Food and Chemical Toxicology 65 (2014) 185–195

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Invited Review

Ferulic acid: Pharmacological and toxicological aspects

Cesare Mancuso [a,*], Rosaria Santangelo [b]

[a] Institute of Pharmacology, Catholic University School of Medicine, Largo Francesco Vito, 1, 00168 Rome, Italy
[b] Institute of Microbiology, Catholic University School of Medicine, Largo Francesco Vito, 1, 00168 Rome, Italy

ARTICLE INFO

Article history:
Received 26 September 2013
Accepted 18 December 2013
Available online 25 December 2013

Keywords:
Aging
Biliverdin reductase
Ferulic acid
Free radicals
Heme oxygenase
Neurodegenerative disorders

ABSTRACT

Ferulic acid (FA) belongs to the family of phenolic acids and is very abundant in fruits and vegetables. Over the past years, several studies have shown that FA acts as a potent antioxidant by scavenging free radicals and enhancing the cell stress response through the up-regulation of cytoprotective systems, e.g. heme oxygenase-1, heat shock protein 70, extracellular signal-regulated kinase 1/2 and the proto-oncogene Akt. Furthermore, FA was shown to inhibit the expression and/or activity of cytotoxic enzymes, including inducible nitric oxide synthase, caspases and cyclooxygenase-2. Based on this evidence, FA has been proposed as a potential treatment for many disorders including Alzheimer's disease, cancer, cardiovascular diseases, diabetes mellitus and skin disease. However, despite the great abundance of preclinical research, only a few studies were carried out in humans, the majority of which used foods containing FA, and therefore the clinical efficacy of this mode of administration needs to be further documented. New efforts and resources are needed in clinical research for the complete evaluation of FA therapeutic potential in chronic diseases.

Contents

Abbreviations: Aβ, amyloid-β-peptide; AD, Alzheimer's disease; BR, bilirubin; BV, biliverdin; BVR, biliverdin reductase; CAT, catalase; CCNA2, gene encoding for cyclin-A2; CCNB1, gene encoding for G2/mitotic-specific cyclin-B1; CEP2, centrosomal protein 2; C_{max}, peak plasma concentration; CYP, cytochrome P-450; eNOS, endothelial nitric oxide synthase; ERK 1/2, extracellular signal-related kinase 1/2; FA, ferulic acid; FAEE, ferulic acid ethyl ester; GFAP, glial fibrillary acidic protein; h, hour(s); HO, heme oxygenase; Hsp, heat shock protein; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LD, lethal dose; ODC1, gene encoding for ornithine decarboxylase; PPB, plasma protein binding; RABGAP1, RAB GTPase activating protein 1; ROS, reactive oxygen species; SF, sodium ferulate; SMC1L1, structural maintenance of chromosomes 1-like 1; SOD, superoxide dismutase; TGF-β, transforming growth factor-β; THD, thiazolidinedione(s); T_{max}, time to reach the C_{max}; UGT, UDP-glucuronosyltransferase.

* Corresponding author. Tel.: +39 06 30154367; fax: +39 06 3050159.
E-mail address: cmancuso@rm.unicatt.it (C. Mancuso).

0278-6915/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.fct.2013.12.024

1. Introduction

Ferulic acid [(E)-3-(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid)] (Fig. 1) is a caffeic acid derivative widely found in vegetables, fruits and some beverages such as coffee and beer (D'Archivio et al., 2007; Rechner et al., 2001) (Table 1). Moreover, FA is also a component of Chinese medicinal herbs, such as *Angelica sinensis, Cimicifuga racemosa* and *Ligusticum chuangxiong* (Ou and Kwok, 2004) (Table 1).

Although the earlier interest for FA and other caffeic acid-derivatives traces back to the mid-1950s, when Preziosi and collaborators (1957a–c, 1958) unraveled their coleretic, hypolipidemic and diuretic functions, only recently have these phenolic acids gained attention for their potential role as an adjuvant therapy for several free radical-induced diseases. In particular, FA was proposed as a novel antioxidant compound endowed with a strong cytoprotective activity due to both the ability to scavenge free radicals and activate cell stress response (see below). However, the unfavorable pharmacokinetics, which reduces the bioavailability of FA after ingestion (or oral administration) and the restricted number of clinical studies carried out with the purpose of proving FA efficacy and safety, limited the evidence regarding the potential interest of this phenolic acid in humans.

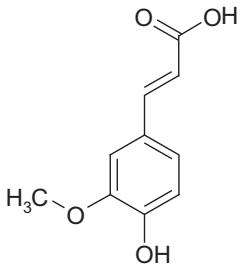

Fig. 1. The chemical structure of ferulic acid.

The aim of this review is to provide the reader with a systematic overview on the pharmacology and toxicology of FA. In addition, the role of FA as a potential therapeutic agent for the prevention and treatment of neurodegenerative disorders, cancer, cardiovascular diseases, diabetes and skin diseases will be critically discussed.

2. Pharmacokinetics of ferulic acid

According to the typical Mediterranean diet, whose characteristics are the abundance of plant foods (3–5 servings/day, including vegetables, fruits, breads and grains) and a low-to-moderate consumption of red meat, fish and wine, the daily amount of FA ingested was calculated around 150–250 mg (16–24 μmol/kg of body weight) (Barone et al., 2009; Zhao and Moghadasian, 2008). However, the amounts of FA ingested and calculated on the basis of the data shown in Table 1 should be considered as theoretical since they can vary according to the eating habits and the number of vegetable/fruit daily servings.

Since in fruits and vegetables FA is covalently conjugated through ester-linkage with mono-, di-, and poly-saccharides [5-O-feruloyl-L-arabinofuranose and 5-O-feruloyl-arabinoxylane are the most common forms of FA in cereals], glycoproteins, polyamines, lignin and the hydroxy fatty acids suberin and cutin (Bourne and Rice-Evans, 1998; Clifford, 1999; Ou and Kwok, 2004; Saulnier et al., 1995), many studies have been carried out to establish if conjugation modifies FA pharmacokinetic parameters.

2.1. Absorption and distribution

After ingestion, both FA and 5-O-feruloyl-L-arabinofuranose are not degraded by the stomach acid environment and undergo

Table 1
Approximate amounts of ferulic acid in some foods and Chinese herbs.

	FA[1] (mg/100 g)	Average daily portion[2] (g/day)	Ingested amount of FA (mg/day)
White wheat bread	8.2	35 (50)	2.87 (4.10)
Pasta	12	100 (80)	12 (9.6)
Cereal brans[3]	1351–3300	5 (20)	68–165 (270–660)
Tomatoes	6	200 (250)	12 (15)
Artichokes	275[4]	250	688
Eggplants	7.3–35	200 (250)	15–70 (18–87)
Broccoli	4.1	200 (250)	8.2 (10.25)
Grapefruit	~11	125 (150)	13.75–16.5
Orange	~9.5	125 (150)	11.88–14.25
Banana	5.4	125 (150)	6.75–8.1
Coffee	9.1–14.3	200	18.2–28.6
Popcorn	313	60	187.8
Angelica sinensis	20–175[5]	3–15[6] (dried root) 3–6[6] (powdered root)	0.6–26.25 0.6–10
Cimicifuga foetida	25[7]	0.04[8]	0.01
Ligusticum chuanxiong	106[7]	Not available	Not available

[1] From Zhao and Moghadsian (2008).
[2] From Zhao and Moghadsian (2008). In brackets the values according to the guidelines of the Italian Society of Human Nutrition.
[3] Include refined corn bran, soft and hard wheat bran and rye bran.
[4] Average content in chlorogenic acid (Mulinacci et al., 2004) which is transformed into ferulic acid (Azzini et al., 2007).
[5] From Yi et al. (2009).
[6] From EFSA Journal (2009).
[7] From Li et al. (2007).
[8] Data not available for *C. foetida*. The average daily portion related to *Cimicifuga racemosa* was reported. WHO Monographs on selected medicinal plants, 1999.

Table 2
The main pharmacokinetic parameters of ferulic acid.

	Ferulic acid pharmacokinetic parameters							
	Biovailability (%)	PPB[a]	T_{max} (min)	C_{max} (μM)	T1/2[a] (min)	Metabolism	Excretion	References
Rat	9–20	–	5–15	~25[b]	30	Liver [glucuronide (3–20%) and sulfoglucuronide (60–90%) derivatives]	Urine	Barone et al. (2009), Rondini et al. (2002, 2004), Zhao and Moghadasian (2008), and Zhao et al. (2003, 2004)
			30[c]	~1.3–23[c]	100[c]			
Humans	~20	70%[e]	24	2–3[d]	42	Liver (glucuronide, sulfoglucuronide and glycine derivatives)	Urine	Bourne and Rice-Evans (1998), Kern et al. (2003), Yang et al. (2007), and Zhao and Moghadasian (2008)
			180[f]	0.2	325			

[a] PPB, Plasma protein binding; T1/2, half-life.
[b] After FA at the dose of 70 mg/kg *per os*.
[c] 5-O-feruloyl-L-arabinofuranose or feruloyl-arabinoxylan.
[d] After FA at the dose of 4.3 μmol/kg *per os*.
[e] From an *in vitro* study by using human serum albumin.
[f] After ingestion of wheat bran (22.5 μmol/kg).

intestinal transit (Zhao et al., 2004). In the colon, bound FA is released from parent compounds by microbial cinnamoyl esterase (Couteau et al., 2001), xylanase and FA esterase (Kroon et al., 1997) and mainly absorbed by passive diffusion (~90%), whereas only a small percentage by active transport *via* the monocarboxylic acid transporter (Poquet et al., 2008). The course of FA upon its absorption has been largely analyzed and the main pharmacokinetic parameters in rats and humans are shown in Table 2. A careful analysis of Table 2, shows how FA is quickly absorbed after oral ingestion and reaches the peak plasma concentration (C_{max}) within 30 min (T_{max}); interestingly, the complexation of FA with mono- or di-saccharides markedly reduces the C_{max} and increases both the T_{max} and half-life with respect to free FA administration in rats and humans.

2.2. Metabolism and excretion

Ferulic acid undergoes extensive presystemic metabolism in the liver through the isoforms 1A1 and 2B7 of the UDP-glucuronosyltransferase (UGT) (Li et al., 2011). As documented in both preclinical and clinical studies, glucuronide (~3–20%) and sulfoglucuronide (~60–90%) are the most abundant metabolites of FA in plasma, whereas only a low percentage of unmodified FA (~9–20%) has been found (Bourne and Rice-Evans, 1998; Rondini et al., 2002, 2004; Zhao et al., 2003, 2004). Both FA and its metabolites are excreted mainly from the kidney. In rats, the urinary excretion of FA is rapid and reaches a plateau 1.5 h after the administration (Rondini et al., 2002), whereas in humans it is much slower with a plateau between 7 h and 9 h after consumption (Bourne and Rice-Evans, 1998). However, the unmodified FA recovered in urine represents only 4–5% of ingested FA and these results are similar in both humans and rodents (Bourne and Rice-Evans, 1998; Rondini et al., 2002). Urinary excretion is influenced by FA conjugation, after bran consumption the FA elimination rate is 15-fold slower than after the intake of the pure molecule (Rondini et al., 2002, 2004).

3. Pharmacodynamics of ferulic acid

Both the 3-methoxy and 4-hydroxyl groups on the benzene ring, which either stabilize the resulted phenoxyl radical intermediate or even terminate the free radical chain reaction, and the carboxylic acid group (with the adjacent unsaturated carbon–carbon double bond) which can further contribute to stabilize the phenoxyl radical intermediate or provides an additional attack site for free radicals (Graf, 1992), are the structural moieties which make FA an efficient scavenger of both reactive oxygen and nitrogen species (ROS and RNS, respectively). On the other hand, several lines of evidence have demonstrated that the cytoprotective effects of FA could be attributable to the down-regulation of pathways involved in cell death [e.g. inducible nitric oxide synthase (iNOS)] and the up-regulation of gene/proteins which are able to enhance the cell stress response [the heme oxygenase/biliverdin reductase (HO/BVR) system, superoxide dismutase (SOD), catalase (CAT) and members of the heat shock protein family] (Fig. 2) (Barone et al., 2009).

3.1. Ferulic acid and free radical scavenging

Ferulic acid [150 mg/kg intraperitoneally (i.p.)] for 4 days counteracted free radical-induced lipid peroxidation and apoptotic cell death in the organ of Corti of guinea pigs exposed to noise (120 dB SPL pure tone sound at a frequency of 6 kHz for 60 min) (Fetoni et al., 2010). Interestingly, FA administration reduced functional damage and improved hearing function in these animals (Fetoni et al., 2010). The antioxidant activity of FA seems to depend on

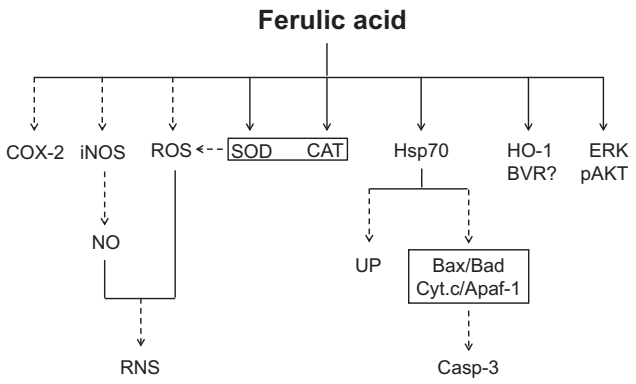

Fig. 2. Some of the main intracellular targets involved in the pharmacological actions of ferulic acid. For further information, see text. Arrows = stimulation; dashed arrows = inhibition; Apaf, apoptotic protease activating factor-1; Bad, Bcl-2-associated death promoter; Bax, Bcl-2-associated X protein; BVR, biliverdin reductase; Casp-3, caspase-3; CAT, catalase; COX-2, cyclooxygenase-2; cyt. C, cytochrome c; ERK, extracellular signal-regulated kinases; HO-1, heme oxygenase-1; Hsp70, heat shock protein-70; iNOS, inducible nitric oxide synthase; NO, nitric oxide; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; and UP, unfolding of proteins.

the radical species involved. As shown by Trombino et al. (2013) in an experimental system of reconstituted rat brain microsomes, FA efficiently inhibited lipid peroxidation triggered by peroxyl radical or peroxynitrite. This *in vitro* evidence is in agreement with the study by Kanski et al. (2002) who demonstrated how FA (25–50 μM) significantly attenuated peroxyl radical-induced cell death in hippocampal neuronal cells, although higher concentrations (250–500 μM) were necessary to reduce both protein oxidation and lipid peroxidation induced by the stronger hydroxyl radical. The ability of FA to scavenge ROS is not restricted to peroxyl or hydroxyl radicals since, at the concentration of ~200 μM, it reduced hydrogen peroxide-induced lipid peroxidation in peripheral blood mononuclear cells (PBMCs) and this effect was more evident than that of other polyphenols such as caffeic acid and ellagic acid (Khanduja et al., 2006).

Ferulic acid was also shown to inhibit the toxicity of secondary free radicals, such as those generated by carbon tetrachloride (CCl4). Srinivasan et al. (2005) have shown that FA (20 mg/kg *per os*) prevented liver damage secondary to carbon tetrachloride administration in female rats. In this study, FA significantly decreased both plasma indicators of liver toxicity and markers of lipid and protein oxidation (Srinivasan et al., 2005).

The *in vitro* administration of FA (0.1–1.6 mM) in cultures of sperm taken from infertile patients with asthenozoospermia has had beneficial effects on the viability and motility of sperm by reducing lipid peroxidation of the cell membrane and increasing intracellular levels of cAMP and cGMP (Zheng and Zhang, 1997).

As for the above mentioned *in vitro* scavenging activity towards peroxynitrite, FA (0–100 μM) inhibited tyrosine nitration in a reconstituted system (Pannala et al., 1998). The cytoprotective effects of FA against RNS are also dependent on its ability to down-regulate NOS isoforms. Cho et al. (2005) showed that FA (0.006% *per os*) for 4 weeks counteracted the over-expression of eNOS induced by amyloid-β-peptide (Aβ) in mouse hippocampal astrocytes. Recently, FA (100 mg/kg intravenously) was shown to prevent iNOS induction and apoptosis in a rat model of cerebral ischemia, such as the middle cerebral artery occlusion (Koh, 2012; Cheng et al., 2010). Similar results on NOS isoforms were obtained by using FA ethyl ester (FAEE) a synthetic and more liposoluble derivative of FA. As shown by Sultana et al. (2005), pre-treatment of rat neuronal cells with 25 μM FAEE for 1 h significantly decreased Aβ-stimulated iNOS up-regulation (Sultana et al., 2005).

3.2. Ferulic acid and antioxidant enzymes

Ferulic acid and FAEE have been shown to enhance the cell stress response by regulating several key enzymes whose main mechanism of action is to counteract free radical-induced damage, such as the heme oxygenase/biliverdin reductase (HO/BVR) system, superoxide dismutase (SOD), catalase (CAT) as well as the chaperone heat shock protein (Hsp)-70 (Fig. 2).

3.2.1. Ferulic acid and the HO/BVR system

Heme oxygenase-1, the inducible form of HO, degrades heme, toxic if produced in excess or under redox imbalance, generating equimolar amounts of ferrous iron, carbon monoxide (CO) and biliverdin (BV) that is then reduced by biliverdin reductase (BVR) to bilirubin (BR) (Maines, 1997). Both CO and BR play a main role in restoring cell homeostasis, the former by interacting with NADPH oxidase or the mitogen activated protein kinase (MAPK) system, whereas the latter is an efficient scavenger for ROS and RNS (Mancuso et al., 2003, 2006, 2012; Mancuso and Barone, 2009; Minetti et al., 1998; Stocker et al., 1987a, 1987b).

Ferulic acid and FAEE (5–50 μM or 150 mg/kg i.p.) were shown to up-regulate HO-1 expression in many preclinical models, including rat neurons, gerbil synaptosomes and dermal fibroblasts and this effect resulted in a significant cytoprotection against ROS- and glucose oxidase-related oxidative damage (Calabrese et al., 2008; Joshi et al., 2006; Kanski et al., 2002; Scapagnini et al., 2004). Ferulic acid (150 mg/kg i.p.) for 4 days, up-regulated HO-1 in the guinea pig organ of Corti with a peak 3 and 7 days after the acoustic trauma (see above); FA-induced improvement of the auditory function was counteracted by the HO inhibitor zinc-protoporphyrin-IX and paralleled the time-course of HO-1 induction over 3–7 days, thus corroborating that the neuroprotective effect of the phenolic acid was due not only to the direct free radical scavenging, but also to the induction of cytoprotective HO-1 (Fetoni et al., 2010). A possible mechanism through which FA up-regulates HO-1 is the over-expression and nuclear translocation of the transcription factor NF-E2-related factor (Nrf2) which binds the antioxidant responsive element in the promoter region of the HO-1 gene, thus increasing the transcription (Ma et al., 2011). A role in FA-activation of Nrf2/HO-1 is played by the extracellular signal-regulated kinase (ERK) since its blockade counteracts the nuclear translocation and transcriptional activity of Nrf2 on the HO-1 gene (Ma et al., 2011),

3.2.2. Ferulic acid and superoxide dismutase or catalase

Superoxide dismutase and CAT play a pivotal role in the detoxification of ROS, since the former is responsible for the transformation of superoxide anion in hydrogen peroxide which is further transformed by CAT into oxygen and water (Fridovich, 1999; Halliwell, 1978). Ferulic acid, at different doses and intervals of administration (50 mg/kg alternative day or 50 mg/kg daily for 8 weeks *per os* or 110 mg/kg/daily for 12 weeks *per os*), restored SOD and CAT levels in myocardium and pancreatic tissue of streptozotocin-induced diabetic rats (Roy et al., 2013; Xu et al., 2012). The potential protective role of FA in diabetes was further supported by the evidence of reduced levels of pro-inflammatory cytokines and apoptosis in the pancreatic β-cells (Roy et al., 2013). As far as cardioprotection is concerned, FA (0.8 g/kg of powdered food) for 4–12 weeks, increased SOD and CAT activities in hypertensive rats (Alam et al., 2013). In the vascular system, FA (0.2% w/w in the food) for 15 weeks increased SOD and CAT activities in hepatocytes and erythrocytes and exerted hypolipidemic and anti-atherogenic properties in Apolipoprotein-E-deficient mice (Kwon et al., 2009, 2010).

Interestingly, FA exhibited antioxidant properties even if administered topically. As shown by Dong et al. (2003), FA (200–800 mg/kg intracolonically) for 7 days increased SOD activity and reduced inflammatory biomarkers in the colonic mucosa in a rat model of acetic acid-induced colitis.

3.2.3. Ferulic acid and heat shock protein 70

Several proteins belong to the heat shock protein family and they are expressed at low levels under physiological conditions although they show a dramatically increased expression in response to oxidative or nitrosative stress (Garrido et al., 2012; Henderson, 2010). From a mechanistic viewpoint, Hsp facilitate the folding of cellular proteins, prevent protein aggregation and target improperly folded proteins to specific degradative pathways (proteasome) (West et al., 2012; Zuiderweg et al., 2013). In addition, Hsp70 is a functional chaperone and exerts cytoprotective activity by regulating the key effectors of the apoptotic machinery (Evans et al., 2010). Only little evidence is available in literature on the FA-based modulation of Hsp and they have been obtained by using the liposoluble FAEE. As shown by Allan Butterfield's group, FAEE up-regulated Hsp70 in rat cortical neurons and prevented ROS- and Aβ-induced toxicity (Joshi et al., 2006; Sultana et al., 2005).

The mechanisms involved in FA-induced SOT, CAT and Hsp70 activation are not clear. However, it is not possible to exclude

the possibility that the antioxidant and cytoprotective effects of FA and its derivatives due to the ability to both scavenge free radicals and activate the HO-1/BVR system and counteract inflammation and apoptosis (Fig. 2) could reduce the harsh pro-oxidant conditions proper of neurodegeneration, diabetes and cardiovascular diseases, thus restoring, or even improving, SOD, CAT and Hsp70 expression or activity.

Considered together, the results of the studies mentioned in this section demonstrated that FA counteracts both ROS- and RNS-induced damage in many tissues or cell types and these effects can be achieved through both its direct free radical scavenging activity and the up-regulation of the HO/BVR system, SOD and CAT whose final aim is to detoxify ROS and RNS (Fig. 2). By doing so, FA prevents free radical-induced damage of cellular lipid, protein and nucleic acid, and protects cells from necrotic or apoptotic death, thus increasing lifespan.

3.2.4. New formulations of ferulic acid

In order to increase FA bioavailability and enhance its cytoprotective effects, new formulations have been prepared in which the phenolic acid is entrapped either in solid lipid nanoparticles (SLN) or in niosomes or is bound to other therapeutic agents through organic moieties (e.g. aminoacids) which serve as carriers (pro-prodrug). These strategies have led to the preparation of FA- or stearylferulate (SF)-based SLN (FA-SLN and SF-SLN, respectively) and L-Lysine-FA-5-ASA pro-prodrug (Cassano et al., 2010; Picone et al., 2009; Trombino et al., 2009). These new formulations significantly enhanced the antioxidant effects of FA against both ROS and RNS in preclinical models (Cassano et al., 2010; Picone et al., 2009; Trombino et al., 2009, 2013) and are a useful platform for the possible translation of this strategy to clinic evaluation.

4. Ferulic acid and Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by progressive cognitive dysfunction and memory loss, the inability to perform activities of daily living and mood disorders (Querfurth and LaFerla, 2010). The main role in the pathogenesis of AD is played by Aβ, a peptide composed of 36–43 amino acids and produced by serial cleavage of the amyloid precursor protein (APP) by the concerted activities of both β- and γ-secretases (Querfurth and LaFerla, 2010). Once produced, Aβ tends to aggregate in the form of oligomers or fibrils (Querfurth and LaFerla, 2010) and form the core of senile (or amyloid) plaques (Butterfield et al., 2007). Importantly, Aβ activates specific kinases, such as GSK3β, cyclin-dependent kinase 5 (cdk5) and DYRK1A (Ballard et al., 2011; Keeney et al., 2012) which, in turn, are responsible for tau hyperphosphorylation and aggregation in neurofibrillary tangles. The accumulation of Aβ oligomers, which precedes the formation of tau protein aggregates, impairs mitochondrial activity in the neuron (Ferrer, 2009; Rhein and Eckert, 2007; Sultana and Butterfield, 2009) and the result is an abnormal increase in the production of ROS, such as superoxide anion and hydrogen peroxide (Ferrer, 2009; Rhein and Eckert, 2007). There is also the activation of tumor necrosis factor type I receptor, which, in the presence of Apaf-1, activates the apoptosis cascade (Li et al., 2004; Rabacchi et al., 2004). It is worth noting that Aβ overproduction decreases SOD-1 and SOD-2 activities leading to increased intracellular levels of ROS, which cause oxidative damage to the lipids and proteins of the neuron (Anantharaman et al., 2006; Bayer et al., 2006). Excess superoxide radicals also react with NO produced by activated microglia, thereby enhancing the formation of peroxynitrite and other RNS involved in protein nitration (Calabrese et al., 2007; Reiter et al., 2000; Smith et al., 1997). The accumulation of ROS/RNS together with the activation of apoptosis and reduction of SOD contribute to the destruction of cholinergic areas involved in cognitive performance, such as amygdala, hippocampus and cortex (Grothe et al., 2010). Ferulic acid, by its antioxidant and anti-inflammatory properties, could exert beneficial effects in AD (Table 3).

In aged rats (21 months), dietary supplementation with sodium ferulate (SF, 100–200 mg/kg body weight) for 4 weeks has counteracted the increase, induced by age, of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and has contributed to preventing the reduction of the activity of proteins, such as ERK1/2 and proto-oncogene Akt, both with a marked neuroprotective action, in the rat hippocampus (Jin et al., 2008).

Pre-treatment with FA (14–19 mg/kg/day *per os*) for 4 weeks significantly counteracted IL-1β production, neuroinflammation and gliosis in the mouse hippocampus induced by the intracerebroventricular (i.c.v.) injection of Aβ and improved memory loss as well (Yan et al., 2001). This last effect could be also associated to the ability of IL-1β to inhibit long-term potentiation in the hippocampus (Katsuki et al., 1990). A strong reduction in inflammatory biomarkers was also obtained in rats, but with higher SF doses (50–250 mg/kg/day orally for 4 weeks); in this species, the SF-related reduction in IL-1β was paralleled by an increase in the phosphorylation of both ERK and Akt in the hippocampal CA1 region (Jin et al., 2005). Similar results, in terms of reduction of neuroinflammation, were obtained in the transgenic APPswe/presenilin 1 (PS1)dE9 (APP/PS1) mouse model of AD; in these animals, the oral administration of FA (5.3 mg/kg/day) for 6 months significantly reduced Aβ deposition and IL-1β levels in the frontal cortex and enhanced cognitive performance (novel-object recognition task) (Yan et al., 2013). In an interesting ex *vivo* study, FA (150 mg/kg i.p.) exhibited strong neuroprotective effects by reducing Aβ-induced ROS and RNS and up-regulating both HO-1 and Hsp70 in gerbil brain synaptosomes (Perluigi et al., 2006).

Similarly, FA (0.002–0.005%) administered for 28 days in drinking water has improved the cognitive deficit induced by trimethyl tin (2.5 mg/kg i.p.), possibly by a mechanism associated with the increase of the enzyme choline acetyltransferase activity (Kim et al., 2007). Neuroprotective and nootropic effects of FA have also become evident in the case of a short-term administration by the

Table 3
A summary of the main effects/mechanisms through which ferulic acid and its derivatives could have therapeutic effects. For further information refer to the text.

Diseases	Effects/mechanisms
Alzheimer's disease	↓ Neuroinflammation (↓IL-1β) ↓ Apoptosis (↓caspase activation) ↓ β-secretase activity ↑ Cytoprotective systems (ERK1/2, Akt) ↑ Antioxidant enzymes (HO-1, Hsp70)
Cancer	↑ Centrosome assembly (↑RABGAP1, CRP2) ↑ Antioxidant enzymes (↑SOD, CAT) ↓ Blockade cell cycle progression (↑SMC1L1, ↓CCNA2, CCNB1, MYC, ODC1) ↓ COX-2 activity
Cardiovascular diseases	↓ Hypertension (↓angiotensin II, ↑NO synthesis, ↓superoxide anion) ↑ Left ventricle performance ↓ Potassium channels and β-adrenoceptors ↑ Kidney function ↓ Serum lipids
Diabetes	↓ NF-kB ↑ Plasma insulin ↓ Glycemia (↑glycogen synthesis, ↑glucokinase) ↓ Maltase and sucrase activities ↓ Aldose reductase activity ↓ TGF-β ↑ Therapeutic effects of metformin and THD

parenteral route. Mamiya et al. (2008) have shown that FA (5 mg/kg subcutaneously for 6 days) reduced brain damage from oxidative stress induced by deprivation of reduced glutathione and has significantly increased the cognitive activity in mice.

As far as the apoptotic cascade is concerned, SF attenuated Aβ-induced caspase activation. In rats treated with Aβ by i.c.v. route, pre-treatment with SF (100 and 200 mg/kg intragastrically for 3 weeks) inhibited caspase-9, -3, and -7 activation thus contributing to preventing neurotoxicity (Jin et al., 2006).

A novel mechanism through which FA could exert neuroprotection in AD is the modulation of β-secretase. As shown by Mori et al. (2013), oral FA administration (30 mg/kg) for 6 months decreased cleavage of the β-carboxyl-terminal APP fragment, reduced β-site APP cleaving enzyme 1 protein stability and activity, attenuated neuroinflammation, and stabilized oxidative stress in a transgenic PS/APP mouse model of AD. As a consequence of these modifications, a significant improvement of cognitive tasks occurred in these animals (Mori et al., 2013).

5. Ferulic acid and cancer

Several factors are involved in the pathogenesis of cancer, such as chronic inflammation, enhanced cell proliferation and/or resistance to apoptosis, free radical formation and the following damage to DNA and cell proteins, abnormal activation of pro-inflammatory pathways including cyclooxygenases (COX) and NOS, etc. In light of this, each of these events not only plays a key role in carcinogenesis *per se*, but also contributes to strengthening the toxic potential of the others, thus amplifying the cell proliferative cascade (Kundu and Surh, 2008). The ability of FA to regulate cell growth and proliferation, scavenge free radicals, stimulate cytoprotective enzymes and inhibit cytotoxic systems in both *in vitro* and *in vivo* experimental models account for the potential adjuvant role of FA in cancer therapy (Table 3).

Ferulic acid (150 μM) for 24 h exhibited antiproliferative effects on Caco-2 colon cancer cells by up-regulating several genes encoding proteins involved in centrosome assembly (RABGAP1 and CEP2) and the gene for the S phase checkpoint protein SMC1L1 as well as down-regulating CCNA2, CCNB1, MYC, and ODC1 (Janicke et al., 2011). As a consequence of these selective effects, cell cycle progression in the S-phase was blocked (Janicke et al., 2011).

Nicotine plays a central role in the pathogenesis of lung cancer as it increases free radical production in many cell types, including leucocytes. Ferulic acid (10–40 mg/kg *per os* for 22 weeks) has significantly reduced plasma levels of lactic dehydrogenase and alkaline phosphatase in nicotine-treated rats, two plasma markers of tissue damage (Adluri et al., 2008). Ferulic acid (100–150 μM) counteracted the nicotine-induced lipoperoxidation and DNA damage vis-à-vis with an increased intracellular levels of SOD, CAT and vitamin A, C and E in rat lymphocytes (Sudheer et al., 2007). The cytoprotective action of FA, which is highest at the concentration of 150 μM, was comparable to that performed by N-acetyl-cysteine, 1 mM (Sudheer et al., 2007). It is worth noting that the administration of only FA has not caused any damage to DNA (Sudheer et al., 2007).

Another possible target for the antineoplastic activity of FA derivatives is COX, which exists as two main isoforms, COX-1 and COX-2, constitutive and inducible, respectively. In particular, COX-2 is up-regulated in many types of cancer, and non-steroidal antinflammatory drugs, which inhibit COX activity, have been proposed as anticancer drugs (Cuzick et al., 2009; Menter et al., 2010). Ferulic acid-octyl and -dodecyl esters, significantly blocked the growth of breast, lung, colon and central nervous system tumor cells with IC_{50} values ranging from 17.05 to 4.29 μg/ml for the breast and colon, respectively (Jayaprakasam et al., 2006). In addition, ferulates inhibited COX-2 activity, although this effect was not strictly selective and decreased considerably for esters with chain length >C8 (Jayaprakasam et al., 2006).

Ferulic acid (40 mg/kg *per os*) or an extract of *Ixora javanica* (200 mg/kg orally), whose active compound was identified as FA, were shown to prevent mammary carcinogenesis induced by 7,12-dimethylbenz[a]anthracene and the 20-methylcolantrene-induced growth of soft tissue fibrosarcomas in rodents (Baskaran et al., 2010; Nair et al., 1991). The mechanisms involved in these antiproliferative effects have not been totally identified, although they can be related to the FA antioxidant activity and the modulatory effect on phase II detoxification enzymes (Baskaran et al., 2010). In addition, FA (200 mg/kg *per os*) counteracted the growth of intraperitoneally transplanted sarcoma-180 and Ehrlich ascites carcinoma tumors and increased the life span of the treated mice (Nair et al., 1991). Finally, FA (given in the feed at 500 mg/kg of feed) for 7 weeks to rats markedly reduced the incidence of tongue neoplasms (squamous cell papilloma and carcinoma) and preneoplastic lesions (hyperplasia and dysplasia) by 32 weeks (Tanaka et al., 1993).

Preclinical data proposed the potential use of FA as an adjuvant agent during chemotherapy or radiotherapy. Ferulic acid potentiated the cytotoxicity of either 5-fluorouracil or platinum-based agents (carboplatin and cisplatin) on human cervical cancer cell line HeLa and erythroleukemic cell line K562, respectively (Hemaiswarya and Doble, 2013; Indap et al., 2006). Interestingly, FA *per se* inhibited HeLa cell growth with IC50 ~320 μM (Hemaiswarya and Doble, 2013). Moreover, FA alone (1–40 μg/ml) or in combination with 2-deoxy-glucose enhanced the radiation-induced death of both HeLa and large cell lung cancer NCI-H460 cells, respectively, with a multifaceted mechanism entailing an alteration in the redox status and expression of pro-apototic pathways such as those related to p53, p21, nuclear factor kB (NF-kB), Bax and caspase-3 (Karthikeyan et al., 2011; Bandugula and Prasad, 2013).

6. Ferulic acid and cardiovascular diseases

Cardiovascular diseases (e.g. heart disease, cerebrovascular diseases) are the leading causes of death worldwide (Pagidipati and Gaziano, 2013). Hypertension and atherosclerosis are among the main risk factors underlying cardiovascular disease and the control of blood pressure and serum lipid levels are considered as important steps in reducing the incidence of such diseases. Earlier studies explained the antithrombotic effect of SF (Wang and Ou-Yang, 2005). In this context, the discovery of the antihypertensive and antihyperlipidemic properties of FA has broken new ground for a potential "clinical" use of this molecule in cardiovascular diseases (Table 3).

Ferulic acid (1–100 mg/kg orally administered) decreased blood pressure in both spontaneously hypertensive rats (SHR) and stroke-prone, spontaneously hypertensive rats (SHRSP) in a dose-dependent way (Alam et al., 2013; Ardiansyah et al., 2008; Suzuki et al., 2002). The maximum reduction in blood pressure was achieved 1–2 h after FA oral administration (Ardiansyah et al., 2008; Suzuki et al., 2002). Interestingly, FA 50 mg/kg exhibited an antihypertensive effect comparable to that obtained with 10 mg/kg of captopril, an angiotensin-converting-enzyme (ACE) inhibitor (Suzuki et al., 2002). The vasodilating effect of FA is to be considered multifactorial, as it involves the reduction of angiotensin II secondary to the inhibition of the ACE, the increase of NO synthesis through the activation of eNOS and finally the reduction of NADPH-dependent production of superoxide anion (Suzuki et al., 2002, 2007). Ferulic acid (50 mg/kg) reduced left ventricular diastolic stiffness, attenuated inflammatory cell infiltration, ferric

iron accumulation, and collagen deposition in the left ventricles and kidneys of SHR (Alam et al., 2013). These cardioprotective effects were obtained both in the case of single FA administration (Ardiansyah et al., 2008) and chronic treatment (Alam et al., 2013; Suzuki et al., 2002). A cardioprotective effect for FA was also demonstrated in some preclinical models of arrhythmias. Ferulic acid (0.6 g/kg, intravenous bolus) increased the threshold dose of ouabain which triggered ventricular premature contractions, ventricular tachycardia or fibrillation and cardiac arrest in guinea pigs (Wang and Ou-Yang, 2005). In this experimental model, FA also delayed the onset of ventricular premature contractions, ventricular tachycardia or fibrillation and cardiac arrest (Wang and Ou-Yang, 2005). Similarly, FA (0.6 g/kg, intravenous bolus) delayed the onset of ventricular premature contractions, shortened the duration of ventricular tachycardia and decreased both the occurrence of ventricular fibrillation and mortality in the rat model of ischemia-induced arrhythmias (Wang and Ou-Yang, 2005). A possible mechanism to explain the antiarrhythmic effect of FA seems to be related to the blockade of potassium channels and β-adrenoceptors (Wang and Ou-Yang, 2005).

The intake of FA (9.5 mg/kg *per os*) has reduced triglycerides in rats and rabbits and cholesterol levels in rats (Ardiansyah et al., 2008; Wang et al., 2004). These lipid lowering effects have led to a significant reduction in the size of atherosclerotic plaques in the aorta of rabbits on a diet rich in fats and have improved the endothelial functions in these animals (Wang et al., 2004).

The potential adjuvant effect of SF in angina pectoris and coronary heart disease was also confirmed by the results of clinical studies carried out in China. Sodium ferulate (200–300 mg/day) for 1–2 weeks, potentiated the therapeutic effects of nitrates, β-blockers, calcium channel blockers and ACE inhibitors as demonstrated by a significant reduction in the incidence of angina attacks, the dose of nitroglycerin and peak levels of myocardial enzymes together with the improvement in heart function tests (Wang and Ou-Yang, 2005). In subjects intolerant to organic nitrates or β-blockers, SF alone, by intravenous route, improved clinical symptoms and electrocardiography changes (Wang and Ou-Yang, 2005).

7. Ferulic acid and diabetes mellitus

Diabetes mellitus (DM) is a chronic disease characterized by an impaired insulin secretion and variable degrees of peripheral insulin resistance leading to an increased concentration of glucose in the blood which, in turn, harms many of the body systems, in particular the blood vessels and nerves. Furthermore, hyperglycemia is responsible for the overproduction of ROS, mainly superoxide anion, through the mitochondrial electron transport chain, which plays a significant role in the pathophysiology of cell dysfunction and diabetes complications (Naudi et al., 2012; Rolo and Palmeira, 2006).

In DM animal models, FA showed beneficial effects by acting at many levels (Table 3). As previously mentioned (see Section 3), FA scavenges free radicals and activates antioxidant enzymes, thus reducing the cellular redox imbalance. In light of this, the potential therapeutic role of FA in DM should be considered. Ferulic acid (10–50 mg/kg *per os*) displayed antioxidant activity, inhibited lipid peroxidation markers, enhanced the cell stress response and reduced NF-kB immunoreactivity in the pancreas, liver, kidney and serum of alloxan-induced diabetic mice and streptozotocin-induced diabetic rats (Ramar et al., 2012; Roy et al., 2013).

From a metabolic point of view, FA (10 and 40 mg/kg *per os*) for 3 weeks reduced blood glucose in streptozotocin-treated diabetic rats (Prabhakar et al., 2013). This finding confirms the results by Jung et al. (2007) who demonstrated that FA administered orally for 17 days, increased plasma insulin and lowered blood glucose in a model of *db/db* mice. In this last experimental model, FA increased both hepatic glycogen synthesis and the activity of glucokinase, a key enzyme in the regulation of blood glucose levels (Jung et al., 2007). Ferulic acid also inhibited rat intestinal maltase and sucrase, thus acting as a natural alpha-glucosidase inhibitor (Adisakwattana et al., 2009).

Both nephropathy and hypertension are common complications in diabetic patients. Several factors have been reported to be involved in the pathogenesis of these complications, among which the activation of the renin-angiotensin system (Giacchetti et al., 2005), activation of protein kinase Cβ (Inoguchi et al., 2003) and acceleration of oxidative stress (Kiritoshi et al., 2003). In a DM rat model, such as the Otsuka Long-Evans Tokushima Fatty rats, FA (10 mg/kg/day for 20 weeks or 0.2% for 12 weeks *per os*) significantly lowered urinary protein level compared to the control group, eliminated the oxidative stress markers as well as the expression of the cytokine transforming growth factor-β1, decreased glomerular basement membrane thickness, glomerular volume and mesangial matrix expansion (Choi et al., 2011; Fujita et al., 2008). Finally, a recent paper reported the ability of FA (20 mg/kg *per os*) for 6 weeks to inhibit aldose reductase in streptozocin-treated rats. As a consequence of this inhibitory effect, FA reduced diabetes-induced hypertension with multiple mechanisms, such as the inhibition of inflammation and ROS formation and the improvement of NO production and vascular contractility (Badawy et al., 2013).

A considerable aspect is the synergistic interaction of FA with hypoglycemic agents. Ferulic acid (10–40 mg/kg *per os*) for 3 weeks potentiated the hypoglycemic effects of metformin (12.5–50 mg/kg *per os*) and thiazolidinedione (2.5–40 mg/kg *per os*) in streptozotocin-induced diabetic rats (Prabhakar et al., 2013). The co-administration of either metformin or thiazolidinedione with FA also ameliorated the blood lipid profile in diabetic animals (Prabhakar et al., 2013). Importantly, FA decreased most of the side effects when administered in combination with thiazolidinedione (Prabhakar et al., 2013).

8. Ferulic acid and skin

Ferulic acid is well absorbed by the skin through cutaneous administration, both at acid and neutral pH, which demonstrates that the molecule can be absorbed by the skin both in dissociated and non-dissociated forms (Saija et al., 2000). Ferulic acid, dissolved in saturated aqueous solution at pH 7.2 and administered topically, has proved effective in protecting the skin from the onset of erythema from UVB rays in healthy subjects (Saija et al., 2000). In addition, FA (0.5%) is present in multiple formulations for topical use which also contain vitamin C (15%) and vitamin E (1%), and this combination provides a double protection compared to that given by acid FA alone or in combination with vitamin C + vitamin E (Lin et al., 2005) in pigs exposed to ultraviolet rays. This formulation has recently been patented by SkinCeuticals and is used not only in the prevention of erythema, but also in the prevention of wrinkles and areas of hyperpigmentation typical of the elderly. Similarly to what has occurred for vitamins C and E, whose effectiveness in preventing skin damage from ultraviolet rays has been proven even after oral administration (Fuchs and Kern, 1998), a protective effect on the skin may be envisaged for FA administered orally.

9. Ferulic acid toxicology

Ferulic acid has a low degree of toxicity after oral administration. Tada et al. (1999) found a reduction in mobility, piloerection and lacrimation in F344 rats treated with FA; in the case of single administration of FA higher than 1929 mg/kg, the death of rats occurred during the first 24 h of the 14-day period of observation

(Tada et al., 1999). By contrast, death from gastrointestinal bleeding occurred 24 h from administration (Tada et al., 1999). Finally, LD_{50}s equal to 2445 mg/kg and 2113 mg/kg were calculated for male and female rats, respectively (Tada et al., 1999; Ou and Kwok, 2004), whereas an acute LD_{50} of 3200 mg/kg was calculated in mice (Wang and Ou-Yang, 2005). This low toxicity has been confirmed by numerous experimental studies.

Ferulic acid, at a concentration of 50–100 nmoles/L, reduced the genotoxicity of acridine orange (216 μmol/L) and ofloxacin (3 μmol/L) in strains of *Salmonella typhimurium* with a mechanism dependent on its scavenging of ROS (Belicová et al., 2001). In hamsters treated with 7,12-dimethylbenz[a]anthracene, FA (40 mg/kg *per os*) for 5 days significantly reduced the number of micronucleated polychromatic erythrocytes and the percentage of chromosomal aberrations in the bone marrow (Balakrishnan et al., 2007). Ferulic acid (5–100 μM) had no additional clastogenic effects in lymphocytes isolated from human peripheral blood treated with mitomycin C (Stagos et al., 2007).

Ferulic acid reduced the activity of isoform 1A of cytochrome P450 (Ferguson et al., 2005) and increased the activity of UGT. The latter effect, evident at both hepatic and intestinal level, is responsible for a better detoxifying effect of carcinogenic compounds (Van der Logt et al., 2003). Despite the modulations of drug metabolizing enzymes, there is no clinical evidence in literature that the intake of FA may significantly increase the blood concentration of common drugs.

10. Conclusions

Despite the preclinical evidence supporting the potentially important role of FA in free radical-induced diseases, the clinical use of FA is still debated. One of the main issues that has limited the clinical use of FA so far, namely the low bioavailability after oral administration, could be overcome by the preparation of lipid-based formulations, such as SLN or liposomes. These new delivery systems have allowed better absorption of FA and its concentration has increased in many organs, even though in the brain it was still low (Li et al., 2008; Qin et al., 2007). Another limitation in the full comprehension of the clinical use of FA is related to the fact that many studies on humans were carried out by using foods containing FA, e.g. artichokes, tomatoes, etc., rather than the purified substance. This approach does not allow titration of the exact "dose" of FA that could be effective to achieve specific clinical aims, for instance the amelioration of cognitive functions in AD subjects or the reduction in blood pressure in hypertensive patients, and therefore may reduce the clinical benefits related to an appropriate dose. Furthermore, almost all these studies were designed with the aim to explore the pharmacokinetic parameters of FA (Table 2), whereas only a few clinical studies were performed keeping in mind a pharmacodynamic target or a specific disease. A possible reason to explain this low number of studies performed in humans is that, unlike drugs, dietary supplements, including FA, do not have to undergo phase II-III studies to demonstrate clinical efficacy and safety in order to be marketed. Therefore, FA is commercially available in several Countries even in the absence of extensive clinical research.

It is possible to conclude that clinical research on FA and its potential use in human diseases is still in its embryonic stage and needs to be encouraged. To date, the "therapeutic" use of FA in some human, age-related pathologies can only be considered as a guide for future work.

Conflict of Interest

C.M. reports funding from Menarini I.F.R. R.S. has nothing to disclose. This work was supported by a PRIN 2009 grant of the Italian Ministry of Education, University and Research and by Fondi Ateneo to C.M.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.fct.2013.12.024.

Acknowledgement

The Authors are grateful to Prof. Paolo Preziosi MD, Emeritus of Pharmacology at the Catholic University School of Medicine in Roma, for his helpful comments and suggestions and for reading the manuscript.

References

Adisakwattana, S., Chantarasinlapin, P., Thammarat, H., Yibchok-Anun, S., 2009. A series of cinnamic acid derivatives and their inhibitory activity on intestinal alpha-glucosidase. J. Enzyme Inhib. Med. Chem. 24, 1194–1200.

Adluri, R.S., Nagarajan, D., Periyaswamy, V., Venugopal, P.M., 2008. Dose-response effect of ferulic acid against nicotine-induced tissue damage and altered lipid levels in experimental rats: a pathohistological evaluation. Fundam. Clin. Pharmacol. 22, 557–567.

Alam, M.A., Sernia, C., Brown, L., 2013. Ferulic acid improves cardiovascular and kidney structure and function in hypertensive rats. J. Cardiovasc. Pharmacol. 61, 240–249.

Anantharaman, M., Tangpong, J., Keller, J.N., Murphy, M.P., Markesbery, W.R., Kiningham, K.K., St Clair, D.K., 2006. Beta-amyloid mediated nitration of manganese superoxide dismutase: implication for oxidative stress in a APPNLH/NLH X PS-1P264L/P264L double knock-in mouse model of Alzheimer's disease. Am. J. Pathol. 168, 1608–1618.

Ardiansyah, Ohsaki, Y., Shirakawa, H., Koseki, T., Komai, M., 2008. Novel effects of a single administration of ferulic acid on the regulation of blood pressure and the hepatic lipid metabolic profile in stroke-prone spontaneously hypertensive rats. J. Agric. Food Chem. 56, 2825–2830.

Azzini, E., Bugianesi, R., Romano, F., Di Venere, D., Miccadei, S., Durazzo, A., Foddai, M.S., Catasta, G., Linsalata, V., Maiani, G., 2007. Absorption and metabolism of bioactive molecules after oral consumption of cooked edible heads of *Cynara scolymus* L. (cultivar Violetto di Provenza) in human subjects: a pilot study. Br. J. Nutr. 97, 963–969.

Badawy, D., El-Bassossy, H.M., Fahmy, A., Azhar, A., 2013. Aldose reductase inhibitors zopolrestat and ferulic acid alleviate hypertension associated with diabetes: effect on vascular reactivity. Can. J. Physiol. Pharmacol. 91, 101–107.

Balakrishnan, S., Menon, V.P., Manoharan, S., Rajalingam, K., 2007. Antigenotoxic effect of ferulic acid in 7,12-dimethyl benz(a)-anthracene (DMBA) induced genotoxicity. Afr. J. Tradit. Complement. Altern. Med. 5, 32–38.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., Jones, E., 2011. Alzheimer's disease. Lancet 377, 1019–1031.

Bandugula, V.R., Prasad, N.R., 2013. 2-Deoxy-D-glucose and ferulic acid modulates radiation response signaling in non-small cell lung cancer cells. Tumour Biol. 34, 251–259.

Barone, E., Calabrese, V., Mancuso, C., 2009. Ferulic acid and its therapeutic potential as a hormetin for age-related diseases. Biogerontology 10, 97–108.

Baskaran, N., Manoharan, S., Balakrishnan, S., Pugalendhi, P., 2010. Chemopreventive potential of ferulic acid in 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in Sprague-Dawley rats. Eur. J. Pharmacol. 637, 22–29.

Bayer, T.A., Schäfer, S., Breyhan, H., Wirths, O., Treiber, C., Multhaup, G., 2006. A vicious circle: role of oxidative stress, intraneuronal Abeta and Cu in Alzheimer's disease. Clin. Neuropathol. 25, 163–171.

Belicová, A., Krizková, L., Nagy, M., Krajcovic, J., Ebringer, L., 2001. Phenolic acids reduce the genotoxicity of acridine orange and ofloxacin in *Salmonella typhimurium*. Folia Microbiol. (Praha) 46, 511–514.

Bourne, L.C., Rice-Evans, C., 1998. Bioavailability of ferulic acid. Biochem. Biophys. Res. Commun. 253, 222–277.

Butterfield, D.A., Reed, T., Newman, S.F., Sultana, R., 2007. Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment. Free Radic. Biol. Med. 43, 658–677.

Calabrese, V., Mancuso, C., Calvani, M., Rizzarelli, E., Butterfield, D.A., Stella, A.M., 2007. Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. Nat. Rev. Neurosci. 8, 766–775.

Calabrese, V., Calafato, S., Puleo, E., Cornelius, C., Sapienza, M., Morganti, P., Mancuso, C., 2008. Redox regulation of cellular stress response by ferulic acid ethyl ester in human dermal fibroblasts: role of vitagenes. Clin. Dermatol. 26, 358–363.

Cassano, R., Trombino, S., Cilea, A., Ferrarelli, T., Muzzalupo, R., Picci, N., 2010. L-lysine pro-prodrug containing trans-ferulic acid for 5-amino salicylic acid colon delivery: synthesis, characterization and in vitro antioxidant activity evaluation. Chem. Pharm. Bull. (Tokyo) 58, 103–105.

Cheng, C.Y., Su, S.Y., Tang, N.Y., Ho, T.Y., Lo, W.Y., Hsieh, C.L., 2010. Ferulic acid inhibits nitric oxide-induced apoptosis by enhancing GABA(B1) receptor

expression in transient focal cerebral ischemia in rats. Acta Pharmacol. Sin. 31, 889–899.
Cho, J.Y., Kim, H.S., Kim, D.H., Jan, J.J., Suh, H.W., Song, D.K., 2005. Inhibitory effects of long-term administration of ferulic acid on astrocyte activation induced by intracerebroventricular injection of beta-amyloid peptide (1–42) in mice. Prog. Neuropsychopharmacol. Biol. Psychiatr. 29, 901–907.
Choi, R., Kim, B.H., Naowaboot, J., Lee, M.Y., Hyun, M.R., Cho, E.J., Lee, E.S., Lee, E.Y., Yang, Y.C., Chung, C.H., 2011. Effects of ferulic acid on diabetic nephropathy in a rat model of type 2 diabetes. Exp. Mol. Med. 43, 676–683.
Clifford, M.N., 1999. Chlorogenic acids and other cinnamates–nature, occurrence and dietary burden. J. Sci. Food Agric. 79, 362–372.
Couteau, D., McCartney, A.L., Gibson, G.R., Williamson, G., Faulds, C.B., 2001. Isolation and characterization of human colonic bacteria able to hydrolyse chlorogenic acid. J. Appl. Microbiol. 90, 873–881.
Cuzick, J., Otto, F., Baron, J.A., Brown, P.H., Burn, J., Greenwald, P., Jankowski, J., La Vecchia, C., Meyskens, F., Senn, H.J., Thun, M., 2009. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 10, 501–507.
D'Archivio, M., Filesi, C., Di Benedetto, R., Gargiulo, R., Giovannini, C., Masella, R., 2007. Polyphenols, dietary sources and bioavailability. Ann. Ist. Super. Sanita 43, 348–361.
Dong, W.G., Liu, S.P., Yu, B.P., Wu, D.F., Luo, H.S., Yu, J.P., 2003. Ameliorative effects of sodium ferulate on experimental colitis and their mechanisms in rats. World J. Gastroenterol. 9, 2533–2538.
EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009. Scientific opinion on the substantiation of health claims related to *Angelica sinensis* (Oliv.) Diels. and maintenance of joints (ID 2392) and oxygen transport (ID 3845) pursuant to Article 13(1) of Regulation (EC) No. 1924/2006. EFSA J. 7, 1281.
Evans, C.G., Chang, L., Gestwicki, J.E., 2010. Heat shock protein 70 (hsp70) as an emerging drug target. J. Med. Chem. 53, 4585–4602.
Ferguson, L.R., Zhu, S.T., Harris, P.J., 2005. Antioxidant and antigenotoxic effects of plant cell wall hydroxycinnamic acids in cultured HT-29 cells. Mol. Nutr. Food Res. 49, 585–593.
Ferrer, I., 2009. Altered mitochondria, energy metabolism, voltage-dependent anion channel, and lipid rafts converge to exhaust neurons in Alzheimer's disease. J. Bioenerg. Biomembr. 41, 425–431.
Fetoni, A.R., Mancuso, C., Eramo, S.L., Ralli, M., Piacentini, R., Barone, E., Paludetti, G., Troiani, D., 2010. In vivo protective effect of ferulic acid against noise-induced hearing loss in the guinea-pig. Neuroscience 169, 1575–1588.
Fridovich, I., 1999. Fundamental aspects of reactive oxygen species, or what's the matter with oxygen? Ann. NY Acad. Sci. 893, 13–18.
Fuchs, J., Kern, H., 1998. Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. Free Radic. Biol. Med. 25, 1006–1012.
Fujita, A., Sasaki, H., Doi, A., Okamoto, K., Matsuno, S., Furuta, H., Nishi, M., Nakao, T., Tsuno, T., Taniguchi, H., Nanjo, K., 2008. Ferulic acid prevents pathological and functional abnormalities of the kidney in Otsuka Long-Evans Tokushima Fatty diabetic rats. Diabetes Res. Clin. Pract. 79, 11–17.
Garrido, C., Paul, C., Seigneuric, R., Kampinga, H.H., 2012. The small heat shock proteins family: the long forgotten chaperones. Int. J. Biochem. Cell Biol. 44, 1588–1592.
Giacchetti, G., Sechi, L.A., Rilli, S., Carey, R.M., 2005. The renin–angiotensin–aldosterone system, glucose metabolism and diabetes. Trends Endocrinol. Metab. 16, 120–126.
Graf, E., 1992. Antioxidant potential of ferulic acid. Free Radic. Biol. Med. 13, 435–448.
Grothe, M., Zaborszky, L., Atienza, M., Gil-Neciga, E., Rodriguez-Romero, R., Teipel, S.J., Amunts, K., Suarez-Gonzalez, A., Cantero, J.L., 2010. Reduction of basal forebrain cholinergic system parallels cognitive impairment in patients at high risk of developing Alzheimer's disease. Cereb. Cortex. 20, 1685–1695.
Halliwell, B., 1978. Biochemical mechanisms accounting for the toxic action of oxygen on living organisms: the key role of superoxide dismutase. Cell Biol. Int. Rep. 2, 113–128.
Hemaiswarya, S., Doble, M., 2013. Combination of phenylpropanoids with 5-fluorouracil as anti-cancer agents against human cervical cancer (HeLa) cell line. Phytomedicine 20, 151–158.
Henderson, B., 2010. Integrating the cell stress response: a new view of molecular chaperones as immunological and physiological homeostatic regulators. Cell Biochem. Funct. 28, 1–14.
Indap, M.A., Radhika, S., Motiwale, L., Rao, K.V., 2006. Inhibitory effect of cinnamoyl compounds against human malignant cell line. Indian J. Exp. Biol. 44, 216–220.
Inoguchi, T., Sonta, T., Tsubouchi, H., Etoh, T., Kakimoto, M., Sonoda, N., Sato, N., Sekiguchi, N., Kobayashi, K., Sumimoto, H., Utsumi, H., Nawata, H., 2003. Protein kinase C-dependent increase in reactive oxygen species (ROS) production in vascular tissues of diabetes: role of vascular NAD(P)H oxidase. J. Am. Soc. Nephrol. 14, S227–S232.
Janicke, B., Hegardt, C., Krogh, M., Onning, G., Akesson, B., Cirenajwis, H.M., Oredsson, S.M., 2011. The antiproliferative effect of dietary fiber phenolic compounds ferulic acid and p-coumaric acid on the cell cycle of Caco-2 cells. Nutr. Cancer 63, 611–622.
Jayaprakasam, B., Vanisree, M., Zhang, Y., Dewitt, D.L., Nair, M.G., 2006. Impact of alkyl esters of caffeic and ferulic acids on tumor cell proliferation, cyclooxygenase enzyme, and lipid peroxidation. J. Agric. Food Chem. 54, 5375–5381.
Jin, Y., Yan, E.Z., Fan, Y., Zong, Z.H., Qi, Z.M., Li, Z., 2005. Sodium ferulate prevents amyloid-beta-induced neurotoxicity through suppression of p38 MAPK and upregulation of ERK-1/2 and Akt/protein kinase B in rat hippocampus. Acta Pharmacol. Sin. 26, 943–951.
Jin, Y., Fan, Y., Yan, E.Z., Liu, Z., Zong, Z.H., Qi, Z.M., 2006. Effects of sodium ferulate on amyloid-beta-induced MKK3/MKK6-p38 MAPK-Hsp27 signal pathway and apoptosis in rat hippocampus. Acta Pharmacol. Sin. 27, 1309–1316.
Jin, Y., Yan, E.Z., Li, X.M., Fan, Y., Zhao, Y.J., Liu, Z., Liu, W.Z., 2008. Neuroprotective effect of sodium ferulate and signal transduction mechanisms in the aged rat hippocampus. Acta Pharmacol. Sin. 29, 1399–1408.
Joshi, G., Perluigi, M., Sultana, R., Agrippino, R., Calabrese, V., Butterfield, D.A., 2006. In vivo protection of synaptosomes by ferulic acid ethyl ester (FAEE) from oxidative stress mediated by 2,2-azobis(2-amidino-propane)dihydrochloride (AAPH) or Fe(2+)/H(2)O(2): insight into mechanisms of neuroprotection and relevance to oxidative stress-related neurodegenerative disorders. Neurochem. Int. 48, 318–327.
Jung, E.H., Kim, S.R., Hwang, I.K., Ha, T.Y., 2007. Hypoglycemic effects of a phenolic acid fraction of rice bran and ferulic acid in C57BL/KsJ-db/db mice. J. Agric. Food Chem. 55, 9800–9804.
Kanski, J., Aksenova, M., Stoyanova, A., Butterfield, D.A., 2002. Ferulic acid antioxidant protection against hydroxyl and peroxyl radical oxidation in synaptosomal and neuronal cell culture systems in vitro: structure-activity studies. J. Nutr. Biochem. 13, 273–281.
Karthikeyan, S., Kanimozhi, G., Prasad, N.R., Mahalakshmi, R., 2011. Radiosensitizing effect of ferulic acid on human cervical carcinoma cells in vitro. Toxicol. In Vitro 25, 1366–1375.
Katsuki, H., Nakai, S., Hirai, Y., Akaji, K., Kiso, Y., Satoh, M., 1990. Interleukin-1 beta inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. Eur. J. Pharmacol. 181, 323–326.
Keeney, J.T., Swomley, A.M., Harris, J.L., Fiorini, A., Mitov, M.I., Perluigi, M., Sultana, R., Butterfield, D.A., 2012. Cell cycle proteins in brain in mild cognitive impairment: insights into progression to Alzheimer disease. Neurotox. Res. 22, 220–230.
Kern, S.M., Bennett, R.N., Mellon, F.A., Kroon, P.A., Garcia-Conesa, M.T., 2003. Absorption of hydroxycinnamates in humans after high-bran cereal consumption. J. Agric. Food Chem. 51, 6050–6055.
Khanduja, K.L., Avti, P.K., Kumar, S., Mittal, N., Sohi, K.K., Pathak, C.M., 2006. Anti-apoptotic activity of caffeic acid, ellagic acid and ferulic acid in normal human peripheral blood mononuclear cells: a Bcl-2 independent mechanism. Biochim. Biophys. Acta 1760, 283–289.
Kim, M.J., Choi, S.J., Lim, S.T., Kim, H.K., Heo, H.J., Kim, E.K., Jun, W.J., Cho, H.Y., Kim, Y.J., Shin, D.H., 2007. Ferulic acid supplementation prevents trimethyltin-induced cognitive deficits in mice. Biosci. Biotechnol. Biochem. 71, 1063–1068.
Kiritoshi, S., Nishikawa, T., Sonoda, K., Kukidome, D., Senokuchi, T., Matsuo, T., Matsumura, T., Tokunaga, H., Brownlee, M., Araki, E., 2003. Reactive oxygen species from mitochondria induce cyclooxygenase-2 gene expression in human mesangial cells: potential role in diabetic nephropathy. Diabetes 52, 2570–2577.
Koh, P.O., 2012. Ferulic acid modulates nitric oxide synthase expression in focal cerebral ischemia. Lab. Anim. Res. 28, 273–278.
Kroon, P.A., Faulds, C.B., Ryden, P., Robertson, J.A., Williamson, G., 1997. Release of covalently bound ferulic acid from fiber in the human colon. J. Agric. Food Chem. 45, 661–667.
Kundu, J.K., Surh, Y.J., 2008. Inflammation: gearing the journey to cancer. Mutat. Res. 659, 15–30.
Kwon, E.Y., Cho, Y.Y., Do, G.M., Kim, H.J., Jeon, S.M., Park, Y.B., Lee, M.K., Min, T.S., Choi, M.S., 2009. Actions of ferulic acid and vitamin E on prevention of hypercholesterolemia and atherogenic lesion formation in apolipoprotein E-deficient mice. J. Med. Food 12, 996–1003.
Kwon, E.Y., Do, G.M., Cho, Y.Y., Park, Y.B., Jeon, S.M., Choi, M.S., 2010. Anti-atherogenic property of ferulic acid in apolipoprotein E-deficient mice fed Western diet: comparison with clofibrate. Food Chem. Toxicol. 48, 2298–2303.
Li, R., Yang, L., Lindholm, K., Konishi, Y., Yue, X., Hampel, H., Zhang, D., Shen, Y., 2004. Tumor necrosis factor death receptor signaling cascade is required for amyloid-beta protein-induced neuron death. J. Neurosci. 24, 1760–1771.
Li, F., Cao, Q.E., Ding, Z., 2007. Separation and determination of three phenylpropanoids in the traditional Chinese medicine and its preparations by capillary electrophoresis. J. Chromatogr. Sci. 45 (6), 354–359.
Li, F.Q., Su, H., Wang, J., Liu, J.Y., Zhu, Q.G., Fei, Y.B., Pan, Y.H., Hu, J.H., 2008. Preparation and characterization of sodium ferulate entrapped bovine serum albumin nanoparticles for liver targeting. Int. J. Pharm. 349, 274–282.
Li, X., Shang, L., Wu, Y., Abbas, S., Li, D., Netter, P., Ouzzine, M., Wang, H., Magdalou, J., 2011. Identification of the human UDP-glucuronosyltransferase isoforms involved in the glucuronidation of the phytochemical ferulic acid. Drug Metab. Pharmacokinet. 26, 341–350.
Lin, F.H., Lin, J.Y., Gupta, R.D., Tournas, J.A., Burch, J.A., Selim, M.A., Monteiro-Riviere, N.A., Grichnik, J.M., Zielinski, J., Pinnell, S.R., 2005. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. J. Invest. Dermatol. 125, 826–832.
Ma, Z.C., Hong, Q., Wang, Y.G., Liang, Q.D., Tan, H.L., Xiao, C.R., Tang, X.L., Shao, S., Zhou, S.S., Gao, Y., 2011. Ferulic acid induces heme oxygenase-1 via activation of ERK and Nrf2. Drug Discov. Ther. 5, 299–305.
Maines, M.D., 1997. The heme oxygenase system: a regulator of second messenger gases. Annu. Rev. Pharmacol. Toxicol. 37, 517–554.
Mamiya, T., Kise, M., Morikawa, K., 2008. Ferulic acid attenuated cognitive deficits and increase in carbonyl proteins induced by buthionine-sulfoximine in mice. Neurosci. Lett. 430, 115–118.

Mancuso, C., Bonsignore, A., Di Stasio, E., Mordente, A., Motterlini, R., 2003. Bilirubin and S-nitrosothiols interaction: evidence for a possible role of bilirubin as a scavenger of nitric oxide. Biochem. Pharmacol. 66, 2355–2363.
Mancuso, C., Bonsignore, A., Capone, C., Di Stasio, E., Pani, G., 2006. Albumin-bound bilirubin interacts with nitric oxide by a redox mechanism. Antioxid. Redox. Signal. 8, 487–494.
Mancuso, C., Barone, E., 2009. The heme oxygenase/biliverdin reductase pathway in drug research and development. Curr. Drug Metab. 10, 579–594.
Mancuso, C., Barone, E., Guido, P., Miceli, F., Di Domenico, F., Perluigi, M., Santangelo, R., Preziosi, P., 2012. Inhibition of lipid peroxidation and protein oxidation by endogenous and exogenous antioxidants in rat brain microsomes in vitro. Neurosci. Lett. 518, 101–105.
Menter, D.G., Schilsky, R.L., DuBois, R.N., 2010. Cyclooxygenase-2 and cancer treatment: understanding the risk should be worth the reward. Clin. Cancer Res. 16, 1384–1390.
Minetti, M., Mallozzi, C., Di Stasi, A.M., Pietraforte, D., 1998. Bilirubin is an effective antioxidant of peroxynitrite-mediated protein oxidation in human blood plasma. Arch. Biochem. Biophys. 352, 165–174.
Mori, T., Koyama, N., Guillot-Sestier, M.V., Tan, J., Town, T., 2013. Ferulic acid is a nutraceutical β-secretase modulator that improves behavioral impairment and alzheimer-like pathology in transgenic mice. PLoS ONE 8, e55774.
Mulinacci, N., Prucher, D., Peruzzi, M., Romani, A., Pinelli, P., Giaccherini, C., Vincieri, F.F., 2004. Commercial and laboratory extracts from artichoke leaves: estimation of caffeoyl esters and flavonoidic compounds content. J. Pharm. Biomed. Anal. 34, 349–357.
Nair, S.C., Panikkar, B., Akamanchi, K.G., Panikkar, K.R., 1991. Inhibitory effects of Ixora javanica extract on skin chemical carcinogenesis in mice and its antitumour activity. Cancer Lett. 60, 253–258.
Naudi, A., Jove, M., Ayala, V., Cassanye, A., Serrano, J., Gonzalo, H., Boada, J., Prat, J., Portero-Otin, M., Pamplona, R., 2012. Cellular dysfunction in diabetes as maladaptive response to mitochondrial oxidative stress. Exp. Diabetes Res. 2012, 696215.
Ou, S., Kwok, K.C., 2004. Ferulic acid: pharmaceutical functions, preparation and applications in food. J. Sci. Food Agric. 84, 1261–1269.
Pagidipati, N.J., Gaziano, T.A., 2013. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. Circulation 127, 749–756.
Pannala, A.S., Razaq, R., Halliwell, B., Singh, S., Rice-Evans, C.A., 1998. Inhibition of peroxynitrite dependent tyrosine nitration by hydroxycinnamates: nitration or electron donation? Free Radic. Biol. Med. 24, 594–606.
Perluigi, M., Joshi, G., Sultana, R., Calabrese, V., De Marco, C., Coccia, R., Cini, C., Butterfield, D.A., 2006. In vivo protective effects of ferulic acid ethyl ester against amyloid-beta peptide 1–42-induced oxidative stress. J. Neurosci. Res. 84, 418–426.
Picone, P., Bondi, M.L., Montana, G., Bruno, A., Pitarresi, G., Giammona, G., Di Carlo, M., 2009. Ferulic acid inhibits oxidative stress and cell death induced by Ab oligomers: improved delivery by solid lipid nanoparticles. Free Radic. Res. 43, 1133–1145.
Poquet, L., Clifford, M.N., Williamson, G., 2008. Transport and metabolism of ferulic acid through the colonic epithelium. Drug Metab. Dispos. 36, 190–197.
Prabhakar, P.K., Prasad, R., Ali, S., Doble, M., 2013. Synergistic interaction of ferulic acid with commercial hypoglycemic drugs in streptozotocin induced diabetic rats. Phytomedicine 20, 488–494.
Preziosi, P., Loscalzo, B., Bianchi, A., 1957a. Pharmacodynamic research on the active principle of Cynara scolimus (1,4-dicaffeiylquinic acid): effect on choleresis. Boll. Soc. Ital. Biol. Sper. 33, 672–674.
Preziosi, P., Loscalzo, B., 1957b. Pharmacodynamic research on the active principle of Cynara scolimus (1,4-dicaffeiylquinic acid): effect on blood cholesterol values & on triton-induced hypercholesterolemia. Boll. Soc. Ital. Biol. Sper. 33, 679–682.
Preziosi, P., Loscalzo, B., 1957c. Experimental evaluation of 1,4-dicaffeiylquinic acid, the active principle of artichoke. Arch. Ital. Sci. Farmacol. 7, 249–296.
Preziosi, P., Loscalzo, B., 1958. Pharmacological properties of 1,4 dicaffeylquinic acid, the active principle of Cynara scolimus. Arch. Int. Pharmacodyn. Ther. 117, 63–80.
Qin, J., Chen, D., Hu, H., 2007. Body distributioin of RGD-mediated liposome in brain-targeting drug delivery. Yakugaku Zasshi 127, 1497–1501.
Querfurth, H.W., LaFerla, F.M., 2010. Alzheimer's disease. N. Engl. J. Med. 362, 329–344.
Rabacchi, S.A., Friedman, W.J., Shelanski, M.L., Troy, C.M., 2004. Divergence of the apoptotic pathways induced by 4-hydroxynonenal and amyloid beta-protein. Neurobiol. Aging 25, 1057–1066.
Ramar, M., Manikandan, B., Raman, T., Priyadarsini, A., Palanisamy, S., Velayudam, M., Munusamy, A., Marimuthu Prabhu, N., Vaseeharan, B., 2012. Protective effect of ferulic acid and resveratrol against alloxan-induced diabetes in mice. Eur. J. Pharmacol. 690, 226–235.
Rechner, A.R., Pannala, A.S., Rice-Evans, C.A., 2001. Caffeic acid derivatives in artichoke extract are metabolised to phenolic acids in vivo. Free Radic. Res. 35, 195–202.
Reiter, C.D., Teng, R.J., Beckman, J.S., 2000. Superoxide reacts with nitric oxide to nitrate tyrosine at physiological pH via peroxynitrite. J. Biol. Chem. 275, 32460–32466.
Rhein, V., Eckert, A., 2007. Effects of Alzheimer's amyloid-beta and tau protein on mitochondrial function – role of glucose metabolism and insulin signalling. Arch. Physiol. Biochem. 113, 131–141.
Rolo, A.P., Palmeira, C.M., 2006. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. Toxicol. Appl. Pharmacol. 212, 167–178.
Rondini, L., Peyrat-Maillard, M.N., Marsset-Baglieri, A., Berset, C., 2002. Sulfated ferulic acid is the main in vivo metabolite found after short-term ingestion of free ferulic acid in rats. J. Agric. Food Chem. 50, 3037–3041.
Rondini, L., Peyrat-Maillard, M.N., Marsset-Baglieri, A., Fromentin, G., Durand, P., Tomé, D., Prost, M., Berset, C., 2004. Bound ferulic acid from bran is more bioavailable than the free compound in rat. J. Agric. Food Chem. 52, 4338–4343.
Roy, S., Metya, S.K., Sannigrahi, S., Rahaman, N., Ahmed, F., 2013. Treatment with ferulic acid to rats with streptozotocin-induced diabetes: effects on oxidative stress, pro-inflammatory cytokines, and apoptosis in the pancreatic β cell. Endocrine 44, 369–379.
Saija, A., Tomaino, A., Trombetta, D., De Pasquale, A., Uccella, N., Barbuzzi, T., Paolino, D., Bonina, F., 2000. In vitro and in vivo evaluation of caffeic and ferulic acids as topical photoprotective agents. Int. J. Pharm. 199, 39–47.
Saulnier, L., Vigouroux, J., Thibault, J.F., 1995. Isolation and partial characterization of feruloylated oligosaccharides from maize bran. Carbohydr. Res. 272, 241–253.
Scapagnini, G., Butterfield, D.A., Colombrita, C., Sultana, R., Pascale, A., Calabrese, V., 2004. Ethyl ferulate, a lipophilic polyphenol, induces HO-1 and protects rat neurons against oxidative stress. Antioxid. Redox Signal. 6, 811–818.
Smith, M.A., Richey Harris, P.L., Sayre, L.M., Beckman, J.S., Perry, G., 1997. Widespread peroxynitrite-mediated damage in Alzheimer's disease. J. Neurosci. 17, 2653–2657.
Srinivasan, M., Rukkumani, R., Ram Sudheer, A., Menon, V.P., 2005. Ferulic acid, a natural protector against carbon tetrachloride-induced toxicity. Fundam. Clin. Pharmacol. 19, 491–496.
Stagos, D., Spanou, C., Margariti, M., Stathopoulos, C., Mamuris, Z., Kazantzoglou, G., Magiatis, P., Kouretas, D., 2007. Cytogenetic effects of grape extracts (*Vitis vinifera*) and polyphenols on mitomycin C-induced sister chromatid exchanges (SCEs) in human blood lymphocytes. J. Agric. Food Chem. 55, 5246–5252.
Stocker, R., Yamamoto, Y., McDonagh, A.F., Glazer, A.N., Ames, B.N., 1987a. Bilirubin is an antioxidant of possible physiological importance. Science 235, 1043–1046.
Stocker, R., Glazer, A.N., Ames, B.N., 1987b. Antioxidant activity of albumin-bound bilirubin. Proc. Natl. Acad. Sci. USA 84, 5918–5922.
Sudheer, A.R., Muthukumaran, S., Kalpana, C., Srinivasan, M., Menon, V.P., 2007. Protective effect of ferulic acid on nicotine-induced DNA damage and cellular changes in cultured rat peripheral blood lymphocytes: a comparison with N-acetylcysteine. Toxicol. In Vitro 21, 576–585.
Sultana, R., Ravagna, A., Mohmmad-Abdul, H., Calabrese, V., Butterfield, D.A., 2005. Ferulic acid ethyl ester protects neurons against amyloid beta-peptide(1–42)-induced oxidative stress and neurotoxicity: relationship to antioxidant activity. J. Neurochem. 92, 749–758.
Sultana, R., Butterfield, D.A., 2009. Oxidatively modified, mitochondria-relevant brain proteins in subjects with Alzheimer disease and mild cognitive impairment. J. Bioenerg. Biomembr. 41, 441–446.
Suzuki, A., Kagawa, D., Fujii, A., Ochiai, R., Tokimitsu, I., Saito, I., 2002. Short- and long-term effects of ferulic acid on blood pressure in spontaneously hypertensive rats. Am. J. Hypertens. 15, 351–357.
Suzuki, A., Yamamoto, M., Jokura, H., Fujii, A., Tokimitsu, I., Hase, T., Saito, I., 2007. Ferulic acid restores endothelium-dependent vasodilation in aortas of spontaneously hypertensive rats. Am. J. Hypertens. 20, 508–513.
Tada, Y., Tayama, K., Aoki, N., 1999. Acute oral toxicity of ferulic acid, natural food additive, in rats. Ann. Rep. Tokyo Metr. Lab. P.H. 50, 311–313.
Tanaka, T., Kojima, T., Kawamori, T., Wang, A., Suzui, M., Okamoto, K., Mori, H., 1993. Inhibition of 4-nitroquinoline-1-oxide-induced rat tongue carcinogenesis by the naturally occurring plant phenolics caffeic, ellagic, chlorogenic and ferulic acids. Carcinogenesis 14, 1321–1325.
Trombino, S., Cassano, R., Muzzalupo, R., Pingitore, A., Cione, E., Picci, N., 2009. Stearyl ferulate-based solid lipid nanoparticles for the encapsulation and stabilization of beta-carotene and alpha-tocopherol. Colloids Surf. B: Biointerf. 72, 181–187.
Trombino, S., Cassano, R., Ferrarelli, T., Barone, E., Picci, N., Mancuso, C., 2013. Trans-ferulic acid-based solid lipid nanoparticles and their antioxidant effect in rat brain microsomes. Colloids Surf. B: Biointerf. 109, 273–279.
van der Logt, E.M., Roelofs, H.M., Nagengast, F.M., Peters, W.H., 2003. Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogens. Carcinogenesis 24, 1651–1656.
Wang, B., Ou-Yang, J., Liu, Y., Yang, J., Wei, L., Li, K., Yang, H., 2004. Sodium ferulate inhibits atherosclerogenesis in hyperlipidemia rabbits. J. Cardiovasc. Pharmacol. 43, 549–554.
Wang, B.H., Ou-Yang, J.P., 2005. Pharmacological actions of sodium ferulate in cardiovascular system. Cardiovasc. Drug Rev. 23, 161–172.
West, J.D., Wang, Y., Morano, K.A., 2012. Small molecule activators of the heat shock response: chemical properties, molecular targets, and therapeutic promise. Chem. Res. Toxicol. 25, 2036–2053.
Xu, X., Xiao, H., Zhao, J., Zhao, T., 2012. Cardioprotective effect of sodium ferulate in diabetic rats. Int. J. Med. Sci. 9, 291–300.
Yan, J.J., Cho, J.Y., Kim, H.S., Kim, K.L., Jung, J.S., Huh, S.O., Suh, H.W., Kim, Y.H., Song, D.K., 2001. Protection against beta-amyloid peptide toxicity in vivo with long-term administration of ferulic acid. Br. J. Pharmacol. 133, 89–96.
Yan, J.J., Jung, J.S., Kim, T.K., Hasan, A., Hong, C.W., Nam, J.S., Song, D.K., 2013. Protective effects of ferulic acid in amyloid precursor protein plus presenilin-1 transgenic mouse model of Alzheimer disease. Biol. Pharm. Bull. 36, 140–143.

Yang, C., Tian, Y., Zhang, Z., Xu, F., Chen, Y., 2007. High-performance liquid chromatography–electrospray ionization mass spectrometry determination of sodium ferulate in human plasma. J. Pharm. Biomed. Anal. 43, 945–950.
Yi, L., Liang, Y., Wu, H., Yuan, D., 2009. The analysis of Radix Angelicae Sinensis (Danggui). J. Chromatogr. A 1216, 1991–2001.
Zhao, Z., Egashira, Y., Sanada, H., 2003. Ferulic acid sugar esters are recovered in rat plasma and urine mainly as the sulfoglucuronide of ferulic acid. J. Nutr. 133, 1355–1361.
Zhao, Z., Egashira, Y., Sanada, H., 2004. Ferulic acid is quickly absorbed from rat stomach as the free form and then conjugated mainly in liver. J. Nutr. 134, 3083–3088.
Zhao, Z., Moghadasian, M.H., 2008. Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: a review. Food Chem. 109, 691–702.
Zheng, R.L., Zhang, H., 1997. Effects of ferulic acid on fertile and asthenozoospermic infertile human sperm motility, viability, lipid peroxidation, and cyclic nucleotides. Free Radic. Biol. Med. 22, 581–586.
Zuiderweg, E.R., Bertelsen, E.B., Rousaki, A., Mayer, M.P., Gestwicki, J.E., Ahmad, A., 2013. Allostery in the Hsp70 chaperone proteins. Top Curr. Chem. 328, 99–153.