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Caffeic acid: a brief overview of its presence, metabolism, and bioactivity

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ABSTRACT

Caffeic acid is a bioactive compound found in a variety of plants including vegetables, fruits, herbs, and drinks. It belongs to the huge group of chemicals called polyphenols and is a major representative of the polyphenol subgroup of hydroxycinnamic acids. In foods, caffeic acid occurs mostly as a quinic acid ester called chlorogenic acid. Caffeic acid, like other polyphenols, is believed to exhibit many health benefits associated with their antioxidant properties, including the prevention of inflammation, cancer, neurodegenerative diseases, and diabetes. Nowadays, the use of naturally occurring bioactive substances, including caffeic acid, is becoming a very common phenomenon. Thus, information about their functions and properties is very important.

Keywords: caffeic acid, polyphenols, bioactive compound, oxidative stress

REVIEW

Caffeic acid (3,4-dihydroxy-cinnamic acid) is an organic compound, a major representative of hydroxycinnamic acids, and, in foods, occurs mostly as a quinic acid ester called chlorogenic acid. Hydroxycinnamic acids represent a subgroup of a very large group of chemicals called polyphenols. Polyphenols are organic compounds characterized by the presence of large multiples of phenol structural units, which act as the bases of unique physical, chemical, and biological properties for individual members of the class. This considerable structural diversity greatly affects their bioavailability [1]. Polyphenols are well known mostly for their strong antioxidant properties.

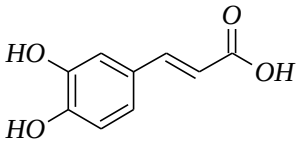

Figure 1. Chemical structure of caffeic acid

The protective effect of caffeic acid on the human body is explained due to its antioxidant properties, which are attributed to its chemical structure. Antioxidant properties of caffeic acid are associated with the presence of two hydroxyl groups on its aromatic ring (Figure 1), which allow it to donate the hydrogen and stabilize the resulting phenoxyl radical. Additionally, the presence of a double bond in the carbon chain (the unsaturated side chain 2,3 double bond) increases the stability of the phenoxyl radical. It has also been suggested that caffeic acid has the ability to form chelates with divalent metals. For example, those that are catalysts for oxidation reactions or cofactors of enzymes catalyzing reactions related to the formation of reactive oxygen species (ROS) and modulation of gene expression function in anti-inflammatory and immunoregulatory responses [2]. These chemical factors associated with the caffeic acid molecule allow the elimination of free radicals and prevent ROS formation, which has beneficial effects on the human body and can prevent various types of diseases.

Presence of caffeic acid in the food

Caffeic acid is naturally found in various foods, beverages, nuts, herbs, vegetables, fruits, and oils (Table 1). This compound can be found in plants or released from the metabolization of other molecules, especially chlorogenic acids in coffee or caftaric acid in grape [3].

Table 1. Some examples of foods containing caffeic acid. (Edited from [4])

Food type	Mean content
Fruits and fruit products	
Plum, prune	1.11 mg/100 g FW
Date, dried	2.52 mg/100 g FW
American cranberry	2.31 mg/100 g FW
Black chokeberry	141.14 mg/100 g FW
Cloudberry	1.00 mg/100 g FW
Lingonberry, raw	6.34 mg/100 g FW
Grapefruit	2.00e-03 mg/100 g FW
Peach, peeled	0.63 mg/100 g FW
Date, fresh	3.37 mg/100 g FW
Apple (Dessert), whole, raw	0.33 mg/100 g FW
Pear, peeled	0.14 mg/100 g FW
Vegetables	
Cauliflower, raw	1.00e-02 mg/100 g FW
Eggplant (Purple), whole, raw	0.38 mg/100 g FW
Olive (Black), raw	2.10 mg/100 g FW
Olive (Green), raw	1.33 mg/100 g FW
Tomato, whole, raw	0.45 mg/100 g FW
Carrot, raw	0.02 mg/100 g FW
Potato, raw	1.62 mg/100 g FW
Alcoholic beverages	
Beer (Alcohol free)	0.01 mg/100 ml
Beer (Dark)	0.03 mg/100 ml
Beer (Regular)	0.03 mg/100 ml
Wine (Red)	1.88 mg/100 ml
Wine (Rosé)	0.33 mg/100 ml
Wine (White)	0.24 mg/100 ml
Non-alcoholic beverages	
Coffee beverage (Filter)	0.03 mg/100 ml

Food type	Mean content
Grape (Green), pure juice	0.16 mg/100 ml
Plum, prune, juice from concentrate	5.10 mg/100 ml
Apple (Cider), juice from concentrate	0.24 mg/100 ml
Apple (Cider), pure juice	0.34 mg/100 ml
Apple (Dessert), juice from concentrate	0.15 mg/100 ml
Apple (Dessert), pure juice	0.68 mg/100 ml
Pear, pure juice	0.74 mg/100 ml
Pomegranate, pure juice	0.07 mg/100 ml
Oils	
Olive, oil, extra virgin	0.02 mg/100 g FW
Olive, oil, virgin	0.02 mg/100 g FW
Soy, oil	8.00e-04 mg/100 g FW
Seeds and Nuts	
Walnut, dehulled	0.24 mg/100 g FW
Sunflower seed, meal	8.17 mg/100 g FW
Cereals and cereal products	
Bread, rye, whole grain flour	0.77 mg/100 g FW
Common wheat, whole grain flour	0.04 mg/100 g FW
Maize, refined flour	0.04 mg/100 g FW
Oat, refined flour	0.04 mg/100 g FW
Oat, whole grain flour	0.16 mg/100 g FW
Rice, parboiled	0.34 mg/100 g FW
Rice, whole grain	0.05 mg/100 g FW
Rye, whole grain flour	0.20 mg/100 g FW
Seasonings (herbs, spices)	
Common sage, dried	26.40 mg/100 g FW
Common sage, fresh	7.42 mg/100 g FW
Common thyme, dried	21.28 mg/100 g FW
Common thyme, fresh	11.70 mg/100 g FW
Italian oregano, fresh	10.40 mg/100 g FW
Marjoram, dried	1.90 mg/100 g FW
Oregano, dried (wild marjoram)	10.70 mg/100 g FW
Rosemary, dried	9.67 mg/100 g FW
Rosemary, fresh	2.08 mg/100 g FW
Spearmint, dried	25.00 mg/100 g FW
Welsh onion, fresh	0.02 mg/100 g FW
Vinegar	0.28 mg/100 ml
Caraway	16.40 mg/100 g FW
Ceylan cinnamon	24.20 mg/100 g FW
Cumin	16.60 mg/100 g FW
Ginger, dried	15.50 mg/100 g FW
Nutmeg	16.30 mg/100 g FW
Star anise	20.20 mg/100 g FW

FW, food weight; mg, milligram; g, gram; ml, milliliter.

Currently, there is insufficient information on what the suitable dose of caffeic acid is, but some scientists agree on the sufficient amount of total cinnamates, which ranges from almost zero to 1 g in humans [5].

Metabolism of caffeic acid

Hydrolyzation is a very important stage in the human metabolism of caffeic acid which occurs in the intestine due to the presence of esterases, enzymes capable of hydrolyzing chlorogenic acid to produce caffeic acid. Caffeic acid is found in its ester within foods, which is very difficult to absorb; the absorption of ingested caffeic acid is 95±4%. The ingestion of this compound begins in the stomach where a very small amount of it is passively absorbed. Followed by the action of microbial esterases in the colon, the caffeic acid is cleaved in free form and absorbed by the intestinal mucosa (most 95%). Through active transport mediated by monocarboxylic acid transporters, the caffeic acid is then transported through the membranes of the intestinal cells. One hour after the ingestion of food, the maximum plasma concentration of caffeic acid was observed to rapidly decrease. The compound is made more hydrophilic immediately after absorption through the detoxification process (i.e. methylation, sulphation, and glucuronidation), thus reducing its toxicity and facilitating its elimination. The small intestine is likely to be a site for the cleavage of feruoylquinic acids releasing caffeic acid and ferulic acid, the metabolism of caffeic acid to its 3- and 4-O-sulfates, and the methylation of caffeic acid to form isoferulic acid and its subsequent 3-O-sulfation and glucuronidation. The colon is probably the site for the metabolism of caffeic acid to dihydrocaffeic acid, which is further metabolized to dihydro-isoferulic acid. Caffeic acid is excreted primarily through urine, with measures of urinary excretion between 5.9 – 27 % [6-8].

Figure 2. The presumed mechanism of the absorption and metabolization of phenolic compounds

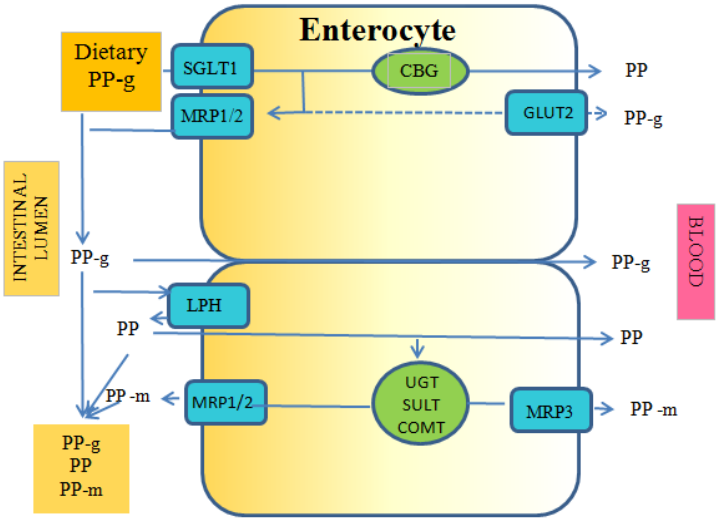

Figure 2. PP, (poly)phenol aglycone; PP-g, (poly)phenol glycoside; PP-m, polyphenol sulfate/glucuronide/methyl metabolites; SGLT1, sodium-dependent glucose transporter 1; GLUT2, glucose transporter 2; LPH, lactase phlorizin hydrolase; MRP1-2–3, multidrug-resistant proteins; CBG, cytosolic β-glucosidase; COMT, catechol-*O*-methyl transferase; SULT, sulfotransferase; UGT, uridine-5′-diphosphate glucuronosyltransferase. (Edited from [3]).

Caffeic acid bioactivity

Caffeic acid is claimed to have many health benefits including anti-inflammatory, anticancer, and antiviral capabilities. Caffeic acid is also an antioxidant that can reduce the oxidative stress that is formed in the body due to the effect of free radicals. Oxidative stress is defined as an imbalance

between the production of reactive oxygen species and the antioxidant defense. As a result of this imbalance, oxidative stress is often responsible for the development or enhancement of human diseases including cancer, atherosclerosis, cardiovascular diseases, major depression, Parkinson's disease, Alzheimer's disease, and many others [9]. The protective effect of caffeic acid as an antioxidant on α-tocopherol in low-density lipoproteins (LDL) has previously been shown [10]. Moreover, its combination with other products such as chlorogenic acid and caftaric acid has shown more potent antioxidant activity in a variety of different systems in vitro and in vivo and plays a major role in the protective effect of chlorogenic acid against ischemia-reperfusion injury [11-13]. Caffeic acids have also received attention as promising photoprotective agents and have been used in skincare products due to their antioxidant activity. However, the literature shows little evidence of the usefulness of hydroxycinnamic acids in protecting the skin from photo-oxidative damage [14].

Consumption of foods rich in caffeic acid has also been shown to protect against carcinogenesis due to its antioxidant and pro-oxidant properties. Caffeic acid exhibits pro-oxidative properties in cancer cells that are associated with oxidative DNA (deoxyribonucleic acid) damage and, followed by its subsequent signaling, the induction of death in apoptotic cancer cells. This anticancer effect of caffeic acid through pro-oxidative properties was first demonstrated in the study by Kanimozhi and Prasad (2015). They observed increased apoptotic morphological changes in cancer cell lines treated with caffeic acid, where the use of caffeic acid increased lipid peroxidation markers in HeLa and ME-180 cancer cell lines. They also observed elevated levels of reactive oxygen species and modified mitochondrial membrane potential [15]. In 2017, Kabała-Dzik *et al* conducted a comparative study of cytotoxic activity and migration rate inhibition using caffeic acid and caffeic acid phenethyl ester (doses of 50 and 100 μm) against triple-negative MDA-MB-231 breast adenocarcinoma line cells. Their study confirmed that both used compounds suspended the migration rate of breast cancer MDA-MB-231 cells, with better results obtained from caffeic acid phenethyl ester treatment [16]. Even though caffeic acid phenethyl ester was directly reported as a growth inhibitor of breast cancer cells, it has also been demonstrated that caffeic acid inhibits the viability and migration process of oral carcinoma SCC-25 cells as well as head and neck squamous carcinoma cells [17, 18]. Rosendahl *et al.* (2015) tested caffeine and caffeic acid specifically against breast cancer cells MCF-7, T47D, and MDA-MB-231. In their study, they demonstrated that caffeic acid inhibited breast cancer cell proliferation, affecting downstream effectors and cell cycle progression. The highest impact of caffeic acid was observed in the MCF-7 cells (estrogen-positive), where it suppressed the proliferation of breast cancer cells [19]. The positive effect of caffeic acid was observed against hepatocarcinoma, where the anticancer activity of this compound was associated with its antioxidant and prooxidant properties. This compound has been shown to prevent excessive ROS formation, assist in killing tumor cells by DNA oxidation and angiogenesis by reducing VEGF-induced (vascular endothelial growth factor) vascularization, and suppressing MMP-2 (matrix metalloproteinase 2) and MMP-9 (matrix metalloproteinase 9) expression [7].

An antidepressive-like activity of caffeic acid was also observed with a dose of 4 mg/kg by Takeda *et al.* (2002) [20]. Similar results reported the antidepressant effects of caffeic acid phenethyl ester, the main representative component of propolis, in the study of Lee *et al.* (2014) [21].

Similarly to other antioxidants, caffeic acid may affect aging by improving skin elasticity and lend to a positive anti-wrinkle effect due to naturally occurring bioactive compounds. In addition to the strong antioxidant activity of caffeic acid, increased collagen production, and prevention of premature aging, the antimicrobial activity of this compound has also been shown, making it a suitable and promising substance in the treatment of skin diseases [22]. Furthermore, it has been shown to have anti-wrinkle activity in vivo [23]. Bastianini *et al.* (2018) reported on the successful preparation of an innovative raw material for cosmetic applications. They described successful vehiculation of caffeic acid into anionic clay, which is a very promising hybrid for the cosmetic market because of its higher bioavailability and prolonged antioxidant activity [24].

Chao *et al.* (2009) studied the anti-inflammatory properties of caffeic acid and ellagic acid and in their study, they demonstrated a cardioprotective effect of the tested compounds against dyslipidemia, hypercoagulability, oxidative stress, and inflammation in diabetic mice. It was further observed that the dietary supplementation of caffeic and ellagic acid improved lipid metabolism and glycemic control in diabetic mice. Ultimately, both compounds showed anti-oxidative, anti-inflammatory, triglyceride-lowering, anti-coagulatory protection for the heart tissue of diabetic mice [25].

The antihyperglycemic effect of caffeic acid has also been investigated in the study of Hsu *et al.* (2000). They tested two rat models: streptozotocin-induced and insulin-resistant. In diabetic rats, a dose-related decrease in plasma glucose was observed following intravenous injection of caffeic acid. It was also shown to reduce increases in the plasma glucose levels of insulin-resistant rats, following a glucose test. According to these results, an increase in glucose utilization by caffeic acid seems to be responsible for the lowering of plasma glucose [26].

CONCLUSIONS

Consumption or supplementation of naturally occurring compounds has been shown to be helpful for the prevention of many diseases. Interest in caffeic acid as one of the bioactive compounds is increasing due to its role in treating or preventing diseases such as cancer, inflammation, and diabetes with the use of its positive antioxidant properties. Caffeic acid could also prove to be useful in the production of new cosmetics due to its anti-wrinkle properties. However, further studies to elucidate the activity of this substance in humans, as well as studies assessing the appropriate administration and dosage of caffeic acid, are needed.

List of abbreviations: FW, food weight; g, gram; mg, milligram; ml, milliliter; CBG, cytosolic β-glucosidase; COMT, catechol-*O*-methyl transferase; GLUT2, glucose transporter; LPH, lactase phloridzin hydrolase; MRP1-2–3, multidrug-resistant proteins; PP, (poly)phenol aglycone; PP-g, (poly)phenol glycoside; PP-m, polyphenol sulfate/glucuronide/methyl metabolites; SGLT1, sodium-dependent glucose transporter; SULT, sulfotransferase; UGT, uridine-5′-diphosphate glucuronosyltransferase; LDL, low-density lipoprotein; DNA, deoxyribonucleic acid; MDA-MB-231; HeLa; ME-180; MCF-7 and T47D cancer cell lines; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; MMP-2 and MMP-9, matrix metalloproteinases 2 and 9.

Competing interests: There are no conflicts of interest to declare.

Authors' contributions: CB and BA designed the concept of the manuscript, carried out the literature poll, wrote the manuscript. HB, BB, MM contributed to the writing of the manuscript.

BA, HB prepared figures. All authors discussed and contributed to the final version of the manuscript.

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