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Coffea arabica: A Plant with Rich Content in Caffeine

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Abstract

Coffea arabica L. is the most well-known and studied *Coffea* taxa, which is very popular in both scientific and social fields. This comprehensive work was created in order to describe its phytochemical composition and to present the metabolism of caffeine, which is the most important alkaloid from this plant. The analytical methods used for caffeine determination such as chromatographic, electrochemical, and spectroscopic techniques are also presented. In addition, this work emphasizes the medicinal importance of caffeine, which can present both important beneficial and secondary effects for human body.

Keywords: caffeine, coffee, phytochemistry, analytical methods, *Coffea arabica*, medicinal importance

1. Introduction

Coffea species are well-known tropical plants, which are mostly used for preparing the famous beverage called coffee. Coffee plants present a tremendous importance in the scientific, agricultural, social, and commercial fields being on the second place after petrol in the international market [1].

The genus *Coffea* belongs to the Rubiaceae family and comprises up to 124 species. The most famous and used species are *Coffea arabica* L., *Coffea robusta* L. Linden (syn.: *Coffea canephora* Pierre ex A. Froehner), and *Coffea liberica* Hiern. (syn.: *Coffea dewevrei* De Wild. & T. Durand) [2, 3]. Nowadays, the Arabic coffee makes up to 75% from the total coffee production of the world; meanwhile, the Robusta coffee makes up to 24%, and the Liberian coffee 1%, respectively [4].

There are some legends about the discovery of coffee seeds and their utilization as beverage and food. The coffee seeds initially were consumed as snacks. The seeds were mixed with animal fat, and these were eaten by people during their long trips [5]. A kind of wine was also obtained from the fermented fruits of coffee [6]. One story tells that in the fifteenth century, there was a goat herder who noticed the stimulating effect of the coffee fruits when his goats ate these berries. He went to the nearest monastery to tell the monks his experience and they started to drink it during their long morning prayers [5].

The caffeine consumption has a long history dating back to antiquity. There are more than 60 plant species, which have been identified as containing caffeine. Plants like coffee, guarana, yoco, mate, and cassina were successfully used for the preparation of caffeine-containing beverages. According to history, tea is the oldest caffeine-containing beverage which had already been mentioned by the Chinese emperor Shen Nung in 2737 B.C., and it had been listed in a Chinese dictionary in about 350 AD [6].

The Arabic countries used to prohibit the consumption of coffee among men by referring to the Koran. In the sixteenth century, special places were established in Constantinople where Turkish dignitaries were served with coffee. As Turkish men spent a lot of time in these establishments, the mosques began to be abandoned, so imams opposed to the coffee consumption, which was forbidden by a law ordered by Muhammad. Due to this reason, Sultan Murad banned the coffee consumption, but later this law was modified when the use of tobacco started to become more popular [7].

Nowadays, approximately 7 million tons of coffee is used for the preparation of the famous coffee beverage according to Food and Agriculture Organization of the United Nations [8].

2. *Coffea arabica* L.: geographical distribution, cultivation, and processing

Coffea species belong to the Rubiaceae family, which includes 450 genera and more than 6500 species. *Coffea* species are originated from Africa and Madagascar being cultivated in both Ethiopian and Yemen regions as the geographical and climate conditions are the same. Then, they have also spread in other continents and nowadays they are present in all the tropical and subtropical regions, including Australia and China. It is interesting that wild species do not occur in America, native taxa are found only in Africa and in the South Asian regions [2, 9]. They grow in forests at an altitude of 950–2000 m and at 18–22°C, the most favorable altitude being between 1300 and 1600 m [2, 3, 10]. There are also coffee shrubs, which are cultivated at higher regions, and they are named "high grown" coffee with an outstanding quality [11].

The coffee crops are spread in Central and South America, Africa, and Asia leading to a total of about 11 million hectares of plantations and an annual yield of about 6 million tons of green coffee [11]. *C. arabica* is often cultivated in large-scale plantations and in small holder farms too. In addition, they are also planted on cooler mountain ranges, at the base of shady trees, which protect them against strong sunlight. A shrub plant yields well for more than 20 years, and the ripe and red fruits are individually hand-picked [12].

Coffee products are processed in two methods: wet and dry processes. The dry procedure is popular in Brazil and the other one in Central America. During the dry method, the fruits are dried in open air for 2–3 weeks before the fermentation step [11, 13]. In addition, the wet method can be used only for ripe fruit as the fermentation positively affects the quality of seeds, external morphological aspects, and the taste [11, 13].

The roasting process, which is responsible for the characteristic aroma of the seeds, takes place only in customer country at 200–250°C [14]. This roasting process presents three phases such as an initial drying phase (during this endothermic step, the wet is eliminated and the color is turned yellowish), the roasting phase (based on several complex pyrolytic reactions resulting in many chemical compounds which will confer the coffee aroma and taste, the beans are transformed to dark brown during exothermic and endothermic phases), and the cooling phase (using air or water in order to end the last exothermic process [14].

3. Phytochemical features of *Coffea arabica* L.

The plant part of the coffee being officially used is the seed (*Coffeae semen*), which contains among other compounds polyphenols and alkaloids as biologically active substances. These two groups of chemicals made coffee popular in both scientific and social fields. The chemical composition of coffee seeds contains a large variety of substances among which the most representative groups are purine alkaloids (caffeine, theobromine, theophylline), polyphenols (chlorogenic acid, caffeic acid, etc.), alkaloids (trigonelline), fatty oil, carotenoids, enzymes, phytosterols (sitosterol, dihydro-sitosterol, stigmasterol), tannin, wax, carbohydrates as monosaccharides (fructose, glucose, etc.), oligosaccharides (sucrose, etc.) and polymers (cellulose, hemicelluloses), and nonvolatile and volatile aliphatic acids (citric, oxalic, acetic, isovaleric, decanoic acids, etc.) [2, 15]. In addition, they contain also some minerals such as K (40%), P (4%), Na, Mg (with variation between species), Ca, and S; and trace minerals with a variation according to the soil composition such as Zn, Sr, Mn, Fe, Cu, Ba, B, and Al. Nicotinic acid (vitamin PP) is formed from trigonelline demethylation during roasting process [15].

The characteristic aroma of coffee appears during the roasting process. The principal volatile compounds include derivatives of: sulfur (thiols, hydrogen sulfide, thiophenes, thiazoles), pyrazine (pyrazine itself, thiol and furfuryl derivatives, alkyl derivatives), pyridine, pyrrole, oxazole, furan, aldehydes, ketones, and phenols [14, 15]. Caffeine is present in all plant parts with the highest concentration in the immature seeds. This alkaloid with a bitter taste can be quantitatively reduced during the roasting and decaffeination processes [16].

Caffeine can present autotoxic and inhibiting effect on the mitosis and cell plate formation in rootlet. Studies demonstrated that the cell divisions in root tips started only after that it was pushed away from the caffeine-rich endosperm by elongation of the hypocotyl and maintained through the cell elongation. Caffeine is introduced into the embryonic cotyledons mostly after the cell division is completed there [17]. Some authors suggested that the physiological significance of caffeine could be the prevention of predation by animals and these alkaloids function as allochemicals in the pericarp and seeds [18]. Josef et al. mentioned in their work about insecticidal effect of caffeine, which can also synergize the effects of pesticides [19].

Polyphenols are another representative group from the coffee seeds composition containing kaempferol, quercetin, ferulic, sinapic, nicotinic, quinolic, tannic, and pyrogallic acids which present important effects such as antioxidant, hepatoprotective, antibacterial, antiviral, anti-inflammatory, and hypolipidemic ones [2, 20–27]. In addition, caffeic, chlorogenic, p-coumaric, ferulic and sinapic acids, rutin, quercetin, kaempferol, and isoquercitrin were identified in fruits of *C. arabica* and *C. benghalensis* Roxb. ex Schult. The nonhydrolyzed extract of the pericarp of both species presented important quantities of chlorogenic acids [28].

In one of our previous study, a high phenolic content was observed in the immature pericarp of *C. benghalensis* and *C. liberica* compared with that of *C. arabica.* In addition, the immature pericarp of Bengal coffee and the immature seed of Arabic coffee showed a significant polyphenol content too [29]. Other phytochemical studies showed that the total hydroxycinnamic acid content of *C. arabica* was significantly higher than that of *Coffea sessiliflora* Bridson, *Coffea resinora* Hook.f., and *Coffea leroyi* A.P.Davis. The mangiferin, isomangiferin and caffeoylquinic acid were present in higher concentration in the young leaves than in other plant parts [30–32]. *Coffea anthonyi* Stoff. & F. Anthony and *Coffea salvatrix* Swynn. & Philipson presented higher concentration of mangiferin than *C. arabica*, *Coffea eugenoides*, *Coffea heterocalyx* Stoff., *Coffea pseudozanguebariae*, or *C. sessiliflora*. Campa et al. studied the mangiferin and hydroxycinnamic acid ester content in 23 *Coffea* leaves. Their histochemical observations revealed that mangiferin was present in low concentration in *C. arabica* mainly in the exocarp, mesocarp, and fruits [30, 33]. Alves et al. determined that, even though 90% of tocopherols content remains unchanged after the roasting process of Arabica and Robusta coffee seeds, the concentration of β-tocopherol is reduced by 25% in Robusta coffee, aspect which can be used as a discrimination tool between the two *Coffee* species [34].

4. Metabolism of caffeine in *Coffea arabica* L.

4.1. Biosynthesis of caffeine

Caffeine biosynthesis takes place in the upper leaves and in the pericarp, and it is absent in the second and third leaves, cotyledons, lower stem, and root. After the biosynthesis, caffeine is accumulated in the mature leaves of coffee, but when the seed starts growing inside the fruit, it is translocated through the membranes being accumulated in the endosperm. The final quantity of caffeine is reached in 8 months after flowering [10, 35]. *C. arabica* leaves have the highest caffeine content, meanwhile *C. salvatrix*, *C. eugenioides*, and *C. bengalensis* leaves contain three to seven times lower concentrations [36].

The caffeine biosynthesis in leaves is age-dependent which means that it occurs usually at the very early stages of the leaf development reaching a maximum when the leaves are fully opened. The same age-dependent biosynthesis was observed in the fruits of coffee and in the leaves, flowers, and fruits of tea plants. Naoko and Hiroshi studied the levels of purine alkaloids and the metabolism of adenine in the first and in the second leaves from the shoot apices of coffee plants. Even though theobromine and caffeine were found in these leaves, theophylline was not detected. Studies showed that adenine was converted to theobromine and caffeine in the first leaves and the degradation of adenine nucleotides was low in both types of leaves [18].

Caffeine is 1, 3, 7-trimethylxanthine having a xanthine skeleton derived from purine nucleotides. The purine compound initially involved in the biosynthesis pathway of caffeine is xanthosine, which is a substrate for the methyl group donated by *S*-adenosyl methionine (SAM). The most important pathway for caffeine biosynthesis, which was proposed by Hiroshi and Thomas, is as follows: xanthosine → 7-methylxanthosine →7-methylxanthine → theobromine → caffeine. The first methylation step is the conversion of xanthosine to 7-methylxanthosine being catalyzed by 7-methylxanthosine synthase (an N-methyltransferase). The next step of 7-methylxanthosine hydrolysis to 7-methylxanthine is catalyzed by methylxanthine nucleosidase. The conversions of 7-methylxanthine to theobromine and then theobromine to caffeine are catalyzed by N-methyltransferases (firstly identified 26 years ago by Takeo Suzuki and Ei-ichi Takahashi). The caffeine synthase is a monomeric enzyme with an optimum pH of 8.5. This enzyme is not inhibited by caffeine, but instead, there is a complete inhibition by low concentrations of S-adenosyl-L-homocysteine (SAH), therefore its activity is regulated by SAM:SAH ratio. Caffeine synthase is found in chloroplast, but it is not affected by light, thus the caffeine synthesis takes place also in darkness [35, 37]. By summing up, the N-methyltransferases, which are involved in caffeine biosynthesis pathway, are: 7-methylxanthine 3-N-methyltransferase, caffeine xanthine methyltransferase 1, caffeine methylxanthine methyltransferase 2, and caffeine dimethylxanthine methyltransferase [38].

The caffeine synthesis is affected mostly by the enzymes activity, which can appear as limiting factors in the biosynthesis: xanthosine N-methyltransferase, 7-methylxanthosine nucleosidase, 7-methylxanthine N-methyltransferase, and theobromine N-methyltransferase. The observation from the tea leaves indicated that their activity is also affected by seasons [18]. Caffeine accumulation seems to be regulated by the genes, which encode N-methyltransferase and caffeine (7-N) demethylase [36].

4.2. Catabolism of caffeine

The catabolism of caffeine is a slow process, which begins with the removal of the three methyl groups from the skeleton resulting in xanthine which is further decomposed to CO_2 and NH_3. These degradation reactions are catalyzed by various demethylases that have different levels of activity in the *Coffee* species (higher in *C. eugenioides* than in *C. arabica*). The major rate-limiting step in caffeine catabolism is the caffeine conversion into theophylline [35]. Catabolism pathways involve the conversion of caffeine into theophylline, 3-methylxanthine, xanthine, uric acid, allantoin, allantoic acid, urea and finally results in CO_2 + NH_3 [36].

Even though the degradation of caffeine is negligible in the leaves of *C. arabica*, *C. salvatrix*, and *C. bengalensis*, the leaves of *C. eugenioides* with low caffeine content metabolize caffeine rapidly by degradation to CO_2 within 24 hours. The explication could be that this taxon contains higher levels of N-7-demethylase than *C. arabica*; therefore, caffeine is efficiently converted to theophylline being quickly metabolized afterwards [35, 36].

The catabolism of caffeine can also be achieved by various bacteria like *Pseudomonas cepacia*, *Pseudomonas putida*, and *Serratia marcescens*. Bacterial degradation is different from other

pathways since caffeine is transformed to theobromine, after that to 7-methylxanthine, xanthine, and finally to NH_3. The conversion of caffeine to theobromine is catalyzed by N-1-demethylase, which was successfully isolated from *Pseudomonas putida* [35].

Some studies elaborated by Suzuki also showed that theophylline and xanthine were more quickly metabolized in the immature fruit; meanwhile, the caffeine degradation was performed in both mature and immature coffee fruits. The results showed that adenine was a more effective precursor than guanine and L-methyl-methionine for the biosynthesis of N7-methylxanthine, theobromine, and caffeine. These results underlined that the caffeine biosynthesis occurred mostly in immature fruits through methylation of N-methylxanthine and theobromine; meanwhile, its biodegradation occurred through theophylline, which is accumulated after that the seed is full size and the fruit is mature [39].

5. Analytical methods used for caffeine determination

Caffeine is a deeply studied alkaloid and, as it presents a significant importance for science and human body, many analytical methods have been developed over the years for its determination. The aim of these analytical methods was to identify and quantify this compound with different origin (from plants, beverages, and medicines). The most important and the most used techniques are the chromatographic methods coupled with spectrometry which allow a qualitative and quantitative determination of caffeine. Since these methods are quite expensive, there are a lot of scientific reports about different new low cost techniques. Electroanalytical methods recently became more popular since they are faster, more convenient, present lower costs, and are environmentally friendly in comparison with the other conventional analytical methods.

5.1. Chromatographic methods

The biochemical diversity of wild accessions of *C. arabica* (38 genotypes) and *C. canephora* (38 genotypes) was analyzed by high performance liquid chromatography (HPLC) method by Ky et al. The analyzed compounds responsible for coffee aroma were caffeine, trigonelline, chlorogenic acids, and sucrose. Sucrose was analyzed using anion-exchange chromatography coupled to pulsed amperometric detection. An aqueous solution (containing triethylamine and acetic acid) and methanol were used as mobile phases for caffeine and trigonelline, meanwhile their ultraviolet (UV) detection was carried out at 272.8 nm (maximum absorption of caffeine) and 263.3 nm (trigonelline maximum absorption) wavelength. *C. arabica* contained more trigonelline and sucrose, meanwhile *C. canephora* presented higher concentration of chlorogenic acids and caffeine. The results underlined that *C. canephora* has a higher compounds diversity than *C. arabica* excepting trigonelline and sucrose. In addition, there were not identified differences for alkaloids and sucrose between *C. canephora* accessions [40].

Mazwfera et al. used HPLC method for qualitative and quantitative determinations of caffeine, theobromine, and theophylline in aqueous extracts of endosperm from immature and mature fruits of *C. arabica*, *C. canephora*, *C. benghalensis*, *C. dewevrei*, *C. eugenioides*, *C. stenophylla*, and *C. salvatrix*. The highest concentration of caffeine was found in *C. canephora* in

both immature and mature endosperms; meanwhile, caffeine was not detected in extracts of *C. bengalensis* mature fruit. Moreover, caffeine was more slowly metabolized by *C. arabica* and *C. canephora* immature endosperm than the other five species [41].

Nowadays, science also pays attention for low-pressure chromatography, which presents advantages such as easier assembly and handling, lower implementation cost, and more widespread application regarding separation of neutral or ionic compounds than other separation techniques. By using this method, caffeine was determined from six different coffee beverages: three regular, one decaffeinated, one soluble, and one chicory blended coffees. The results showed similar values for caffeine compared with the reference method (HPLC-UV) with 5% relative deviations, with no signal for theobromine or theophylline. Even though low-pressure chromatography uses a short column which implies reduced resolution, this methodology can be a competitive alternative to usual HPLC for caffeine determination in different materials due to its advantages such as higher determination rate, lower consumption of reagents, and no need to degas the mobile phase [42].

5.2. Spectroscopic methods

Frizzarin used the dispersive liquid-liquid microextraction and spectrophotometric determination for caffeine in different coffee beverages. This lab-in-syringe sequential injection analysis system is a fast and simple procedure, which uses dichloromethane with high extraction capacity and good selectivity and methanol as dispersing agent. The developed technique presented linear response range from 2 to 75 mgL^{-1}, limit of detection of 0.46 mgL^{-1} and limit of quantification of 1.54 mgL^{-1}, being successfully applied for caffeine determination from brewed, instant, and decaffeinated coffee samples [43].

For the determination of caffeine, formic acid, trigonelline, and 5-(hydroxyl-methyl) furfural, there was applied the proton nuclear magnetic resonance technique (1H NMR) without any derivatization. The limits of detection were 1.32 mg/g for caffeine, 0.58 mg/g for trigonelline, and 0.30 mg/g for 5-(hydroxyl-methyl) furfural. In addition, HPLC was also used for the determination of these compounds employing a diode-array detector at 273 nm for caffeine, 265 nm for trigonelline, and 284 nm for 5-(hydroxyl-methyl) furfural [44].

Alesso used spectrofluorimetric method for caffeine determination, which was developed by using the quenching effect on fluorescent emission of bovine serum albumin molecule (λ_{em} = 338 nm, λ_{ex} = 280 nm). During the investigation, the sampling rate was increased to 60 samples/hour using potassium dihydrophosphate buffer (pH 6.8) as carrier with a flow rate of 1.5 $mLmin^{-1}$. Several parameters were optimized such as the nature and the concentration of both the buffer and the fluorophore, and the carrier flow rate, leading to a linear range from 6.68×10^{-6} to 4.0×10^{-3} $molL^{-1}$. This sensitive and selective method was successfully employed for caffeine determination from various matrices such as energy drinks, dietary supplements, and slimming infusion samples without any pretreatment [45].

A comparative study about caffeine content in roasted ground coffee and in China black tea was performed using a liquid-liquid extraction. A simple and rapid spectrophotometric method was described for the determination of caffeine indicating that caffeine concentration in roasted coffee is lower than its concentration in black tea [46].

5.3. Electrochemical methods

Rotko and Beczkowska elaborated a Nafion covered lead film sensor leading to a sensitive, selective, and low cost method applied for caffeine determination in tea, coffee, soft and energy drink samples, and pharmaceutical products. Two anodic peaks were detected at 0.86 and 1.40 V (versus Ag/AgCl) in acidic medium, and the corresponding detection limits were equal to 1.7×10^{-8} and 2.2×10^{-7} molL^{-1}, respectively, at 120 seconds of accumulation time. The results were in good agreement with the concentrations mentioned by the manufacturer and with those reported by using the spectrophotometric method [47].

Similar studies were reported by Gao et al. who modified a glassy carbon electrode (GCE) with large mesoporous carbon and Nafion composites (LMC/Nafion) achieving a simultaneous determination of theophylline and caffeine in serum and beverages. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were employed for the investigation of the electrochemical behaviors of theophylline and caffeine on the LMC/Nafion/GCE. Simultaneous determination of these two alkaloids was successfully obtained at the modified electrode since peak-to-peak separation of the two DPV peaks was about 150 mV. The sensor performances included detection limits of theophylline and caffeine of 0.37 and 0.47 μM, and a linear range between 0.8–180.0 and 1.3–230.0 μM, respectively [48].

The boron doped diamond electrode was also successfully used for simultaneous determination of caffeine and chlorogenic acid by CV and adsorptive stripping voltammetry, applied on commercial beverages. Various experimental parameters such as dependence of peak current and potential on pH, scan rate, and accumulation time were optimized. The oxidation peak potentials of caffeine and chlorogenic acid from binary mixtures were separated with 0.4 V in acidic medium by employing square-wave stripping voltammetry. The analytical performances of this sensor indicated detection limits of 0.107 mgmL^{-1} ($5.51 \cdot 10^{-7}$ M) for caffeine and of 0.448 mgmL^{-1} (1.26×10^{-6} M) for chlorogenic acid [49].

Samanidou reviewed in her work several electroanalytical methods for caffeine determination. One example was constituted by polymer-modified glassy carbon electrode, which was electropolymerized with 4-amino-3-hydroxynaphthalene sulfonic acid. This sensor was suitable for a high sensitive, selective, and stable caffeine determination in coffee without any interference. The polymer-modified electrode presented a linear range of 6×10^{-8}–4×10^{-5} molL^{-1} and a detection limit of 1.37×10^{-7} molL^{-1} [44]. Other authors employed 1,4-benzoquinone modified carbon paste electrode for indirect voltammetric determination of caffeine by using square wave voltammetry (SWV) and CV with detections limits of 0.3 and 5.1 μmolL^{-1}, respectively [44].

Fritea et al. studied the formation of inclusion complexes between β-cyclodextrin (β-CD) and caffeine. The relationship between the oxidation peak currents and the concentration of caffeine in the presence of β-CD was examined by SWV indicating that the molar ratio of 1:1 is convenient for complexation [50]. Voltammetric methods were successfully applied for the simultaneous determination of some alkaloids (caffeine, aminophylline, theophylline, codeine phosphate, and papaverine hydrochloride) in different pharmaceutical combinations and in urine samples by using an electrochemically activated GCE [51, 52].

6. Medicinal importance of coffee and caffeine

6.1. Ethnomedicinal knowledge of coffee

There are several references related to the application of coffee plants in traditional medicine underlying multiple healing potentials. In addition to the official drug (*Coffeae semen*) utilization, there are data about the use of other plant parts in the Equator region. These coffee plant parts were used to treat various diseases in both human and veterinary medicines.

Ross presented an ethnomedicinal map about the use of *Coffee* species (different plant parts and different routes of administration) as a medicine throughout the world describing a wide range of diseases or symptoms, such as diarrhea, intestinal pain, HIV/AIDS, flu, anemia, edema, asthenia, liver diseases, migraine, stomach pain, fever; against bleeding that accompanied abortion; as astringent, aphrodisiac, cough suppressant; for cardiotonic and neurotonic effects, for tiredness, asthma, scorpion bites, and for the production of prolactin [2, 53–55].

In traditional medicine, the coffee coal was used for the inflammatory diseases of mouth and pharynx, but also it was used as a treatment of festering wounds [56]. In Nepal, *C. benghalensis* flowers were used as a treatment for excessive bleeding during menstruation [2, 57]. Different plant parts of *C. canephora* were used for backache, measles, coughing, and jaundice [2, 58].

There are information about utilization of coffee leaves and seeds as infusion or decoction having different regional names such as "giser" in Yemen [2, 12]. Native people from Ethiopia drank a beverage named "hoja" for diarrhea and nausea, which were caused by poisoning [2, 59]. In some regions of Indonesia and Ethiopia, people used to prepare a tea from *C. arabica* or *C. robusta* leaves, named "copi daon" or "leaf coffee" [2, 60]. In Liberia, women used to prepare a coffee leaf infusion for their children. The infusion from *C. arabica* leaves was tested on the London markets, but people said that it was undrinkable [2, 60].

Schmid et al. presented a study about the veterinary use of coffee in Swiss provinces indicating that farmers used coffee as a beverage to treat the reproductive, gastrointestinal, and metabolic disorders and infertility in animals. The authors showed that a subcutaneous injection of 10 mL coffee seed extract increased the healing rate of the newborn calves from diarrhea in 30% of the cases compared with the control subjects [2, 61].

6.2. Medicinal importance of coffee

The seed extracts of *Coffea* species have presented several health benefits due to the polyphenols content being used in cosmetics and pharmaceutical industry. The pharmacological benefits included a wide range of effects such as antioxidant, detoxifying, lipid reducing, cardioprotective, anti-inflammatory, analgesic, antineoplastic, diuretic, antibacterial, antiviral, antifungal, antiosteoporotic, anticelulitic, and anti-age activity, the effect on central nervous and gastrointestinal systems, and on blood vessels [62]. According to Rodriguez et al., the hydroalcoholic extract of coffee silverskin can be used for topical application because it has no irritant effects. Three different extracts were studied in this case performing *in vitro* and *in vivo* skin and ocular irritation assays [2, 63].

Nowadays, many decaffeinated beverages are produced in order to overcome the negative withdrawal effects of caffeine by using different extraction methods, which involve some toxic solvents. Due to these methods, they may be harmful for the human body; therefore, many studies were performed in order to obtain new and less toxic extraction methods. Among these new techniques, it can be mentioned: the microbiological caffeine degradation by using *Pseudomonas* and *Aspergillus* strains, enzymatic caffeine removal, and the genetically reduction of caffeine in plant [2, 64]. Even though many new decaffeination methods were successfully tested, the decaffeinated coffee still contains a minimum quantity of caffeine, aspect which has to be taken into consideration by patients vulnerable to caffeine effects. McCusker et al. have evaluated the caffeine concentration in various decaffeinated coffee drinks collected from different sources obtaining a caffeine content of 0–13.9 and 12.0–13.4 mg/16-oz serving [65].

Ross mentioned in his work many scientific tests about the topical utilization of green seed extracts. The results showed that these extracts have a significant anti-inflammatory activity. Other tests made on mice showed that the extracts of dried seeds have anticancer effect and they can also decrease blood sugar levels. However, seven cups of coffee per day with alcohol and cigarette can increase the suicidal tendency and the gastric acid level [2, 53]. The regular consumption of coffee mainly reduces the occurrence of kidney and liver cancers; meanwhile, premenopausal, breast, and colon cancers are less influenced. These effects are attributed to the content in caffeine, diterpenoids, caffeic acid, polyphenols, essential oils, and heterocyclic molecules [2, 66].

Cooper and Kronenberg tested the topical effect of coffee seed extract on 30 patients with dermatological problems. During this study, the product was applied on the whole facial area of 20 patients. In the case of 10 patients, it was applied only on the half of their face and the remaining area was treated with a placebo cream. The investigated cream presented noticeable effects such as appearance of fine lines and reduction of wrinkles and pigmentation [2, 67].

Jessen et al. have proved that thermogenic effect of nicotine can be improved by caffeine. They have studied this effect by using chewing gums with different concentration of nicotine and caffeine. They have found that the thermogenic effect of 1 mg of nicotine can be doubled by 100 mg of caffeine; therefore, caffeine could be used for weight gain prevention after smoking cessation [68]. It was also demonstrated that regular consumption of coffee presented benefits for the respiratory system in patients with asthma and smokers. In addition, the regular coffee consumption can reduce the occurrence probability of type II diabetes by 60%. The effect was not generated by caffeine since both caffeinated and decaffeinated beverages were studied obtaining the same result. Therefore, the compounds which are responsible for this effect are still unknown. Due to this reduced risk for diabetes development, coffee may be indicated as "functional food" efficient for the metabolic diseases prevention. Coffee presents high antioxidant properties due to the presence of flavonoids and polyphenols in its composition. The antioxidant activity was significantly increased after consumption of unfiltered coffee because of the glutathione increase [2, 69, 70].

Wagemaker et al. characterized the lipid fraction of the coffee seeds determining the variable concentration of wax, oil, and unsaponifiable material in the case of 10 *Coffea* species. The sunscreen effect was calculated between 0.0 and 4.1 SPF depending on the species indicating that the presence of linoleic and oleic acids is very useful for cosmetic products [2, 71]. Phenolic acids presented inhibitory effect on skin tumor in mice [2]. The influence of 13 phenolic acids on the phenol sulfotransferase enzyme activity was investigated since this enzyme is involved in the detoxification process. Some acids have inhibited the enzyme by 21–30% (chlorogenic, syringic, protocatechuic, vanillic, sinapic, and caffeic acids), while other acids have enhanced its activity (p-hydroxybenzoic, gallic, gentisic, o-coumaric, p-coumaric, m-coumaric, and ferulic acids) [23].

Other studies reported that isoquercitrin and rutoside had anti-atherosclerotic effect, quercitrin had positive chronotropic, positive inotropic, and anti-arrhythmic effects, which were tested on guinea pigs. Both quercetin and rutoside are used as therapeutic agents for capillary fragility and phlebosclerosis [2, 22]. Some flavonoids such as rutoside, gossypin, naringenin, (+)-Cyanidanol-3, quercetin, kaempferol, and rutin exhibit antiulcer activity by enhancing the gastric protection conferred by mucous content and inhibiting the platelet activating factor. Quercetin, kaempferol, and rutin showed antidiarrhetic effect and also benefits in other intestinal diseases since their actions are mediated through α2-adrenergic and calcium systems. Some flavonoids such as rutin and venorutin were also proved to exhibit hepatoprotective effects. In addition, kaempferol, rutoside, and quercetin showed antioxidant, antiviral, antifungal, antibacterial, anti-inflammatory, and antiallergic activity [22].

In one of our previous studies, the antioxidant activity of three *Coffea* species was tested using enhanced chemiluminescence (ECL), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and oxygen radical absorbance capacity (ORAC). Even though trolox equivalent values obtained by ECL and DPPH methods showed loose correlation, values obtained by ORAC assay were higher without correlation in each plant. The differences in the reactive antioxidant compounds among the assays and the altered reactivity with the reporter molecules might be responsible for this much higher antioxidant activities measured by the ORAC assay. However, a closer correlation was observed between the ECL method and the scavenging potential of the DPPH technique in each species, much higher DPPH antioxidant activity was observed at the immature pericarp of *C. benghalensis* than in case of the other species [29].

The hepatoprotective effect of coffee brews was proven by Lima et al. The two enzymes (aspartate aminotransferase and alanine aminotransferase)that are relevant for liver damage, the thiobarbituric acid reactive species, and total lipids, all were decreased. This effect was not negatively influenced by decaffeination process; meanwhile, it was indicated that the roasted coffee brews had a better protection against liver disease compared with green coffee brews [2, 72]. The vascular effects of coffee polyphenols were investigated by Ochiai et al., and the results showed that the peripheral endothelial function was improved after glucose loading in healthy person due to the ingestion of coffee polyphenols; meanwhile, no radical changes of the antioxidant activity were noticed [2, 73]. Chandra successfully assessed the *in-vitro*

anti-inflammatory effect of the *C. arabica* aqueous extract with different concentrations against the denaturation of protein by incubation with egg albumin. The anti-inflammatory activity of the coffee extract was related to the polyphenols content and it was higher in comparison with the effect of diclofenac sodium [2, 74].

6.3. Medicinal importance of caffeine

Caffeine is absorbed 99% from stomach (20%) and small intestine (80%) [75]. The most popular effect of caffeine is its stimulant effect on the central nervous system. Moreover, there is a wide range of various effects that are also attributed to caffeine such as increase of the painkillers effect, reduction of tiredness and of migraine (as it has a vasoconstrictor activity in the brain), increase of the stomach acid secretion, stimulation of the heart function (with hypertensive effects), stimulation of kidney function (with diuretic effect), stimulation of respiration, and decrease of the vitamin B concentration [2]. In addition, it is supposed that the occurrence of Parkinson's disease may be reduced by a regular consumption of coffee and cola [2].

Armanian showed that this alkaloid presents significant preventive effect of apnea in premature infants. Only 15.4% of the infants treated with caffeine have developed apnea in comparison with 61.5% of the control group [76].

As it was mentioned before, caffeine has a lot of beneficial effects, but in excess, it can generate plenty of secondary effects on the gastrointestinal, central nervous, circulating, and respiratory systems such as intestinal irritability, vomiting, diarrhea, stomach ulcers, tremors, sleep disturbances, headache, hallucinations, epileptic convulsions, high blood pressure, arrhythmic tachycardia, numbness, muscle spasms, and respiratory paralysis [2]. The excessive coffee consumption can lead to caffeinism which is an addiction because caffeine stimulates the central nervous system and also possesses negative withdrawal effects. Due to those secondary effects, coffee consumption should be avoided by people having cardio-vascular, kidney, neurological and gastric diseases, hyperthyroidism, and caffeine sensitivity [2]. In addition, caffeine is not recommended during pregnancy and lactation as it can cause spontaneous abortion and it can be secreted in the breast milk [2].

7. Conclusions

Based on this comprehensive work, we can conclude that *C. arabica* is the most studied and used plant both in scientific and social fields from the past up to the present. This plant presents a rich content of caffeine, a purine alkaloid, which is the most popular and well-known compound from the coffee plant. This substance showed important physiological effects on human body, but also including some serious secondary effects. Moreover, the scientific research is focused mostly on the physiological effects of coffees, but both the metabolism and extraction methods of caffeine have to be well studied in order to achieve a safer use of caffeine.

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