Caftaric acid: an overview on its structure, daily consumption, bioavailability and pharmacological effects

Khaled Mohamed Mohamed Koriem
Department of Medical Physiology, Medical Research Division, National Research Centre, Dokki, Cairo, Egypt
*corresponding author e-mail address: kkoriem@yahoo.com | Scopus ID 24477156100

ABSTRACT
Caftaric acid is simply known as phenolic derivative and it is present in high concentrations in grape seeds and juice. The chemical structure of caftaric acid is C_{12}H_{14}O_{9}, with molar mass of the acid equal to 312.230 g/mol. Caftaric acid is formed united of caffeic acid and tartaric acid. This paper reviews caftaric acid structure, daily consumption, bioavailability and pharmacological effects. The caftaric acid quickly passes to the stomach and duodenum and increases the absorption of the acid in the intestinal Caco-2 cells. The antioxidant effect of grape stem was related to its caftaric acid constituent. The grape juice has anti-inflammatory effect and this anti-inflammatory effect is correlated with the main constituent of this juice which is caftaric acid. Caftaric acid has antimutagenic effect in an animal model suggesting that caftaric acid participates in chemopreventive effect of the Yamabudo juice. The "liver detoxifying" effect is observed and correlated with oral supplementation with aqueous decoctions of Cichorium spinosum and Cichorium intybus in Greece where caftaric acid is the major constituent of these two aqueous decoctions. The caftaric acid possesses a double effect through decreasing high blood glucose and high blood pressure so this acid can be used in the treatment of diabetes and hypertension. The caftaric acid increases granulocyte/macrophage-colony forming cells from femurs of female animals' models by 70%. In conclusion, caftaric acid is presented about 5 mg/100 cm$^3$ grape juice. The acid is quickly passes into the stomach and duodenum. The trans-caftaric acid represents 85% of the total phenolic content in the Concord grape juice with a total concentration of 444 μmol/L. The caftaric acid has many pharmacological effects such as antioxidant, anti-inflammatory, antimutagenic and anticarcinogenic, hepatoprotective, anti-diabetic and anti-hypertensive, anti-obesity and anti-metabolic syndrome and neuroprotective effects.

Keywords: Caftaric acid; Antioxidant; Anti-diabetic; Anti-inflammatory; Anti-carcinogenic; Anti-obesity.

1. INTRODUCTION
Caftaric acid is simply known as phenolic derivative and it is present in high concentrations in grape seeds and juice[1,2]. Many names of caftaric acid are used such as butanedioic acid, trans-caftaric acid, cis-caftaric acid, trans-cafeoyl tartaric acid, monocaffeyl tartaric acid, cis-cafeoyl tartaric acid. The chemical structure of caftaric acid is C_{12}H_{14}O_{9} (Fig 1), with molar mass of the acid equal to 312.230 g/mol. The caftaric acid is formed due to the united of two famous acids (caffeic acid which produce from the medicinal plants and tartaric acid which is the main acid present in grape berries) and consequently caftaric acid is existing in high and sufficient quantities in all types of grape juices[2].

![Figure 1. Chemical structure of caftaric acid.](image)

Caftaric acid is present mainly in a sufficient and high amounts in grape juice among various hydroxycinnamic acids in the grape juice and its amount equal to 5 mg/100 cm$^3$ of grape juice[3]. The grape with olive oil increases the human health benefits of caftaric acid and all hydroxycinnamic acid derivatives in the grape [4]. The improving of immunity and antioxidant effects of purple coneflower is correlated with polyphenols compound such as caftaric acid. The purple coneflower is a fish dietary supplement. Consequently, fish feed on purple coneflower is a dietary supplement in fish disease inhibition by oxidative stress [5]. The pharmacokinetic investigation with mass spectrometric analysis of caftaric acid showed that it was eliminated slowly in rat blood [6].

The caftaric acid is a major polyphenol present in the most Mediterranean diet that prevents several diseases that associated especially with endothelial damage and this effect is correlated with antioxidant effect of caftaric acid [7]. The HPLC method identified twenty-three phenolic compounds from coneflower where caftaric acid was the major polyphenol compound and purple coneflower leaves contained nearly 2673.31 mg of caftaric acid/100 g of the dry leaves weight [8].

The grape contains caftaric acid that has an antioxidant effect on human health. The grape caftaric acid improved many genes expressions correlated with both cytoskeleton and differentiation[9]. The caftaric acid is mainly present in Cichorium intybus (common chicory) and at the same time the caftaric acid is the main constituent of Echinacea purpurea (Eastern purple coneflower). The caftaric acid has many usefulness biological impacts inside both animal and human biological body where trans-caftaric acid was identified in animal model plasma beside its derivative trans-fertaric acid[10]. In recent research the caftaric acid possesses a double effect through decreasing high blood glucose and high blood pressure so this acid can be used in the treatment of diabetes and hypertension[11]. The liquid chromatography associated with mass spectrum method is used to...
identify the phenolic constituents of fruit extracts from two species (Solanum indicum and Solanum surattense) of Solanaceae.

The data collected proved the presence of caftaric acid in Solanum indicum plant[12]. The well-known and famous grape of Southern Italy is Vitis vinifera cv Falanghina (Table 1 and Table 2). The caftaric acid is the main phenolic constituent in the Falanghina leaves and the high presence of this acid, which is a good antioxidant effect supported the use of grape vine leaves as a cheaper source of natural products in the food industry and pharmaceutical companies[13]. The caftaric acid is available and occurs in high concentrations in Berry shrivel affected grape. The Berry shrivel affected grapes increase the acidity and decreasing the sugar contents in the grape[14]. The caftaric acid (trans-caftaric acid) is the most abundant polyphenol in rosé sparkling wines[15]. The caftaric acid is anti-mutagenic ingredient in the Vitis coignetiae juice where this juice has anti-tumorigenic and anti-inflammatory effects on 2,6-dimethoxy-1,4-benzoquinone[16].

The high performance liquid chromatography method exhibits the presence of caftaric acid as a major phenolic compound in Ficus carica L. which is one of the oldest trees of mulberry family. It has nutritional and medicinal benefits[17].

This review inspects biological activities of caftaric acid including antioxidant, anti-inflammatory, antimutagenic and anticarcinogenic, hepatoprotective, anti-diabetic and anti-hypertensive, anti-obesity and anti-metabolic syndrome and neuroprotective effects. This is a review and all the data in this review was collected from online databases: PubMed (National Library of Medicine and National Institutes of Health), Web of Science, Google and Scopus data bases descending from 2020.

| Vitis species       | Juice brix | Berry wt (g) | Trans (mg/l) | Cis (mg/l) | % Cis | Trans (mg/l) | Cis (mg/l) | % Cis |
|---------------------|------------|--------------|--------------|------------|-------|--------------|------------|-------|
| aestuinalis         | 25.2       | 0.55         | 1337         | 16         | 1.2   | 1.5          | 0.2        | ---   |
| monnicola           | 19.8       | 0.57         | 1155         | 4          | 0.3   | 2.5          | 0.6        | ---   |
| monnicola           | 21.8       | 0.57         | 1010         | 6          | 0.6   | 1.0          | 0.1        | ---   |
| rafotomentosa       | 15.1       | 0.21         | 772          | 2          | 0.2   | 0.6          | 0.1        | ---   |
| simpsonii (pixiala) | 23.3       | 0.34         | 664          | 6          | 1.0   | 1.0          | 1.0        | ---   |
| arizonica           | 21.4       | 0.20         | 484          | 0.2        | 0.1   | 0.1          | 0.1        | ---   |
| labrusca            | 19.1       | 2.18         | 462          | 6          | 1.3   | 1.3          | 1.3        | ---   |
| smalliana           | 7.2        | 0.42         | 443          | 2          | 0.4   | 0.4          | 0.4        | ---   |
| releasei            | 15.8       | 0.61         | 405          | 2          | 0.4   | 0.4          | 0.4        | ---   |
| carkandas            | 23.2       | 0.41         | 403          | 4          | 1.1   | 1.1          | 1.1        | ---   |
| lincecumii           | 16.6       | 1.60         | 246          | 4          | 1.8   | 1.8          | 1.8        | ---   |
| Aghanjan source     | 21.6       | 0.44         | 220          | 3          | 1.2   | 1.2          | 1.2        | ---   |
| golidana            | 16.1       | 0.34         | 207          | 1          | 0.4   | 0.4          | 0.4        | ---   |
| shuttleworthii      | 20.1       | 1.17         | 185          | 2          | 1.1   | 1.1          | 1.1        | ---   |
| amurensis           | 17.8       | 0.57         | 128          | 2          | 1.7   | 1.7          | 1.7        | ---   |
| california          | 22.5       | 1.46         | 122          | 3          | 2.8   | 2.8          | 2.8        | ---   |
| berlandieri         | 14.8       | 0.35         | 89           | 1          | 1.1   | 1.1          | 1.1        | ---   |
| nova-angliae        | 24.1       | 1.38         | 71           | 4          | 5.0   | 5.0          | 5.0        | ---   |
| doamiana            | 18.6       | 1.42         | 57           | 0.5        | 0.8   | 0.8          | 0.8        | ---   |
| cinerea             | 16.6       | 0.27         | 53           | trace      | ---   | ---          | ---        | ---   |
| dainini             | 22.8       | 0.57         | 48           | trace      | ---   | ---          | ---        | ---   |
| longii              | 21.4       | 0.69         | 43           | trace      | ---   | ---          | ---        | ---   |
| champini            | 20.4       | 0.74         | 43           | trace      | ---   | ---          | ---        | ---   |
| riparia             | 18.9       | 0.29         | 41           | trace      | ---   | ---          | ---        | ---   |
| rupestris           | 16.3       | 0.29         | 40           | trace      | ---   | ---          | ---        | ---   |
| solonis             | 19.6       | 0.79         | 17           | trace      | ---   | ---          | ---        | ---   |
| cordifolia          | 22.6       | 0.20         | 5            | trace      | ---   | ---          | ---        | ---   |
| rotundifolia(Thomas)| 15.1       | 4.47         | 0            | 0          | 0     | 0            | 0          | ---   |
| rotundifolia(Creek) | 16.1       | 3.18         | trace        | 0          | 0     | 0            | 0          | ---   |
| rotundifolia        | 18.1       | 0.95         | 1.5          | trace      | ---   | ---          | ---        | ---   |

| Cultivar            | Juice brix | Berry wt (g) | Trans (mg/l) | Cis (mg/l) | % Cis | Trans (mg/l) | Cis (mg/l) | % Cis |
|---------------------|------------|--------------|--------------|------------|-------|--------------|------------|-------|
| Palomino            | 20.2       | 2.42         | 295          | 4          | 1.5   | 1.5          | 0.2        | ---   |
| Pinot blanc         | 20.8       | 1.44         | 266          | 3          | 1.2   | 1.2          | 0.2        | ---   |
| Semilion            | 11.3       | 1.13         | 197          | 2          | 1.0   | 1.0          | 0.1        | ---   |
| Semilion            | 21.2       | 2.77         | 98           | 1          | 1.3   | 1.3          | 0.3        | ---   |
| Rkatsiteli          | 20.8       | 2.05         | 181          | 4          | 2.4   | 2.4          | 0.6        | ---   |
| St. Emilion         | 20.6       | 1.79         | 179          | 5          | 2.9   | 2.9          | 0.9        | ---   |
| Emerald Riesling    | 21.3       | 1.84         | 154          | 2          | 1.5   | 1.5          | 0.5        | ---   |
| Muscat blanc        | 22.4       | 2.11         | 143          | 4          | 2.6   | 2.6          | 0.6        | ---   |
| Muscat Alexandria   | 17.0       | 3.57         | 141          | 3          | 1.9   | 1.9          | 0.6        | ---   |
| French Colombard    | 8.7        | 1.15         | 142          | 1          | 0.7   | 0.7          | 0.2        | ---   |
| French Colombard    | 19.8       | 1.79         | 97           | 2          | 2.5   | 2.5          | 0.8        | ---   |
| Chardonnay          | 22.1       | 1.14         | 135          | 1          | 0.4   | 0.4          | 0.1        | ---   |
| Chardonnay          | 21.0       | 1.55         | 122          | 3          | 2.6   | 2.6          | 0.8        | ---   |
The addition of glutathione onto caftaric acid is called the favored reaction where the substitution of the sulfanyl group of cysteine with the aromatic ring. Moreover, NMR analysis showed the effect of both UV and MS spectra in the aromatic ring for each of the isomers occurs [18]. The caftaric acid is identified as non-flavanoid polyphenols hydroxycinnamic acid from grape juice and concentrates from Crimea and Krasnodar regions [19]. The trans-caftaric acid represents 85% of the total polyphenol concentration (444 μmol/L) from the analysis of Concord grape juice by HPLC with mass spectra and fluorescence detection where 60 flavonoids and related phenolic compounds were detected [20]. The main substrate of polyphenoloxidase from Melon B. and Sauvignon blanc grape juices is caftaric acid [21]. Caftaric acid prevails among hydroxycinnamic acids presented in grape juice (with an average 5 mg/100 cm²). The industrial grape juice contains, on average, 6-10% of the human daily need for potassium, about 5-

### Table 3. Enzymatic oxidation of caftaric acid in the presence of added compounds[51].

| Phenol oxidized | Compound added | % Phenol retained | HPLC retention time (min) | Product % to origin | % of loss |
|-----------------|----------------|-------------------|--------------------------|---------------------|-----------|
| Caftaric acid (36 mg/L) | None | 100 | 7.8 | 0 | 0 |
| Caftaric acid (36 mg/L) | None | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Proline | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Lysine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Adenine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Guanosine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Xanthine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Methionine | 47 | 7.8 | 0 | 53 |
| Caftaric acid (36 mg/L) | Cysteine | 35 | 7.8 | 0 | 65 |
| Caftaric acid (36 mg/L) | Cysteine | 0 | 7.0 | 77 | 23 |
| Caftaric acid (36 mg/L) | Glutathione | 0 | 8.7 | 76 | 24 |
| Caftaric acid (36 mg/L) | Sodium sulfide (H2S) | 0 | 9.3 | 20 | 80 |
| Caftaric acid (36 mg/L) | 1,4-Dithiole retiol | 0 | 0 | 0 | 100 |
| Caftaric acid (36 mg/L) | 2-Mercaptoethanol | 0 | 14.7 | 48 | 52 |
| Caftaric acid (36 mg/L) | Mercaptoethanolamine | 0 | 10.2 | 54 | 46 |
| Caftaric acid (36 mg/L) | α-Mercaptopropionyl glycine | 0 | 16.0 | 41 | 59 |
| Caftaric acid (36 mg/L) | 2-Amino-6-mercaptopurine | 0 | 18.3 | 43 | 57 |
| Caftaric acid (36 mg/L) | α-Thioglycerol | 0 | 11.7 | 28 | -- |

2. CAFTAIC ACIDS LEVELS IN GRAPE JUICE AND ESTIMATED DAILY CONSUMPTION THROUGH GRAPE JUICE

The wine color darkening was produced by exposing grape polyphenol such as caftaric acid to enzymatic oxidation (Table 3). The addition of glutathione onto caftaric acid is called the favored reaction where the substitution of the sulfanyl group of cysteine at C-2 of the aromatic ring. Moreover, NMR analysis showed the effect of both UV and MS spectra in the aromatic ring for each of the isomers occurs [18]. The caftaric acid is identified as non-flavanoid polyphenols hydroxycinnamic acid from grape juice and concentrates from Crimea and Krasnodar regions [19]. The trans-caftaric acid represents 85% of the total polyphenol concentration (444 μmol/L) from the analysis of Concord grape juice by HPLC with mass spectra and fluorescence detection where 60 flavonoids and related phenolic compounds were detected [20]. The main substrate of polyphenoloxidase from Melon B. and Sauvignon blanc grape juices is caftaric acid [21]. Caftaric acid prevails among hydroxycinnamic acids presented in grape juice (with average 5 mg/100 cm²). The industrial grape juice contains, on average, 6-10% of the human daily need for potassium, about 5-

| Phenol oxidized | Compound added | % Phenol retained | HPLC retention time (min) | Product % to origin | % of loss |
|-----------------|----------------|-------------------|--------------------------|---------------------|-----------|
| Caftaric acid (36 mg/L) | None | 100 | 7.8 | 0 | 0 |
| Caftaric acid (36 mg/L) | None | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Proline | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Lysine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Adenine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Guanosine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Xanthine | 0 | -- | 0 | 100 |
| Caftaric acid (36 mg/L) | Methionine | 47 | 7.8 | 0 | 53 |
| Caftaric acid (36 mg/L) | Cysteine | 35 | 7.8 | 0 | 65 |
| Caftaric acid (36 mg/L) | Cysteine | 0 | 7.0 | 77 | 23 |
| Caftaric acid (36 mg/L) | Glutathione | 0 | 8.7 | 76 | 24 |
| Caftaric acid (36 mg/L) | Sodium sulfide (H2S) | 0 | 9.3 | 20 | 80 |
| Caftaric acid (36 mg/L) | 1,4-Dithiole retiol | 0 | 0 | 0 | 100 |
| Caftaric acid (36 mg/L) | 2-Mercaptoethanol | 0 | 14.7 | 48 | 52 |
| Caftaric acid (36 mg/L) | Mercaptoethanolamine | 0 | 10.2 | 54 | 46 |
| Caftaric acid (36 mg/L) | α-Mercaptopropionyl glycine | 0 | 16.0 | 41 | 59 |
| Caftaric acid (36 mg/L) | 2-Amino-6-mercaptopurine | 0 | 18.3 | 43 | 57 |
| Caftaric acid (36 mg/L) | α-Thioglycerol | 0 | 11.7 | 28 | -- |
8% for magnesium, iron and manganese. The content of flavonoids per serving is about 25% of the adequate level of daily consumption, and the content of hydroxycinnamic acids exceeds it [3]. The caftaric acid is the principal ingredient of aqueous preparations that traditionally prepared from Cichorium spinosum.

3. BIOAVAILABILITY OF CAFTARIC ACID

The caftaric acid is the main ingredient occurs in Crepidiastrum denticulatum medicinal plant and this acid quickly passes into the stomach and duodenum and increases the absorption of the acid in the intestinal Caco-2 cells. The digestive stability and bio-accessibility of caftaric acid from Crepidiastrum denticulatum were declined following fake digestion and still slightly in the ileum. The caftaric acid cell permeability was very high and consequently there were a rapid passes of the acid in both stomach and duodenum, which leads to increase the absorption of the acid in Caco-2 cells [23]. The trans-caftaric acid represents 85% of the total phenolic content, with a total concentration of 444 μmol/L from the concord grape juice analyzed by HPLC with and fluorescence detection [20]. In all types of grapes especially the dried grapes (raisins) the caftaric acid is the most abundant polyphenol ingredient was occurring. The raisins had beneficial effects on human health such as decreased insulin response, reduced sugar absorption, affect some oxidative biomarkers, and promote satiety[24].

4. PHARMACOLOGICAL EFFECTS OF CAFTARIC ACID

The HPLC method correlated with mass spectra identified phenolic compounds in coneflower. The caftaric acid was the main phenolic compound in coneflower, especially purple coneflower. Caftaric acid, has health promoting effects, was extracted best in a water solution from purple coneflower leaves (2673.31 mg/100 g dry weight) [8]. Caftaric acid was detected by LC-MS in grape and this acid has beneficial human effects, especially antioxidant effect, on human health upon its consumption. This caftaric acid constituent in grape improved the cytoskeleton expression and all genes that correlated with cell differentiation [9]. The caftaric acid resembles the major polyphenol that occurs in the Cretan diet (the basis of the Mediterranean diet) used in folklore medicine for human health. The daily intake with aqueous decoctions of Cichorium spinosum and Cichorium intybus in Greece associated with a liver detoxifying effect. The major antioxidant constituent of these decoctions is caftaric acid and these decoctions had nontoxic in human fibroblasts, declined reactive oxygen species and had a powerful antioxidant effect [22].

4.1. Antioxidant effect.

The caftaric acid increases at 50% management allowable depletion levels, in both two green leafy lettuce cultivars (Lollo Bionda and Vera) at harvest indicating an increasing antioxidant effect. Consequently, the lettuce cv. Vera was a suitable cultivar for deficit irrigation (at 50% management allowable depletion levels) due to increasing dietary phytochemicals and crop quality without compromising fresh mass for marketing [25]. The antioxidant effect of grape (Vitis vinifera L.) stem was related to its caftaric acid constituent by recent research [26] which testing antioxidant effects on radical scavenging capacity (DPPH and ABTS), cell viability, anti-inflammatory effect, and its ability to ameliorate reactive oxygen species, glutathione and lipid peroxidation in human keratinocytes in vitro in control and oxidative states.

In another study [27], the caftaric acid is the main and principal ingredient in seed extract of romaine lettuce compared to its leaf extract. Consequently, the antioxidant effect of the leaf extract was significantly less than that of the seed extract which contains caftaric acid. So, romaine lettuce protects from the oxidative stress induced by sleep disturbance due to its constituent and Cichorium intybus which constitute the Cretan diet (the traditional remedies for the general well-being of people) through the long-established consumption of cooked wild greens and vegetables [22].

The cytokine levels were declined as a result of low and high doses of caftaric acid intake. So, caftaric acid showed anti-inflammatory effect in indomethacin-induced gastric ulcer in animals’ models research study [31].

4.2. Anti-inflammatory effect.

The Vitis coignetiae juice has anti-inflammatory effect and this anti-inflammatory effect is correlated with the main constituent of this juice which is caftaric acid. The caftaric acid had a decline effect on nitric oxide production in animal model leukemic monocyte and consequently, caftaric acid was isolated as anti-inflammatory constituent from the Vitis coignetiae juice [16]. The cytokine levels were declined as a result of low and high doses of caftaric acid intake. So, caftaric acid showed anti-inflammatory effect in indomethacin-induced gastric ulcer in animal models [31]. An oral intake with Vitis coignetiae Pulliat (Yamabudo) grape juice into animal model declined the inflammation process recorded. An oral intake with the Yamabudo juice counteracted the increase in COX-2 activity in the inflammation process. Caffaric acid was isolated and identified from the Yamabudo juice which prevented inflammation in animal model, suggesting that caftaric acid have a chemopreventive role of Yamabudo juice [32].
4.3. Antimutagenic and anticarcinogenic effects.

The liquid chromatography was used to identify the genoprotective effect of caftaric acid, which represents one of the total phenols found in three cucurbitaceae seeds extracts which belong to Cucurbitaceae family which represents one of most spreading plant species for human food.

The seeds extract production was 20-41% (w/w) and the extracts had 16-40% total phenols. The application of acidified methanol increased seeds extraction, production by 1.4 to 10-fold, increased phenolic content of the seeds extracts, increased antioxidant effect such as DPPH radical quenching and improved genoprotective effect of the seeds extracts by using the pBR322 plasmid test [33]. The supplementation with Vitis coignetiae (Yamabudo) grape juice declined the incidence and the total number of tumors in the animal model skin. The Vitis coignetiae (Yamabudo) juice had an antimutagenic effect in carcinogenic materials in in vitro model. Caftaric acid is the main constituent in this juice had antimutagenic effect in an animal model, suggesting that caftaric acid participates in chemopreventive effect of the Yamabudo juice [32].

The caftaric acid has an anti-mutagenic effect in Yamabudo juice. Caftaric acid declines protein-protein interactions process. The intake of the juice of Vitis coignetiae purple berries DNA double strans formation in liver, lungs, colon and kidneys of animal model exposed to carcinogenic materials. The Yamabudo juice declined the clastogenicity and mutagenicity of carcinogenic materials in the micronucleus and Ames tests. At the same time, the juice declined the phase I enzymes activities and increase phase II enzyme activities [34]. The oral intake with Champagne wine for 6 weeks ameliorates brain neurotrophic factor, c-Adenosine Mono Phosphate response-element-binding protein (CREB), p38 gene, mammalian target of rapamycin (mTOR), dystrophin and Bcl-xL in Champagne group compared with control drink. There is amelioration in mTOR, Bcl-xL, and CREB in Champagne wine compared with the alcohol group. The caftaric acid (the main constituent of Champagne wine) is capable of exerting improvements in spatial memory through the amelioration of hippocampal signaling and protein expression[35].

4.4. Hepatoprotective effect.

The “liver detoxifying” effect is observed and correlated with oral supplementation with aqueous decoctions of both Cichorium spinosum and Cichorium intybus in Greece. Where the Cretan diet (the basis of the Mediterranean diet) applied in folklore medicine for the human health through the long consumption of cooked wild vegetables and the caftaric acid is the major constituent of these two aqueous decoctions [22]. The caftaric acid represents the hepatic metabolites of choricric acid by using HPLC with mass spectrum method and the caftaric acid had a strong effect on scavenging free radicals and increases reactive oxygen species levels in the cells in pre-adiocytes and consequently decreasing cell life [36]. Methamphetamine intoxication induced acute hepatic failure through increased liver enzymes, cholesterol, malondialdehyde in liver, liver nitric oxide levels while decreased proteins in liver, brain neurotransmitters, liver antioxidants enzymes but caftaric acid before methamphetamine exposure decreased liver enzymes, cholesterol, malondialdehyde in liver, liver nitric oxide levels while increased proteins in the liver, brain neurotransmitters, liver antioxidant enzymes to approach the control and normal levels so caftaric acid before methamphetamine exposure prevented liver toxicity and oxidative stress [37].

Following 10 and 20 min of caftaric acid consumption, caftaric acid is detected in animal plasma with its derivative fertaric acid. The caftaric acid and fertaric acid are detected in animal kidney but not in animal liver following 20 min of caftaric acid intake and fertaric acid is found in animal urine [38].

4.5. Anti-diabetic and anti-hypertensive effects.

In a recent study, the caftaric acid possesses a double effect through decreasing high blood glucose and high blood pressure so this acid can be used in the treatment of diabetes and hypertension [11]. The trans-caftaric and trans-coutaric acids and trans-fertaric acid represent 29% of the phenolic content (total concentration of phenol= 444 μmol/L) of Concord grape juice from which 85% comprised trans-caftaric acid. The caftaric acid showed an anti-hypertensive effect [20].

Caftaric acid is a major ingredient and one of the polyphenol found in chardonnay white wine. The white wine intake by oral gavage for 6 weeks to diabetic animal model revealed no effect on the indications associated with higher blood glucose. The wine oral intake returned plasma antioxidant levels to control levels and the wine oral intake increases the enlargement of mesenteric arteries which determined by histomorphometry [39]. The trans-caftaric acid as a polyphenol constituent in the grape protects the cardiac tissue from ischemic damage by increasing post-ischemic ventricular recovery while decreasing the size of myocardial infarct [40]. The insulin secretion jumps high from pancreatic islets at caftaric acid concentration range from 10^{-10} to 10^{-6} M. In addition, following prolonged caftaric acid incubation (10^{-8} M), the insulin secretion also jumps to a higher level. The acid does not increase insulin secretion in low glucose concentration. Moreover, caftaric acid caused gene expression of (1) insulin regulatory genes (IRS1, INSR, INS1, INS2 and PDX1), (2) proliferative genes and (3) glucose transporter 2 (GLUT2) in pancreatic islets and consequently the acid plays a significant role in diabetes therapy [41].

4.6. Anti-obesity and anti-metabolic syndrome effects.

The caftaric acid is a major ingredient in Echinacea purpurea ethanolic extract. The ethanolic extract (50 mg aerial part/kg animal weight) increased granulocyte/macrophage-colony forming cells from the femurs of female animal models by 70% when evaluated at 24 h after 7 daily oral intake. The ethanolic extract (200 mg/kg) increased granulocyte/macrophage-colony forming cells exactly double to triple times, respectively [42]. The lead prompted decline kidney weight, serum electrolytes while increased urinary volume, urinary excretion of electrolytes and kidney function. It also lead declined kidney antioxidant enzymes.

The lead declined kidney p53 expression and increased bcl-2 expression. The caftaric acid with lead in animal models returned all the above parameters to approach the normal levels [43]. The caftaric acid played a major role to increase both reduced and oxidized form of glutathione (GSH and GSSH) in wine, where wine oxidation process is the main process in wine manufacture which affecting directly on wine quality [44]. The extract derived from the aerial parts of Crepis japonica plant revealed the presence of caftaric acid as major polyphenol in this
The probiotic bacterium Lactobacillus johnsonii to caftaric acid in a gastrointestinal model resulted in 65% hydrolysis of caftaric acid and increase the physicochemical conditions of the human gastrointestinal tract. There is no caftaric acid hydrolysis that was observed after the cross of gastrointestinal tract in probiotic bacterium Lactobacillus johnsonii lack medium and consequently the caftaric acid is hydrolyzed by gastrointestinal tract microflora earlier to its absorption and metabolism [48].

4.7. Neuroprotective effect.

The lemon balm water extract has higher caftaric acid. The extract concentrations range from 50?200?M have cytotoxic effect and initiate cell death via apoptosis process. Ethanolic extracts contain higher caftaric acid and showed the highest cytotoxic activity on glioblastoma cells. The ethanolic extract increased reactive oxygen species inside the cell and cell death as well via apoptosis and necrosis and consequently lemon balm extract destroyed glioblastoma cells and has a neuroprotective effect [49]. The caftaric acid decreased brain neurotransmitters such as serotonin, norepinephrine and dopamine to approach the normal levels in methamphetamine intoxication and also caftaric acid restores the oxidative stress occurs in brain through an increase of malondialdehyde level in the brain following methamphetamine intoxication and consequently caftaric acid protect neural cells in the brain [37]. Caftaric acid has an important role in hippocampal and cortical proteins especially those proteins incorporated in neuroplasticity, signal transduction, apoptosis and cell cycle controlling and consequently the acid is able to improve in spatial memory via attenuation of hippocampal signaling and protein expression [35]. The caftaric acid was identified and recorded as 180±20 ng/g brain tissue in a few animals models research study [10].

5. CONCLUSIONS

The influence of caftaric acid on the daily polyphenol and antioxidant intake from grape seeds and juice is quite relevant. Few and rare studies have confirmed that caftaric acid is bioavailable and potentially beneficial to human health. However, considering that the caftaric acid concentration in grape seeds and juice depends on a number of factors include inter-individual variability occurs in the metabolism of caftaric acid in humans and the ingested caftaric acid necessary to promote human health benefits, more studies are needed in the future in order to establish a daily dietary recommendation aiming at specific health benefits.

More researches are needed to elucidate the mechanisms involved in the absorption and metabolism of individual major and minor caftaric acid in grape seeds and juice. At the same time, more researches focus on the interactions of food constituents with caftaric acid is also needed in the nearest future.

6. REFERENCES

1. Lee, C.Y.; Jaworski, A. Phenolic Compounds in White Grapes Grown in New York. Am J Enol Vitic. 1987, 38, 277-281.
2. Andrew, W.; Gavin, S.; David, J. Chapter 13: Non-flavonoid Phenolics. In: Understanding Wine Chemistry. Adelaide: Wiley Books. 2016; pp. 112-113, https://doi.org/10.1002/9781118730720.ch13.
3. Ivanova, N.N.; Khomich, L.M.; Perova, I.B.; Eller, K.I. Grape juice nutritional profile. Vopr Pitani. 2018, 87, 95-105, http://doi.org/10.24411/0042-8833-2018-10046.
4. Olivati, C.; de Oliveira Nishiyama, Y.P.; de Souza, R.T.; Jantzntti, N.S.; Mauro, M.A.; Gomes, E.; Hermesin-Gutiérrez, I.; da Silva, R.; Lago-Vanzela, E.S. Effect of the pre-treatment and the drying process on the phenolic composition of raisins produced with a seedless Brazilian grape cultivar. Food Res Int. 2019, 116, 190-199, https://doi.org/10.1016/j.foodres.2018.08.012.
5. Oniszczuk, T.; Oniszczuk, A.; Gondek, E.; Güt, L.; Puk, K.; Kocia, A.; Kusz, A.; Kasprzak, K.; Wójtowicz, A. Active polyphenolic compounds, nutrient contents and antioxidant capacity of extruded fish feed containing purple coneflower (Echinacea purpurea (L.) Moench.). Saudi J Biol Sci. 2019, 26, 24-30, https://doi.org/10.1016/j.sjbs.2016.11.013.
6. Shi, P.; Yang, C.; Su, Y.; Huang, L.; Lin, X.; Yao, H. Simultaneous Determination of Five Phenolic Acids and Four Flavonoid Glycosides in Rat Plasma Using HPLC-MS/MS and Its Application to a Pharmacokinetic Study after a Single Intravenous Administration of Kudiezi Injection. Molecules 2018, 24, https://doi.org/10.3390/molecules24010064.
7. Stagos, D.; Balabanos, D.; Savva, S.; Skaperda, Z.; Priftis, A.; Kerasioti, E.; Mikropoulou, E.V.; Vougogiannopoulou, K.; Mitakou, S.; Halabalaki, M.; Kouretas, D. Extracts from the Mediterranean Food Plants Carthamus lanatus, Cichorium intybus, and Cichorium spinosum Enhanced GSH Levels and
Increased Nr2 Expression in Human Endothelial Cells. Oxid Med Cell Longev. 2018, 2018, https://doi.org/10.1155/2018/6594101.

8. Senica, M.; Mlnešk, G.; Veberic, R.; Mikulic-Petkovsek, M. Which Plant Part of Purple Coneflower (Echinacea purpurea (L) Moench) Should be Used for Tea and Which for Tincture? J Med Food. 2019, 22, 102-108, https://doi.org/10.1089/jmf.2018.0026.

9. Pfifis, A.; Goutzourelas, N.; Halabalaki, M.; Ntasi, G.; Stagos, D.; Amoutzias, G.D.; Skaltsounis, L.A.; Kouretas, D. Effect of polyphenols from coffee and grape on gene expression in myoblasts. Mech Ageing Dev. 2018, 172, 115-122, https://doi.org/10.1016/j.mad.2017.11.015.

10. Vanzo, A.; Cecotti, R; Vrhovsek, U.; Torres, AM; Mattivi, F; Passamonti, S. The fate of trans-cafearic acid administered into the rat stomach. J Agric Food Chem. 2007, 55, 1604-11, https://doi.org/10.1021/jf0626819.

11. Chukwuma, CI.; Matsabisa, MG.; Ibrahim, MA.; Erukinure, O.L.; Chabalala, M.H.; Islam, MS. Medicinal plants with concomitant anti-diabetic and anti-hypertensive effects as potential sources of dual acting therapies against diabetes and hypertension: A review. J Ethnopharmacol. 2019, 235, 329-360, https://doi.org/10.1016/j.ejep.2019.02.024.

12. Yasir, M.; Sultan, B.; Anwar, F. LC-ESI-MS/MS based characterization of phenolic components in fruits of two species of Solanaceae. J Food Sci Technol. 2018, 55, 2370-2376, https://doi.org/10.1007/s13197-017-2702-9.

13. Tartaglione, L.; Gambuti, A.; De Cocco, P.; Ercolano, G.; Ianaro, A.; Tagliatalata-Scafati, O.; Moio, L.; Forino, M. NMR-based phytochemical analysis of Vitis vinifera cv Falanghina leaves. Characterization of a previously undescribed biflavonoid with antiproliferative activity. Fitoterapia 2018, 125, 13-17, https://doi.org/10.1016/j.fitote.2017.12.009.

14. Grieser, M.; Martínez, S.C.; Eitlé, M.W.; Warth, B.; André, C.M.; Schuhmacher, R.; Foronce, A. The ripening disorder berry shrivelling affects anthocyanin biosynthesis and sugar metabolism in Zweigelt grape berries. Planta 2018, 247, 471-481, https://doi.org/10.1007/s00425-017-2795-4.

15. Sartor, S.; Burin, V.M.; Panceri, C.P.; Dos Passos, R.R.; Caliari, V.; Bordignon-Luiz, M.T. Rosé Sparkling Wines: Influence of Winemaking Practices on the Phytochemical Polyphenol During Aging on Lees and Commercial Storage. J Food Sci. 2018, 83, 2790-2801, https://doi.org/10.1111/1750-3841.14379.

16. Kamiyà, T.; Tanimoto, Y.; Fujii, N.; Negishi, T.; Suzuki, T.; Hatano, T.; Arimoto-Kobayashi, S. 2,6-Dimethoxy-1,4- benzoxoquinone, isolation and identification of anti-carcinogenic, anti-mutagenic and anti-inflammatory component from the juice of Vitis coignetiae. Food Chem Toxicol. 2018, 122, 172-180, https://doi.org/10.1016/j.fct.2018.10.028.

17. Nadeem, M.; Zeb, A. Impact of maturity on phenolic composition and antioxidant activity of medicinally important leaves of Ficus carica L. Physiol Mol Biol Plants. 2018, 24, 881-887, https://doi.org/10.12988/ijp.2018.0550-3.

18. Ferreira-Lima, N.; Vallverdu-Queralt, A.; Meudec, E.; Mzaouar, J.; Sommerer, N.; Bordignon-Luiz, M.T.; Cheynier, V.; Le Guenèvè, C. Synthesis, identification, and structure elucidation of adducts formed by reactions of hydroxyacinnacins acids with glutathione or cysteinlyglycine. J Nat Prod. 2016, 79, 2211-22, https://doi.org/10.1021/acs.jnatprod.6b00279.

19. Avidžba, A.M.; Kubhyškin, AV; Guguchkina, T.I.; Markosov, V.A.; Katsev, A.M.; Naumova, N.V.; Shramko, Y.I.; Zaytsev, G.P.; Chemousova, I.V.; Ogay, Y.A.; Fomochkina, I.I. The antioxidant activity of the products of processing of red grape of Cabernet Sauvignon, Merlot, Saperavi. Vopr Pitan. 2016, 85, 99-109.

20. Stalmach, A.; Edwards, C.A.; Wightman, J.D.; Crozier, A. Identification of (poly)phenolic compounds in concord grape juice and their metabolites in human plasma and urine after juice consumption. J Agric Food Chem. 2011, 59, 9512-22, https://doi.org/10.1021/jf2015039.

21. Roland, A.; Vialaret, J.; Razungles, A.; Rigou, P.; Schneider, R. Evolution of S-cysteinylated and S-glutathionylated thiold precursors during oxidation of Melon B and Sauvignon blanc musts. J Agric Food Chem. 2010, 58, 4406-13, https://doi.org/10.1021/jf904164v.

22. Brièdes, V.; Angelis, A.; Vogougiannopoulou, K.; Pratsinis, H.; Kletas, D.; Mitakou, S.; Halabalaki, M.; Skaltsounis, L.A. Phytochemical Analysis and Antioxidant Potential of the Phytonutrient-Rich Decoction of Cichorium spinosum and C. intybus. Planta Med. 2016, 82, 1070-8, https://doi.org/10.1055/s-0042-174772.

23. Lee, H.J.; Cha, K.H.; Kim, C.Y.; Nho, C.W.; Pan, C.H. Bioavailability of hydroxyacinic acids from Cepediastrum dentidulatum using simulated digestion and Caco-2 intestinal cells. J Agric Food Chem. 2014, 62, 5290-5, https://doi.org/10.1021/jf50319h.

24. Williamson, G.; Carughi, A. Polyphenol content and health benefits of raisins. Nutr Res. 2010, 30, 511-9, https://doi.org/10.1016/j.nutres.2010.07.005.

25. Malejane, D.N.; Tinyani, P.; Soundy, P.; Sultanbawa, Y.; Sivakumar, N. Deficit irrigation improves phenolic content and antioxidant activity in leafy lettuce varieties. Food Sci Nutr. 2017, 6, 334-341, https://doi.org/10.1002/fsn3.559.

26. Queiroz, M.; Oppolzer, D.; Gouvinhas, I.; Silva, A.M.; Barros, A.; Dominguez-Perles, R. New grape steins’ isolated phenolic compounds modulate reactive oxygen species, glutathione, and lipid peroxidation in vitro: Combined formulations with vitamins C and E. Fitoterapia 2017, 120, 146-157, https://doi.org/10.1016/j.fitote.2017.06.010.

27. Kim, H.D.; Hong, K.B.; Noh, D.O.; Suh, H.J. Sleep-inducing effect of lettuce (Lactuca sativa) varieties on pentobarbital-induced sleep. Food Sci Biotechnol. 2017, 26, 807-814, https://doi.org/10.1007/s10068-017-1071-1.

28. Li, Y.; Li, L.; Cui, Y.; Zhang, S.; Sun, B. Separation and purification of polyphenols from red wine extracts using high speed counter current chromatography. J Chromatogr B Analyt Technol Biomed Life Sci. 2017, 1054, 105-113, https://doi.org/10.1016/j.jchromb.2017.03.006.

29. Padilha, CV.; Miskinis, G.A.; de Souza, M.E.; Pereira, G.E.; de Oliveira, D.; Bordignon-Luiz, M.T.; Lima, M.D. Rapid determination of flavonoïds and phenolic acids in grape juices and wines by RP-HPLC/DAD: Method validation and characterization of commercial products of the new Brazilian varieties of grape. Food Chem. 2017, 228, 106-115, https://doi.org/10.1016/j.foodchem.2017.01.157.

30. Petropoulos, S.A.; Levizou, E.; Ntasi, G.; Femendes, Á.; Petrotos, K.; Akoumanakis, K.; Barros, L.; Ferreira, I.C.F.R. Salinity effect on nutritional value, chemical composition and bioactive compounds content of Cichorium spinosum L. Food Chem. 2017, 214, 129-136, https://doi.org/10.1016/j.foodchem.2016.07.080.

31. Tanyeli, T.; Akoumianakis, I.; Angelis, A.; Miskinis, K.; Kamiya, T.; Negishi, T.; Okamoto, G. Chemopreventive effects of the juice of Vitis coignetiae Pulliat on two-stage mouse skin carcinogenesis. Nutr Cancer 2013, 65, 440-50, https://doi.org/10.1080/01635581.2013.767916.
Caftaric acid: an overview on its structure, daily consumption, bioavailability and pharmacological effects

33. Yasir, M.; Sultana, B.; Nigam, P.S.; Owusu-Apenten, R. Antioxidant and genoprotective activity of selected cucurbitaceae seed extracts and LC-ESIMS/MS identification of phenolic components. *Food Chem.* 2016, 199, 307-13, https://doi.org/10.1016/j.foodchem.2015.11.138.

34. Zhang, X.; Ishida, R.; Yuhara, Y.; Kamaya, T.; Hatano, T.; Okamoto, G.; Arimoto-Kobayashi, S. Anti-genotoxic activity of *Vitis coignetiae* towards heterocyclic amines and isolation and identification of caftaric acid as an antimutagenic component from the juice. *Mutat Res.* 2011, 723, 182-9, https://doi.org/10.1016/j.mrertox.2011.05.001.

35. Corona, G.; Vauzour, D.; Hercelin, J.; Williams, C.M.; Spencer, J.P. Phenolic acid intake, delivered via moderate champagne wine consumption, improves spatial working memory via the modulation of hippocampal and cortical protein expression/activation. *Antioxid Redox Signal.* 2013, 19, 1676-89, https://doi.org/10.1089/ars.2012.5142.

36. Liu, Q.; Wang, Y.; Xiao, C.; Wu, W.; Liu, X. Metabolism of chicoric acid by rat liver microsomes and bioactivity comparisons of chicoric acid and its metabolites. *Food Funct.* 2015, 6, 1928-35, https://doi.org/10.1039/C5FO0073D.

37. Koriem, K.M.; Soliman, R.E. Chlorogenic and caftaric acids in liver toxicity and oxidative stress induced by methamphetamine. *J Toxicol.* 2014, 2014, https://doi.org/10.1155/2014/583494.

38. Vanzo, A.; Cecotti, R.; Vrhovsek, U.; Torres, A.M.; Mattivi, F.; Passamonti, S. The fate of trans-caftaric acid administered into the rat stomach. *J Agric Food Chem.* 2007, 55, 1604-11, https://doi.org/10.1021/jf06268x19.

39. Landrault, N.; Poucheret, P.; Azay, J.; Krosniak, M.; Gasc, F.; Jenn, C.; Cros, G.; Teissedre, P.L. Effect of a polyphenols-enriched chardonnay white wine in diabetic rats. *J Agric Food Chem.* 2003, 51, 311-8, https://doi.org/10.1021/jf020219s.

40. Falchi, M.; Bertelli, A.; Lo Scalzo, R.; Morassut, M.; Morelli, R.; Das, S.; Cui, J.; Das, D.K. Comparison of cardioprotective abilities between the flesh and skin of grapes. *J Agric Food Chem.* 2006, 54, 6613-22, https://doi.org/10.1021/jf061048k.

41. Casanova, L.M.; Qi, W.; Costa, S.S.; Jeppesen, P.B. Phenolic Substances from *Ocimum Species* Enhance Glucose-Stimulated Insulin Secretion and Modulate the Expression of Key Insulin Regulatory Genes in Mice Pancreatic Islets. *J Nat Prod.* 2017, 80, 3267-3275, https://doi.org/10.1021/acs.jnatprod.7b00699.

42. Ramasahayam, S.; Baraka, H.N.; Abdel Bar, F.M.; Abuasal, B.S.; Widrichner, M.P.; Sayed, K.A.; Meyer, S.A. Effects of chemically characterized fractions from aerial parts of *Echinacea purpurea* and *E. angustifolia* on myelopoesis in rats. *Planta Med.* 2011, 77, 1883-9, https://doi.org/10.1055/s-0031-1279990.

43. Koriem, K.M.M.; Abid, M.S. Role of caftaric acid in lead-associated nephrotoxicity in rats via antioxidant, antidepressant and anti-apoptotic activities. *J Complement Integr Med.* 2017, 15, https://doi.org/10.1515/jcim-2017-0024.

44. Ferreira-Lima, N.; Vallverdu-Queralt, A.; Meudec, E.; Pinasseau, L.; Verbaere, A.; Bordignon-Luiz, M.T.; Le Guernevé, C.; Cheynier, V.; Sommerer, N. Quantification of hydroxycinnamic derivatives in wines by UHPLC-MRM-MS. *Anal Bioanal Chem.* 2018, 410, 3483-3490, https://doi.org/10.1007/s00216-017-0759-y.

45. Constantino, L.F.; Nascimento, L.B.; Casanova, L.M.; Moreira, N.D.; Menezes, E.A.; Esteves, R.L.; Costa, S.S.; Tavares, E.S. Responses of *Crepis japonica* induced by supplemental blue light and UV-A radiation. *Photochem Photobiol Sci.* 2017, 16, 238-245, https://doi.org/10.1039/C6PP00343F.

46. Calabrisko, N.; Scoditti, E.; Massaro, M.; Pellegrino, M.; Storelli, C.; Ingrosso, I.; Giovinazzo, G.; Carluccio, M.A. Multiple anti-inflammatory and anti-atherosclerotic properties of red wine polyphenolic extracts: differential role of hydroxycinnamic acids, flavonols and stilbenes on endothelial inflammatory gene expression. *Eur J Nutr.* 2016, 55, 477-489, https://doi.org/10.1007/s00394-015-0865-6.

47. Ali, K.; Iqbal, M.; Fortes, A.M.; Pais, M.S.; Korthout, H.A.; Verpoorte, R.; Choi, Y.H. Red wines attenuate TNFα production in human histioctytic lymphoma cell line: an NMR spectroscopy and chemometrics based study. *Food Chem.* 2013, 141, 3124-30, https://doi.org/10.1016/j.foodchem.2013.06.001.

48. Bel-Rhild, R.; Fugé-Zoerkler, N.; Fumeaux, R.; Ho-Dac, T.; Chuat, J.Y.; Sauvageat, J.L.; Raab, T. Hydrolysis of chicoric and caftaric acids with esterases and Lactobacillus johnsonii in vitro and in a gastrointestinal model. *J Agric Food Chem.* 2012, 60, 9236-41, https://doi.org/10.1021/jf301317h.

49. Ramanauskienė, K.; Raudonis, R.; Majiene, D. Rosmarinic acid and Melissa officinalis extracts differently affect glioblastoma cells. *Oxid Med Cell Longev.* 2016, 2016, https://doi.org/10.1155/2016/1564257.

50. Singleton, V.L.; Zaya, J.; Trousdale, E.K. Caftaric and coumaric acids in fruit of *Vitis*. *Phytochemistry* 1986, 25, 2127-2133, https://doi.org/10.1016/0031-9422(86)80078-4.

51. Singleton, V.L.; Salguers, M.; Zaya, J.; Trousdale, E. Caftaric acid disappearance and conversion to products of enzymic Oxidationin Grape Must and Wine. *Am J Enol Vitic.* 1985, 36, 50-56.

© 2020 by the authors. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).