mg/mL for the extract, CGA, and acarbose, respectively; in the tests of α-amylase, the IC_{50} values were 15 mg/mL for the extract, 2.8 mg/mL for CGA and 0.008 mg/mL for acarbose (Nemzer *et al*., 2021). Caffeine (1,3,7-trimethylxanthine) is a heterocyclic alkaloid that has a purine base known as xanthine (Figure 5d). Caffeine exerts several physiological effects in humans, most of them associated with the functions of the central nervous system (Jung *et al*., 2021). Caffeine acts as an antagonist of adenosine receptors in the brain; this function is better known as neuromodulation and enhances energy expenditure (Hu *et al*., 2019). In green beans of *C. arabica*, caffeine contents up to 1.45% have been reported, while in the species *C. canephora*, caffeine contents up to 2.38% have been reported (Babova *et al*., 2016). In Arabica coffee from Brazil, 36.2 g of caffeine per kg of the extract was observed; in Robusta beans from Vietnam, the content was 74.3 g/kg (Jeszka-Skowron *et al*., 2016). In the Typica and Bourbon varieties of *C. arabica*, 73% of the caffeine contents were preserved in a light roast, while in medium and dark roasts, the caffeine content was reduced by 58% and 28%, respectively (Górecki & Hallmann, 2020). The caffeine contents in a beverage will depend on the type of mixture and the water/coffee ratio. In a cup of Arabica coffee (150 mL) made with drip infusion (one of the most widely consumed beverages), the caffeine content can range from 80-120 mg; in espresso coffee, the content can range between 50 and 100 mg. (Pietsch, 2017). Studies have shown that the consumption of 400 mg of caffeine per day can benefit health by reducing the risk of Parkinson's disease, Alzheimer's disease and type 2 diabetes mellitus (Awwad *et al*., 2021).

Conclusions

Coffee infusions from green or roasted beans of *C. arabica* and *C. canephora* are the most consumed beverages in the world. The species *C. arabica* and *C. canephora* are predominant in the market and the largest producer countries are not the main consumers. Mexico is a minority producer of coffee due to people prefers consume soluble coffee made with Robusta coffee (*C. canephora*) with high content of caffeine and low content of chlorogenic acid. The Mexican government has promoted the coffee infusion consummation and cultivation of coffee plants. The State of Guerrero is a producer of high-altitude and organic coffee by indigenous populations. Despite controversy related to potential adverse effects from coffee on the central nervous system that have been attributed to caffeine, chemical-biological studies have shown that coffee has important biological properties, such as antioxidant, anti-inflammatory, anti-hyperglucemic and lipid-lowering activities. The compounds responsible for these pharmacological effects are mainly phenolic acids (CGA, caffeic acid, ferulic acid, catechin and epicatechin), whose content is related to the species, cultivation conditions and processing of the beans. Because of the evidence presented herein, it is suggested that infusions of *C. arabica*, which is low in caffeine and high in CGA, can provide compounds that benefit the health of consumers, although it is important to consider the method used for its preparation.

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