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

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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 $C_{13}H_{12}O_9$, 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*-caffeoyl tartaric acid, monocaffeyltartaric acid, *cis*-caffeoyl tartaric acid. The chemical structure of caftaric acid is $C_{13}H_{12}O_9$ (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].

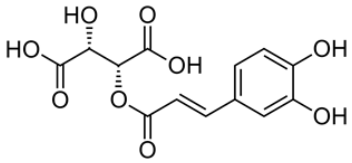

Figure 1. Chemical structure of caftaric acid.

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 hydroxycinammic 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 phenolic 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.

Table 1. Caftaric acid content of juice of berries of *Vifis* species[50].

Vitis species	Juice brix	Berry wt (g)	Caftaric acid		
			Trans (mg/l)	*Cis* (mg/l)	% *Cis*
aestiualis	25.2	0.55	1337	16	1.2
monticola	19.8	0.57	1155	4	0.3
monticola	21.8	0.57	1010	6	0.6
rufotomentosa	15.1	0.21	772	2	0.2
***simpsonii* (pixiala)**	23.3	0.34	664	6	1.0
arizonica	21.4	0.20	484	0.2	0.1
labrusca	19.1	2.18	462	6	1.3
smalliana	7.2	0.42	443	2	0.4
treleasei	15.8	0.61	405	2	0.4
car&cans	23.2	0.41	403	4	1.1
lincecumii	16.6	1.60	246	4	1.8
Afganistan source	21.6	0.44	220	3	1.2
girdiana	16.1	0.34	207	1	0.4
shuttleworthii	20.1	1.17	185	2	1.1
amurensis	17.8	0.57	128	2	1.7
californica	22.5	1.46	122	3	2.8
berlandieri	14.8	0.35	89	1	1.1
novae-angliae	24.1	1.38	71	4	5.0
doaniana	18.6	1.42	57	0.5	0.8
cinerea	16.6	0.27	53	trace	--
slavinii	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	2	3.9
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
rotundifolia (Creek)	16.1	3.18	trace	0	0
rotundifolia	18.1	0.95	1.5	trace	--

Table 2. Caftaric acid content of juice of commercially important white and red varieties of *Vitis uinifera*[50].

White varieties of *Vitis uinifera*

Cultivar	Juice brix	Berry wt (g)	Caftaric acid		
			Trans (mg/l)	*Cis* (mg/l)	% *Cis*
Palomino	20.2	2.42	295	4	1.5
Pinot blanc	20.8	1.44	266	3	1.2
Semillon	11.3	1.13	197	2	1.0
Semillon	21.2	2.17	98	1	1.3
Rkatsiteli	20.8	2.05	181	4	2.4
St. Emilion	20.6	1.79	179	5	2.9
Emerald Riesling	21.3	1.84	154	2	1.5
Muscat blanc	22.4	2.11	143	4	2.6
Muscat Alexandria	17.0	3.57	141	3	1.9
French Colombard	8.7	1.15	142	1	0.7
French Colombard	19.8	1.79	97	2	2.5
Chardonnay	22.1	1.14	135	1	0.4
Chardonnay	21.0	1.55	122	3	2.6

Burger	19.5	2.68	119	2	1.6
Chenin blanc	20.6	1.94	110	2	2.2
White Riesling	20.7	1.91	109	3	2.5
Sauvignon blanc	22.4	1.63	97	2	2.0
Grey Riesling	23.9	1.59	81	2	1.9
Malaga	19.0	3.89	61	2	4.0
Perlette	19.0	2.65	59	3	4.5
Thompson Seedless	21.5	1.34	56	2	3.3
Gewurztraminer	20.1	1.27	54	1	1.8
Calmeria	18.8	4.64	16	0	--
Carnelian	20.7	1.63	430	5	1.1
Ribier	19.7	5.63	294	4	1.3
Grenache (D*)	18.9	1.26	290	4	1.3
Grenache(D)	20.2	1.22	267	2	0.7
Grenache(N)	21.0	1.62	261	3	1.2
Black Corinth	23.4	0.22	221	2	0.9
Mission	20.1	2.23	216	3	1.5
Petite Sirah	21.8	1.62	188	3	1.4
Zinfandel	21.4	2.13	171	4	2.0
Pinot noir(D)	21.7	0.66	160	2	1.3
Pinot noir (N)	19.3	1.20	139	2	1.2
Cabernet Sauvignon(N)	23.2	1.05	140	6	3.9
Cabernet Sauvignon(D)	22.0	1.12	110	1	1.2
Cardinal	17.6	6.12	140	4	2.8
Carignane(D)	20.6	1.54	109	2	1.7
Carignane(N)	19.6	2.16	56	1	2.4
Ruby Cabernet(D)	16.6	1.44	108	2	2.0
Ruby Cabernet(N)	24.2	1.45	103	2	2.3
Flame Tokay	20.2	4.77	93	4	4.5
Merlot	22.4	1.02	79	2	2.1
Ruby Seedless	21.4	2.35	61	2	3.0
Gamay (Napa)	19.5	2.31	57	2	2.9
Emperor	17.4	3.44	48	2	4.2

*D=Davis vineyard (warmer, earlier), if not designated this was the source; N=Napa Valley vineyard (cooler, later).

Table 3. Enzymic 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)	Cystine	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-Dithioth reitol	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-mercapto purine	0	18.3	43	57
Caftaric acid (36 mg/L)	α-Thioglycerol	0	11.7	28	--

2. CAFTARIC 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 caftraic acid is identified as non-flavonoid 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 cm^3). The industrial grape juice contains, on average, 6-10% of the human daily need for potassium, about 5-

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* 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].

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 not cytotoxic 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 vinífera 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 of antioxidant phenolics such as caftaric acid which support romaine lettuce as a sleep substance. On recent research [28], caftaric acid from red wine was isolated within 370min with high yields (0.97mg to 13.79mg) and high purity (90.34% to 98.91%) by high performance liquid chromatography method. In another study [29], the *trans*-caftaric acid ingredient in new grape Brazilian from Northeast Brazil was very high and detected by reversed-phase HPLC. The results obtained revealed linearity, good precision, recovery and limits of detection and quantification and the difference of a run time of only 25min. Consequently, the antioxidant effect of this wine was very high compared with other wines from different regions of the world. In most recent research [5], the purple coneflower has antioxidant effect where caftaric acid is the major ingredient in coneflower. Consequently, fish feed purple coneflower has a good source of antioxidants and these antioxidant effects were correlated with coneflower content. Furthermore, caftaric acid is the main and rich phenolic acid in *Cichorium spinosum* L. plant. The values of salinity exposure during the plant growing state effect on antioxidant status of *Cichorium spinosum* L. plant [30]. The caftaric acid possessed anti-oxidant 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. Caftaric 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 chicoric 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-adipocytes 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 antihypertensive 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

plant. This plant has an antioxidant, antiallergenic, antiviral and antitumor effects which recommended the use of this plant in medicinal field and its nutritional importance [45].

The caftaric acid is a major constituent that present in most Mediterranean diets that prevent several diseases that associated especially with endothelial damage and this effect is correlates with antioxidant effect of caftaric acid. The acid showed *in vitro* antioxidant effect in $ABTS^+$ and O_2^- radicals and declined the peroxyl radical-induced breakdown of DNA plasmids [7]. The grape contains caftaric acid that exerts usefulness effects on human health upon consumption of grape seeds or grape juice.

The caftaric acid constituent in grape attenuated many gene expressions correlated with both cytoskeleton and differentiation [9]. In a recent research, the antioxidant effect of grape (Vitis vinífera L.) stem which contains caftaric acid as a major ingredient was done. The caftaric acid improved the radical scavenging effects (DPPH and ABTS) and cell viability. The acid has an observable effect on the level of reactive oxygen species, antioxidant enzymes and oxidative stress in human keratinocytes in vitro [26]. The high dose of caftaric acid therapy performed gastroprotective effect. In the macroscopic evaluation, there were reductions in ulcer sizes with a low and high dose of caftaric acid intake compared to negative control group [31]. The caftaric acid declined the expression of both adhesion molecules and monocyte chemoattractant protein-1. The decline recorded in the expression of the inflammatory gene was associated with a remarkable decrease in nuclear factor (NF-κB) and AP-1 stimulation [46]. The caftaric acid is the main ingredient in Portugal red wines. The caftaric acid inhibited tumor necrosis factor-α which is the main marker in inflammation [47]. The caftaric acid is a bioactive component of chicory and has many benefits to health benefits.

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.

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