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Phytochemical overview and medicinal importance of *Coffea* species from the past until now

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ABSTRACT

Coffea (coffee) species are grown in almost all countries along the Equator. Many members of the genus have a large production history and an important role both in the global market and researches. Seeds (*Coffeae semen*) are successfully used in food, cosmetic, and pharmaceutical industries due to its caffeine and high polyphenol content. Nowadays, the three best-known coffee species are Arabic (*Coffea arabica* L.), Robusta (*Coffea robusta* L. Linden), and Liberian coffees (*Coffea liberica* Hiern.). Even though, many records are available on coffee in scientific literature, wild coffee species like Bengal coffee (*Coffea benghalensis* Roxb. Ex Schult.) could offer many new opportunities and challenges for phytochemical and medical studies. In this comprehensive summary, we focused on the ethnomedicinal, phytochemical, and medical significance of coffee species up to the present.

1. Introduction

Coffea species are well-known and widespread all over the world. They have an important role in science because of their pharmacological role. In addition, they occupy the second place after petrol on the international market. They also provide an income for more than 20 million families in more than 50 countries every year [1]. However, the most famous species are *Coffea arabica* L. (*C. arabica*), *Coffea robusta* L. Linden (*C. robusta*) (syn.: *Coffea canephora* Pierre ex A. Froehner (*C. canephora*)), and *Coffea liberica* Hiern. (*C. liberica*) (syn.: *Coffea dewevrei* De Wild. & T. Durand. (*C. dewevrei*)), we can also find scientific data on wild coffee species and subspecies cultivated in almost all continents [2]. Wild species are not known in America only in Africa and South Asia [3].

Coffea species grow in tropical and subtropical areas, especially in the Equatorial region at an altitude of 200 m–1 200 m and at 18–22 °C, but a range from 1 300 m to 1 600 m has been identified as an optimum altitude for wild coffee [4,5]. In warm and humid climate, *Coffea* species are susceptible to various fungal infections, which can kill them in large areas [6]. The most common fungal disease of coffee species is caused by *Hemileia vastatrix* Berk. & Broome, a basidiomycota, which causes a decoloration on the lower surface of the leaves. *Colletotrichum kahawae* J. M. Waller & Bridge, *Coffea coffeanum* Noack., and *Glomerella cingulata* Spauld. & H. Schrenk, which turn the fruits to brown and dry, are responsible for the appearance of coffee fruit-disease (“coffee berry disease”) [3,6]. *Meloidogyne exigua* is a root-knot nematode parasite, which is considered as a factor responsible for reduced productivity of the cultivars of *C. arabica* in Brazil. The resistance of coffees to *Meloidogyne exigua* is conferred by the gene *Mex-1* [7]. Coffee berry borer (*Hypothenemus hampei*) was accidentally introduced to Brazil. The reproduction of this insect is higher in highly humid environments. Investigations showed that *Coffea kapakata* (*C. kapakata)* (A. Chev.) Bridson, *Psilanthus bengalensis* (*Coffea eugenioides* (*C. eugenioides*) and *C. kapakata*. Heyne ex Schult.) J.-F.Leroy, *C. eugenioides* S. Moore, and genotypes with *C. eugenioides* genes were resistant to this pest. Could present resistance only at epicarp level, while *Psilanthus bengalensis, C. eugenioides and C. kapakata* could show resistance in =the seeds as well [8]. *Cercospora coffeicola* Berk. & Cooke and *Rhizochtonia* species attack partially *Coffea excelsa* A. Chev (syn.: *C. liberica* var. dewevrei (De Wild. & T. Durand) Lebrun) and *Coffea robusta*, but other parasites and diseases can also attack coffee plants, e.g. *Cuscuta jalapensis*, “Crespera” (an infectious disease; its etiology is uncertain, but a causing agent may be a Gram negative bacilliform bacteria), *Oligonychus ilicis* McGrgor (red mite), *Mycena cirticolor* (Berk. & M.A. Curtis) Sacc, *Gibberella xylarioides* R. Heim & Saccas, and *Leucoptera coffeella* Guer-Men [3,6,9–12].

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The basic genome, which is characteristic to most members of Rubiaceae family, is x = 11. The studied *Coffea* and *Psilanthus* species are all diploids that have 2n = 22 chromosomes, such as in *C. liberica, C. robusta, C. kapakata, Coffea zanguebariae* Lour., *Coffea racemosa* Lour., *Coffea ligustroides* S. Moore, *Coffea mauritiana* Lam., *C. dewevrei*, *Coffea excelsa* A. Chev., *Coffea brevipes* Hiern., *Coffea congensis* A. Froehner, *Coffea stenophylla* G. Don., and *C. eugenioides* [3]. The majority of coffee taxa is self-incompatible except the tetraploid *C. arabica*, as well as the diploid *Coffea heterocalyx* Stoff. and *Coffea anthonyi* Stoff. &- F. Anthony [13]. Moreover, polyploid *C. arabica* species [namely triploid (3n = 33), pentaploid (5n = 55), hexaploid (6n = 66) and octoploid (8n = 88) plants] have also been described in 1960. Occasionally, haploid or dihaploid young plants with narrower leaves also appear [14].

2. Phytochemical features

2.1. Phenolic compounds

In plants, there are about 8 000 known phenolic compounds with aromatic ring produced as secondary metabolites. They protect the plants against pathogens and abiotic stress such as changes in temperature, water content, exposure to UV light, and deficiency of mineral nutrients [15]. They contain two carbon frameworks, namely hydroxycinnamic and hydroxybenzoic structures. Caffeic, p-coumaric, vanillic, ferulic, and protocatechuic acids are present in nearly all coffee taxa [16].

In *Coffea* species, 5-caffeoylquinic acid (5-CQA) is the most abundant soluble ester. The beans of *C. canephora* contain feruloylquinic acids (3-, 4- and 5-FQA) and the isomers of monoester (3-, 4- and 5-CQA) and diester (3,4-, 3,5- and 4,5-diCQA) CQAs. Hydroxycinnamoylquinic acids are involved in the bitterness of coffee beverage due to their degradation into phenolics during roasting [17]. Additionally, various iridoid glycosides, tannins, and anthraquinones have also been detected in coffees [18].

Some studies aimed at the comparison of these compounds among various *Coffea* species or their plant parts. It was found that the total phenol content of the young leaves was not influenced by the fruit production, but it strongly depended on the developmental stage of the plant and the environmental factors, it correlated inversely with the temperature and radiation [19].

A high phenolic content was observed in the immature pericarp of Bengal and Liberian coffees (0.14%) compared with that of *C. arabica* (0.02%), and the immature pericarp of Bengal coffee and the immature seed of Arabic coffee showed a significant polyphenol content (3.6% and 4.14%, respectively) [20]. Campa *et al* studied the presence of mangiferin and hydroxycinnamic acid esters in 23 African coffee leaves. They found that the total hydroxycinnamic acid content of *C. arabica* was significantly higher than that of other species (e.g. *Coffea sessiliflora* Bridson, *Coffea resinora* Hook.f., *Coffea leroyi* A.P.Davis), and mangiferin and isomangiferin were present in higher concentration in the young leaves than in other plant parts [21,22]. Opposite to *C. arabica* and *Coffea humilis* A. Chev, feruloylquinic acids were present in higher amount in *Coffea stenophylla* and 3,4-dicaffeoylquinic acid were found in *C. canephora*. The caffeoylquinic acid content of the adult leaves of *C. canephora* was 10 times lower when compared to the young ones [17]. *Coffea anthonyi* Stoff. & F. Anthony and *Coffea salvatrix* Swynn. & Philipson presented higher concentration of mangiferin than *C. arabica, C. eugenoides, Coffea heterocalyx* Stoff., *Coffea pseudozanguebariae* (*C. pseudozanguebariae*), or *Coffea sesiliflora* Bridson [21,23].

2.2. Alkaloids

The presence of monoterpenoid alkaloids is characteristic to Rubiaceae family. In the synthesis of purine alkaloids, there are involved several enzymes such as caffeine synthase, xanthosine 7-*N*-methyltransferase, 7-methylxanthine 3-*N*-methyltransferase, caffeine xanthinemethyltransferase 1 (CaMXMT1), caffeine methylxanthinemethyltransferase 2 (CaMXMT2), caffeine dimethylxanthinemethyltransferase (CaDXMT1), and theobromine 1-*N*-methyltransferase [24].

Caffeine, the most important alkaloid of coffee species, is synthesized in the young leaves of *C. arabica* seedlings and immature fruits, and it is accumulated in the mature leaves. The active caffeine biosynthesis is carried out in the upper leaves and the upper part of the stem, but it is absent in the second and third leaves, cotyledons, lower stem, and root [25]. *C. liberica* is less cultivated due to its lower caffeine content (1.8% dry matter basis), and to its sensitivity to *Fusarium xyloriodes* [26]. The leaves of *Coffea salvatrix* (*C. salvatrix*), *C. eugenioides*, and *Coffea bengalensis* contain 3–7 times less caffeine than *C. arabica*, hence they are rarely studied and used in the industry nowadays. The degradation of caffeine, which is negligible in the leaves of Arabic coffee, is also very slow in *Coffea salvatrix* and *Coffea bengalensis,* but its catabolism is faster in the young and mature leaves of *C. eugenioides.* Catabolism patways involve the conversion of caffeine into theophylline, 3-methylxanthine, xanthine, uric acid, allantoin, allantoic acid, urea, and finally results in $CO_2 + NH_3$ [27]. The concentration of trigonelline and sucrose (aroma precursors of coffee species) was evaluated in 20 *Coffea* species. The trigonellin content varied between 0.39% and 1.77%, while the sucrose content changed from 3.8% to 10.7% of dry plant material. Their highest concentration was measured in the green beans of *C. arabica*, *C. kapakata,* and *C. salvatrix* [28], while *C. canephora* contained more chlorogenic acids and caffeine [28,29].

2.3. Terpenoids

The characteristic aroma of coffee is due to α-2-furfurylthiol, 4-vinylguaiacol, some alkyl tnd 3-methylbutane yrosine derivatives, furanones, acetaldehyde, propanal, methylpropanal, and 2- acontent [30,31]. Cafesterol and bengalensol have also been isolated and identified by various chromatographic techniques in *Coffea benghalensis* [27,32,33].

2.4. Carotenoids

Carotenoids, which are generally present in leaf, flower, fruit, and shoot of plants, play an important role in the stabilization of lipid membranes, the photosynthesis, and the protecion against strong radiation and photooxidative processes. Experiments with coffee species also showed that the transcript levels of enzymes involved in the synthesis of carotenoids increased under stress conditions [34].

2.5. Enzymes

An adenosine nucleosidase was purified from the young leaves of *C. arabica* cv. *Catimor* shows maximum activity at pH = 6.0 in citrate-phosphate buffer. It hydrolyzes adenosine to adenine and ribose in the purine metabolic pathway, which enables the recycling of these metabolites. It seems to be important in catabolizing tissues e.g. in cotyledons, which makes adenine available for transport and reutilization in other organs. In addition, it has a possible role in the inter-conversion of these growth regulators (interchange between cytokinin base, riboside, and ribotide forms), and consequently in cytokinin transport and activity regulation in plants [35]. Polyphenol oxidases are active mostly in the early developmental stages of the leaf and the endosperm e.g. in the case of *C. arabica* [36].

2.6. Inorganic substances and vitamins

Coffee taxa also contain inorganic materials like K, Mg, Ca, Na, Fe, Cu, Mn, Zn, Rb, Sr, V, Co, Ni, Ba, B, minerals, and a minor amount of B, C, P, and PP vitamins [37].

3. Phytochemical analyses of plant parts of coffees

3.1. Coffee seed

The official drug is the seed (*Coffeae semen*) which contains 1.25%–2.5% caffeine (roasted seeds: 1.36%–2.85%), theobromine, theophylline, 4.4%–7.5% chlorogenic acid (roasted seeds: 0.3%–0.6%), 0.8%–1.25% trigonelline (roasted seeds: 0.3%–0.6%), 0.022% choline, 10%–16% fatty oil, quinic acid, sitosterol, dihidrositosterine, stigmasterol, coffeasterin, tannin, wax, caffeic acid, sugar, cellulose, hemicellulose, non-volatile aliphatic acids (citric, malic, and oxalic acid), volatile acids (acetic, propanoic, butanoic, isovaleric, hexanoic, and decanoic acids), soluble carbohydrates (e.g. monosaccharides: fructose, glucose, galactose, and arabinose), oligosaccharides: sucrose, raffinose, and stachyose, and polymers of galactose, mannose, arabinose, and glucose [30,31,38]. The concentration of caffeine, which occurs partially in free form or forms salt with chlorogenic acid, is reduced during roasting [39]. Theophylline is used as an important smooth muscle relaxant (in bronchospasms) in combination with ethylenediamine (Aminophylline) or choline. These alkaloids are either extracted from natural sources or produced by partial or total syntheses [40].

Coffee seeds are rich in biologically active substances and polyphenols such as kaempherol, quercetin, ferulic, sinapic, nicotinic, quinolic, tannic, and pyrogallic acids which possess antioxidant, hepatoprotective, antibacterial, antiviral, anti-inflammatory, and hypolipidaemic effects [41–49]. Besides the *cis*-isomers of chlorogenic acid in Arabic coffee [50], caffeic, chlorogenic, p-coumaric, ferulic, and sinapic acids, as well as rutin, quercetin, kaempferol, and isoquercitrine were detected in its fruit and that of Bengal coffee [51]. The most significant concentration of chlorogenic acid was observed in the non-hydrolyzed extract of the pericarp in both species [52]. High quantity of esters of feruloylquinic acid was described in the fruit and the green bean of *C. pseudozanguebariae* [21].

The Arabic and Robusta coffee seeds store 10%–16% fatty oil as a storage substance [53]. The oil of the immature seeds can be used as an alternative source of biodiesel, and the seed coat can be used for bioethanol production. Seed coat and cakes pressed from defective beans are useful as adsorbents for the removal of dyes from aqueous media [54]. The lipid fraction of the seeds, including waxes, oils, and unsaponifiable materials, plays an important role in the embryonic development [55].

The biochemical studies of wild species from Africa and Madagascar were focused on qualitative and quantitative assessments of sugar, lipid, caffeine, and esters of hydroxycinnamic acid (HCE) in green coffee beans. However, there are many studies on beans, relatively few experiments deal with the metabolite content of other plant parts (such as the leaf, outer fleshy layer of the fruit, etc.). Moreover, many of these studies are still focusing on cultivated species investigating mostly their HCE content [21].

A cup of coffee contains about 1 mg of vitamin PP (nicotinic acid). Three cups of coffee, which is the maximum suggested quantity of coffee per day, provides 25%–50% of the daily requirement of this vitamin [56].

The whole or grounded silverskin can be used as a possible fertilizer after compost-production as a versatile barrier in reduction of pesticide which leach through the soil, and as a source of oil for biodiesel or biomass for bunker fuel substitution [54]. The spent coffee contains carbon (>58%), nitrogen (<2%), ash (<1%), lipophilic fractions, ethanol, water-soluble compounds, components solubilized in 1% NaOH, lignin, polysaccharides, glucose, mannose, free fatty acids like n-hexadecanoic acid, polyphenols, tannins, lipids, polysaccharides, and chlorogenic acid [57].

3.2. Coffee leaf

Based on our investigations, phenolic acids such as caffeic, chlorogenic, p-coumaric, ferulic, and sinapic acids, as well as rutin, quercetin, kaempferol, and isoquercitrine were identified in the leaf of Arabic and Bengal coffee [51]. *Cis*-isomers of chlorogenic acid were observed in higher amount in the leaf than in the seeds of Arabic coffee. This fact may suggest that UV radiation can provoke geometric isomerization of chlorogenic acid in leaves [50].

Recent researches have great emphasis on the physiological effect of the infusion of *C. arabica* and *C. canephora*, and their mangiferin and isomangiferin content. MS and NMR studies have identified these compounds in the leaves of *C. pseudozanguebariae* (a wild species), and in other species of Rubiaceae family [21,22]. In addition to *C*-glucosylxanthone and mangiferin, high quantity of feruloylquinic acid esters was first detected in its leaf. Mangiferin was initially isolated from the leaves, bark, and peel of mango *(Mangifera indica* L.), and it is well-known for its numerous pharmacological properties such as anti-inflammatory, antidiabetic, antihyperlipidaemic, and neuroprotective activities, as well as it provides antioxidant and antimicrobial effect in biotic stress [21]. Dicaffeoylquinic acids, 5-CQA, and feruloylquinic acids were also detected in the leaf of *C. canephora* [17].

3.3. Coffee coal

Coffee coal (*Coffeae carbo*) is obtainable by the charring of roasted coffee beans. It contains caffeine (75% of the original amount), phenols, tannins, trigonelline, chlorogenic, and caffeic acids. The IVth Hungarian Pharmacopoeia used coffee syrup (*Syrupus coffeae*) as flavor corrigent which was later substituted with chicory syrup (*Syrupus cichorii*). During roasting, coffee seed swells and turnes brown, and it partially loses its water content. The sugar is caramelized, then aromatic substances are produced, which provide the characteristic aroma of coffee beverage [58,59]. Generally, more than 90% of α- and β-tocopherols remain unchanged after roasting except Robusta coffee, in which the concentration of β-tocopherol is reduced by 25% after roasting. This change was not observed in Arabic coffee [60]. The most well-known substitute of coffee is a chicory version extracted from the root of *Cichorium intybus* L. ssp. *sativa* (Lam. et DC.) Janch. convar. *radicosum*. Besides chicory, the fruit of *Ficus carica* L., *Hordeum vulgare* L., *Phaseolus vulgaris* L., *Fagus sylvatica* L., and *Ceratonia siliqua* L., the root of *Taraxacum officinale* agg., as well as crops and malt can also be used to substitute coffee [58,59].

4. Histological localization of metabolites

The occurrence of chlorogenic acid and mangiferin in *C. pseudozanguebariae*, *C. eugenioides*, *C. arabica,* and *C. canephora* was studied by spectral analysis combined with advanced linear unmixing. Based on the differences in phenolics of young leaves, *C. pseudozanguebariae*, *C. eugenioides vs. C. arabica,* and *C. canephora* were classified into two groups. In the first group (*C. pseudozanguebariae* and *C. eugenioides*), based on the presence of 5-CQA and mangiferin, histochemical difference was detected between adaxial and abaxial epidermal tissues: 5-CQA fluorescence was observed in vascular bundles and in the cuticle of the abaxial epidermis and lesser in cells of the adaxial epidermis (it was not detected on the adaxial cuticle). Mangiferin fluorescence was detected in cuticles and in all parenchyma cells (like spongy cells) and at the lower level of the palisade parenchyma. In the second group (*C. arabica* and *C. canephora*), mangiferin was not present in the epidermis only in the parenchyma (as small vesicles), but 5-CQA could be identified in the vacuoles of both tissues [61].

Based on histochemical and microspectrofluorometrical analysis, caffeoylquinic acids (mono- and di-esters) were closely associated with chloroplasts in young leaves of *C. canephora*. During leaf ageing, they intensively accumulate in chlorenchymatous bundle sheath cells and then in the sclerenchyma cells around the phloem. The association with chloroplasts suggests a protective role of caffeoylquinic acids against light damage. In older leaf tissues, they are transported through the phloem which confirms their role in lignification. Similarly to other phenolics, hydroxycinnamoylquinic acids are accumulated in vacuoles or in apoplast. Their biosynthesis apparently takes place with enzymes in the chloroplast. In *C. canephora*, the hydroxycinnamoylquinic acids accumulate in beans, where their content can exceed 10% of dry bean weight. Because it is able to form complexes with caffeine, it is thought to participate in the vacuolar sequestration of this alkaloid. Insoluble phenolics are distributed in cell walls, while soluble compounds are compartmentalized within cell vacuoles. Feruloylquinic acids (3-, 4- and 5-FQA) and caffeoylquinic acids, i.e. the isomers of monoester CQA (3-, 4-, and 5-CQA) and diesters can also be found in the green beans [17].

5. Adaptation to inadequate environmental conditions

Thermal analyses of seed tissues of *C. liberica* suggested that the absence of freezable water is an important factor for successful cryopreservation of excised coffee embryos; their optimal desiccation was carried out at 17.17% moisture, 30 min [62]. Some cultivars of *C. arabica* presented similar tolerance for desiccation and low temperature. Based on earlier reports, *Coffea racemosa* was the most tolerant while *C. liberica* was the least tolerant for desiccation [63]. Cold conditions have a severe impact on the growth, development, photosynthesis, and production of coffees. Studies related to the acclimation ability of *C. canephora* cv. *Apoata*, *C. arabica* cv. *Catuai', C. dewevrei,* and two hybrids, *Icatu* (*C. arabica* × *C. canephora*) and *Piata* (*C. dewevrei* × *C. arabica*) showed, that *Catuai* had an intermediate response through the reinforcement of some antioxidative molecules, usually to a lesser extent than that of *Icatu*. *C. dewevrei* showed the poorest response in terms of antioxidant accumulation, and also showed the greatest increase in OH values [64].

6. Ethnomedicinal data

Several reports have already been published on the traditional use of coffee both in human and veterinary medicines that related to the officially, which applied seed and other plant parts.

The beverage prepared from **seeds** of Arabic coffee was used to treat flu in Brazil, whereas in Cuba the hot water extract of the seeds was known as an aphrodisiac drug. In Haiti, the infusion of the leaves and the roasted seeds were used for anemia, edema, and asthenia., The decoction of seeds was used orally for fever and as an astringent drug in Nicaragua, while the aqueous extract of the dried seeds were known for tiredness in Peru, as a cardiotonic and neurotonic drug in Thailand, and for asthma in West India [65].

Dried **fruits** boiled in water are known as a beverage called “giser” in Yemen [66]. The seeds of *C. canephora* are used locally as a massage for backache, the root extract for measles (as a bandage for children), the leaves orally for cough and jaundice (as a decoction and infusion) [67]. In Ethiopia, native people consumed a beverage called “hoja” to treat poisoning which is accompanied by diarrhea and nausea. It contained milk and honey of the pericarp of coffee berries [68]. In Africa, coffee seeds are used against asthma attacks [69].

The **leaf** sap of Arabic coffee was consumed to treat diarrhea and intestinal pain in Africa. It is used to manage HIV/AIDS in Kamuli, Sembabule, Kabale, and Gulu districts of Uganda [70]. In Cuba, people used the leaves both orally or locally to treat migraine, sometimes they placed the fresh leaves or an infusion onto their painful body parts. Coffee leaves are also mentioned for headache and stomach pains (as a decoction) in Nicaragua, as cough suppressant (as an infusion) in Peru, as well as for fever and stimulation of prolactin's production in Mexico [65]. In Indonesia and Ethiopia, people name the tea of the leaf of Arabic or Robusta coffee “copi daon” or “leaf coffee”. In Liberia, the infusion of the leaf of Arabic coffee was consumed only for its taste, but when it was tried to be sold at the markets of London, it was not found to be popular, rather undrinkable [71]. In Africa, the tea prepared from leaves of Robusta coffee that was used for bleeding accompanying abortion: chopped leaves were mixed with 0.5 L of water, then it was squeezed and consumed [69]. Dried leaves are still used for preparation of a tea named "Quti" in Ethiopia [72]. The salty drink (tea) of the leaf of Liberian coffee was described as a laxative drug [68].

The **flowers** of *Coffea benghalensis* were known for excessive bleeding during menstruation in Nepal [73].

The **root** sap was consumed for scorpion bites in West India [65], and it was chewed or added to food to obtain an aphrodisiac effect in Ethiopia [68].

In folk medicine, the coffee **coal** (charcoal) was used for purulent wounds, pharyngitis, and stomatitis [74].

7. Medicinal importance and applications of coffee

7.1. Antioxidant potential

In oxidative stress, reactive oxygen species (ROS) have been suggested to participate in the initiation and propagation of chronic diseases such as cardiovascular and inflammatory diseases, cancer, or diabetes [75]. Antioxidants, which are found naturally in many foods and beverages, provide health benefits in the prevention of heart diseases and cancer by fighting cellular damage that caused by free radicals in the body. In general, consumers prefer natural antioxidants because they are considered to be safe and environmental friendly [76].

The antioxidant activities of the seed extracts of *C. arabica* were measured by using ferric reducing power assay (for water-soluble components using ascorbic acid) and Rancimat assay (for lipid-soluble portions using sunflower oil as substrate). All coffee extracts improved the oxidative stability of sunflower oil. Based on these results, *Wembera* coffee has higher caffeine content and higher levels of antioxidant activities than *C. arabica* from *Burie, Goncha,* and *Zegie* in Africa [77].

The caffeine content of silverskin (the inner fruit layer surrounding coffee beans) of *C. arabica* was found to be 3.5 times lower than in most coffee brews. The total antioxidant capacity of this part was similar to those of valuable sources of food antioxidants like dark chocolate, herbs, and spices [78]. The extracts of the silverskin of Arabic and Robusta species prepared by supercritical fluid extraction showed antioxidant activity in DPPH radical scavenging capacity and H-ORAC antioxidant assays [79].

Coffee seed extract may also have an important role in UV protection and cancer prevention because of its antioxidants. In a clinical study, 30 patients suffering from dermatological problems were treated locally with seed extracts: the tested cream was applied to the whole facial area in 20 patients and only to the half of the face in 10 patients where the remaining area was treated with a placebo cream. In comparison with the placebo, the investigated product improved visibly the appearance of fine lines and reduced wrinkles and pigmentation, but above all it improved the formation of the facial skin [80].

In another study, the antioxidant activity and the inhibitory effect of skin tumor promotion of ferulic, chlorogenic, and caffeic acids were determined in mice. They were applied to the skin of the mice together with 5 nmoL of 12-O-tetradecanoyl-phorbol-13-acetate (TPA). As a result, they inhibited the number of TPA-induced tumors by 60%, 28%, and 35%, respectively in each mouse, in addition, the increasing concentration of phenolic acids caused more pronounced inhibitory effect [41]. Sinapic, caffeic, and p-coumaric acids also showed antioxidant capacity and modifying effect on sulfate conjugation [44]. The β-cyclodextrin-enclosed chlorogenic acid showed about 2 times higher antioxidant capacity than the crude and purified extract [81].

However, *C. liberica* is less used, the volatile extract of its immature beans possessed higher antioxidant capacity than that of *C. arabica* and *C. robusta* [82]. The fruits of Bengal coffee showed stronger antioxidant activity than ascorbic acid and α-tocopherol [83].

7.2. Effects during pregnancy and lactation

Some studies have shown that coffee consumption can cause spontaneous abortion during pregnancy due to its caffeine content [65] In addition, the use is also not recommended during lactation, because caffeine can appear in the breast milk [84].

7.3. Anticancer effect

The regular consumption of coffee reduces the feasibility of cancers of kidney, liver, premenopausal breast, and colon also due to caffeine, diterpenoid, caffeic acid, polyphenols, essential oil content, and heterocyclic molecules. However, no correlation was found between coffee intake and prostate, pancreatic, and ovarian cancers nowadays [79]. The anticancer effect of the fruit extracts of *C. arabica* has also been confirmed in mouse studies [65].

7.4. Gastrointestinal and systemic effects

A cup of coffee contains about 80 mg of caffeine, but e.g. the high quality Hungarian short coffee contains only approximately 50 mg of caffeine, exactly as much as a cup of tea. Caffeine is rapidly absorbed in the gastrointestinal system bounding to proteins and being transported to many places in the human body. The blood plasma level reaches its maximum 30 min after the intake, and the half-life is 5 h. In the metabolic phase, caffeine is dimethylated and degraded to theobromine, theophylline, and paraxantine. Due to caffeine, coffee beverage has a diuretic and a temporarily hypertensive effect, increases the secretion of the stomach acid, as well as stimulates the function of the heart and the kidney [85]. The theobromine content of the seed also has a diuretic and spasmolytic effect similarly to theophylline [40].

Its aromatic substances increase the gastric secretion [86]: seven cups of coffee per day can increase the gastric acid level and suicidal tendency used simultaneously with alcohol and cigarette [65] The choleretic-cholagogue effect of chlorogenic acid was also documented. In the stomach, chlorogenic acid is hydrolyzed and converted to caffeic acid which is conjugated to form the glucuronate or sulphate [87]. Chlorogenic acid inhibits the glucose-6-phosphatase enzyme which can decrease the glucose production in the liver, while caffeine stimulates the insulin production of β-cells in the pancreas [88].

Recently, some clinical studies confirmed that coffee consumption is not as harmful as one might think. According to an epidemiological study, the active substances of coffee seeds can also reduce the disorders of the gallbladder [86]. Regular coffee consumption can reduce the probability of type II diabetes by 60% in the case both of caffeinated and decaffeinated beverages, therefore caffeine is not involved in this effect, but it is still unknown that substances can be responsible for this [89,90].

Coffee has hepatoprotective effect, regardless of the decaffeination process. Roasted coffee brews have a stronger protective effect against liver damage than green coffee brews [91]. The stomach irritating tannins, which are present in the beverages of coffee and tea shrub (*Camellia sinensis* L.), can be neutralized by milk [92]. Coffee drinks can also reduce the absorbtion of nicotine of nicotine-containing chewing gums [87].

7.5. Dermatological use

The powdered leaf and stem of *C. arabica* can provoke allergic reactions. Scientific tests have proven the anti-inflammatory activity of locally applied green seed extracts [65]. Kaempferol, rutoside, and quercetin showed an antiulcer activity in rats [43], and antiviral, antifungal, antibacterial, anticellulitic, anti-aging [93], anti-inflammatory, and antiallergic activity, as well [43]. Coffee coal possesses astringent effect [86], while *in vitro* and *in vivo* studies showed that the hydroalcoholic extracts of the silverskin has no irritating effect on the skin and can be used by the cosmetic industry [94].

Linolenic acid, which is present in high concentration in green coffee seeds, blocks the harmful UV-rays and has a sunscreen effect, whose property is useful in cosmetics. In another study, the concentration of seed waxes, oils, unsaponifiable materials, and the sunscreen effect were analyzed in 10 coffee species: linoleic acid was found in high concentration, wax from 0.0% to 2.8%, oleic acid from 6.9% to 32.4%, and the unsaponifiable matters from 0.3% to 13.5%. The sunscreen effect was between 0.0 and 4.1 SPF depending on the tested coffee species [55].

7.6. Cardiovascular effects

Isoquercitrin and rutoside extracted from coffee seeds that can be used for atherosclerosis, while quercitrin has positive chronotropic, positive inotropic, and antiarrhythmic effects, as well as protected LDL against oxidative modifications in guinea pig. Quercetin and rutoside have been used in the treatment of capillary fragility and phlebosclerosis [43].

Coffee seeds can also decrease the blood sugar level [65]. In the therapy, caffeine can be used for patients with mild cardiovascular diseases to increase blood pressure, body temperature, and blood circulation [85]. The single ingestion of coffee polyphenols improved the peripheral endothelial function after glucose loading in healthy subjects [95]. The aqueous extract of *C. arabica* possessed *in-vitro* anti-inflammatory effect against protein denaturation on egg albumins which is also due to the polyphenol content [96].

7.7. Effects on the nervous system

Coffee has a well-known stimulant effect on the central nervous system [97]. It can increase the effect of painkillers [69,88] or reduce tiredness [88]. American researchers have shown that the regular consumption of coffee and cola may reduce the incidence of Parkinson's disease [85]. In addition, coffee can be used in migraine therapy combined with ergotamine, because caffeine has a vasoconstrictor activity in the brain [85]. Coffee may facilitate sleeping in small concentration, which potential is used by homeopathic remedies [98].

7.8. Respiratory effects

Coffee seeds can be used, as a respiratory stimulant an unexpected effect of caffeine is to promote quitting smoking [85].

7.9. Use for obesity

Although, some data suggest that caffeine is effective in weight-loss diets through e.g. thermogenesis and fat oxidation [99–101], it is still not fully known. The topical anticellulite effect of siloxanetriol alginate caffeine has also been shown by histological evaluation of fatty tissues in Wistar rats (the diameter of the fatty cells was reduced by 17%) [102].

7.10. Antibacterial effect

Recent studies have shown that the fruits of Bengal coffee have antibacterial properties against *Proteus vulgaris*, *Escherichia coli*, *Klebsiella pneumonia*, *Vibrio cholerae, Salmonella typhimurium*, *Salmonella typhi, Streptococcus faecalis*, and *S. aureus* [83,103,104]. Due to chlorogenic acid and Maillard reaction, products are generated during the roasting of the seed, extract of *C. canephora* showed an inhibitory effect against *Sterptococcus mutans* (which can cause tooth decay) [105–107].

7.11. Veterinary use

In a work, 10 mL of Arabic coffee seed extract were injected under the skin of newborn calves which increased the healing time of the animals by 30% in diarrhea compared with placebo controls. In Swiss provinces like Aargau, Zurich and Schaffhausen farmers brewed drink of coffee seeds to treat reproductive, gastrointestinal, and metabolic disorders, as well as for the infertility of animals [108].

7.12. Secondary effects

Coffee is consumed mainly as a drink all over the world owing to its stimulating effect, but an overdose of caffeine can cause serious secondary effects [97] like intestinal irritability, diarrhea, nervousness, stomach ulcers, anxiety, pancreatic cancer, cholesterol, and an abnormal rise. These abnormalities are caused by the use of coffee combined with excessive tobacco and/or alcohol, as well as by the solvent residues used in decaffeinisation [86]. If caffeine concentration exceeds 1.5 g/day, serious secondary effects may appear like high blood pressure, numbness, muscle spasms, hallucinations, long term spasm of the back muscles, arrhythmic tachycardia, epileptiform convulsions, and respiratory paralysis [84,85]. Moreover, the excessive coffee consumption (more than 5 cups daily) can cause caffeine addiction namely caffeinism. This overdose can provoke irritability, tremors, sleep disturbances, vomiting, diarrhea, headache [31], and rarely death, which were recorded mostly in children. First symptoms include vomiting and stomach cramps. The artificial induction of vomiting, gastric lavage, administration of diazepam and spasmolytical substances are used as first aid [84,85]. The less well-known effects of caffeine include drowsiness among the elderly: it increases the cardiac output and improves blood circulation of the brain, and it makes falling asleep easier [85]. The lethal dose for adults extends from 150 mg to 200 mg caffeine/kg [84,85].

Coffee consumption is not recommended for people suffering from high blood pressure, coronary heart disease, kidney and certain neurological disease, stomach ulcer, hyperthyroidism, anxiety, caffeine sensitivity, as well as during pregnancy and for children [84,85].

7.13. Interactions

Patients taking regularly medicines may drink coffee carefully because several interactions were described. Although, coffee may neutralize the medical effect of herbs, it increases the effect of aspirin and paracetamol. Excessive coffee consumption can decrease the concentration of vitamin B [86]. Human serum albumin also interacts with chlorogenic acid of coffee with high affinity. This statement was studied by fluorescence spectroscopy with using eight polyphenol compounds, four acids (caffeic, ferulic, 5-O-caffeoyl quinic, and 3,4-dimethoxycinnamic acid), and four lactones (3,4-O-dicaffeoyl-1,5-c-quinide, 3-O-[3,4-(dimethoxy)cinnamoyl]-1,5-c-quinide, 3,4-O-bis[3,4-(dimethoxy)cinnamoyl]-1,5-c-quinide, and 1,3,4-O-tris[3,4-(dimethoxy)cinnamoyl]-1,5-c-quinide) of coffee seed. In this study, the dissociation constants of the albumin–chlorogenic acids and albumin–quinides complexes was observed in the micromolar range between 2 and 30 μM [109].

7.14. Caffein-free and decaffeinated products

Caffeine-free species are found mainly at the islands of the Indian Ocean (*Coffea humbertii* J.-F.Leroy, *Coffea vatovavyensis* J.-F.Leroy), and in Africa (*C. pseudozanguebariae, Coffea charrieriana* Stoff. & F. Anthony) [110].

Nowadays, many decaffeinated coffee beverages are prepared by chemical solvents, water, and supercritical fluid extraction. These methods may be harmful to the human body which lead to studies to obtain new and less harmful extractions. The microbiological caffeine metabolisation using *Pseudomonas and Aspergillus* strains, its enzymatical pathway, as well as the genetical reduction of caffeine can be mentioned as the basic point of these analyses in plants [111]. The decaffeinisation of coffee seeds is not completely effective, because decaffeinated coffee also contains a minimum quantity of caffeine (0.08%) [31].

8. Conclusions

Based on this summary we can concluded that *Coffea* species belong to the most studied plants from the past to the present. Although, they have rich historical data and a wide range of applications both in social and scientific life, there are many new and less studied species which have to be investigated, especially wild coffee taxa due to their phytochemical composition. In addition, the science is focused mostly on the physiological effects and genetical diversification of coffees which could cause new utilizations and more resistant species in the future.

Conflict of interest statement

The authors declare that there was no conflict of interest.

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