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Review

# Ferulic acid and derivatives: molecules with potential application in the pharmaceutical field

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Ferulic acid is a phenolic acid widely distributed in the plant kingdom. It presents a wide range of potential therapeutic effects useful in the treatments of cancer, diabetes, lung and cardiovascular diseases, as well as hepatic, neuro and photoprotective effects and antimicrobial and anti-inflammatory activities. Overall, the pharmaceutical potential of ferulic acid can be attributed to its ability to scavenge free radicals. However, recent studies have revealed that ferulic acid presents pharmacological properties beyond those related to its antioxidant activity, such as the ability to competitively inhibit HMG-CoA reductase and activate glucokinase, contributing to reduce hypercholesterolemia and hyperglycemia, respectively. The present review addresses ferulic acid dietary sources, the pharmacokinetic profile, antioxidant action mechanisms and therapeutic effects in the treatment and prevention of various diseases, in order to provide a basis for understanding its mechanisms of action as well as its pharmaceutical potential.

**Uniterms:** Ferulic acid/properties. Ferulic acid/antioxidant activity. Ferulic acid/dietary sources. Ferulic acid/therapeutic effects. Natural products. Pharmacognosy.

O ácido ferúlico é um ácido fenólico amplamente distribuído no reino vegetal. Ele apresenta uma ampla gama de potenciais efeitos terapêuticos utéis no tratamento do câncer, diabetes, doenças pulmonares e cardiovasculares, bem como efeitos hepáticos, neuro e fotoprotetores, atividades antimicrobianas e anti-inflamatórias. O potencial farmacêutico do ácido ferúlico pode ser atribuído à sua capacidade em sequestrar radicais livres. No entanto, estudos recentes revelaram que o ácido ferúlico apresenta propriedades farmacológicas, além da sua atividade antioxidante, como a capacidade de inibir competitivamente a HMG-CoA redutase e ativar a glucoquinase, contribuindo para reduzir a hipercolesterolemia e hiperglicemia, respectivamente. A presente revisão aborda as fontes dietéticas de ácido ferúlico, o perfil farmacocinético, os mecanismos de ação como antioxidante e efeitos terapêuticos no tratamento e prevenção de várias doenças, de modo a proporcionar uma base para a compreensão dos seus mecanismos de ação, bem como os seus potenciais farmacêuticos.

**Unitermos:** Ácido ferúlico/propriedades. Ácido ferúlico/atividade antioxidante. Ácido ferúlico/fontes dietéticas. Ácido ferúlico/efeitos terapêuticos. Produtos naturais. Farmacognosia.

## INTRODUCTION

Natural antioxidants exhibit therapeutic potential for a variety of diseases such as cancer, diabetes, and cardiovascular and neurodegenerative diseases (Kayahara *et al*., 1999; Kim *et al*., 2003; Soobrattee *et al*., 2005) where free radicals play a key role in development (Prior *et al*., 1998). Recently there has been increased public and scientific interest in employing natural antioxidants instead of synthetic antioxidants, due to their potential adverse effects on health which may include carcinogenicity (Ito *et al*., 1983; Würtzen, 1990; Osawa *et al*., 1990).

Antioxidants found in vegetables can act as sequesters, reducing agents, enzyme inhibitors, metal chelators or free radical scavengers (Wang *et al*., 2000). Phenols are widely distributed in the plant kingdom and diet vegetables. There are found in significant concentrations in fruits, vegetables and beverages and

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have been indicated as effective antioxidants (Clifford, 1999; Pimentel *et al*., 2005).

Ferulic acid (Figure 1) is one of the most abundant phenolic acids in plants and might be found in high concentrations in foods such as navy bean, corn bran, wheat bran, eggplant, artichokes and beets (Rosazza *et al*., 1995; Kroon *et al*., 1997; Rechner *et al*., 2001; D'archivio *et al*., 2007). It can be found free, dimerized or esterified with proteins and polysaccharides in the cell wall, such as arabinoxylans in grasses and xyloglucans in bamboo (Iiyama *et al*., 1994; Rumbold *et al*., 2003; Fazary, Ju, 2007). Ferulic acid (FA) is an important biological and structural component of the plant cell wall. Due to its ability to stop radical chain reactions by resonance followed by polymerization, FA offers protection against UV-radiation and is responsible for cross-linking polysaccharides and other cell wall polymers (Sánchez *et al*., 1996; Kroon *et al*., 1999, Santos *et al*., 2008).

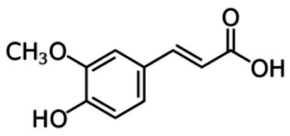


**FIGURE 1 -** Chemical structure of ferulic Acid (FA).

FA can be obtained from plant cell walls via alkaline chemical (Taniguchi *et al*., 1999) or biotechnological treatments employing feruloyl esterases (EC 3.1.1.73) a subclass of the carboxylesterases produced by microorganisms that are able to hydrolyze ester bonds formed between cell wall polysaccharides and FA or its dimers, but more research is necessary to make biotechnological route economically attractive (Faulds *et al*., 1997; Kroon *et al*., 1999; Wong, 2005; Damásio *et al*., 2012). These enzymes have been produced and purified from a wide range of microorganisms, including bacteria and fungi such as *Pseudomonas fluorescens, Penicilium funiculosum, Talaromyces stipitatus, Aspergillus niger* (Faulds *et al*., 1995; De Vries *et al*., 2002).

FA has received great attention in oriental research where it has been used as an antioxidant in food additives in Japan (Itagaki *et al*., 2009) and especially in medical studies in China after being proven to be an effective component of medicinal herbs used by Chinese traditional medicine, such as *Angelica sinensis, A. cimicifuga* and *A. heracleifolia lignsticum chuangxiong* (Sakai *et al*., 1999). FA can be absorbed by the small intestine and excreted in the urine, where therapeutic efficacy is dependent on its physiological concentrations and pharmacokinetic properties, which include absorption, distribution, metabolism and excretion of metabolites (Choudhury *et al*., 1999). The present article updates the therapeutic properties of FA, reviewing its sources, mechanisms of action and pharmacokinetics in order to provide concise information for researchers interested in the field.

## NATURAL SOURCES

FA[3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid] may be found as a monomer, dimer, free oligomer or making up polymers, covalently linked by ester bonds with polysaccharides, polyamines and glycoproteins, as well as ether linked to lignin (Durán, Padilla, 1993; Bourne, Rice-Evans, 1998; Kroon *et al*., 1999). FA has two isomers: *cis* (yellow oily liquid) and *trans* (white crystal), the last corresponding to 90% of its natural occurrence (Fulcher, 1983). It is synthesized in the shikimate/phenylpropanoid pathway mainly from L-phenylalanine, or in grasses from L-tyrosine (Figure 2). The phenylpropanoid path starts with deamination of L-phenylalanine to produce cinnamic acid, a reaction catalyzed by phenylalanine ammonia-lyase (PAL). Cinnamic acid is hydroxylated to give *p*-coumaric acid, in a reaction catalyzed by cinnamate 4-hydroxylase (C4H). Alternatively, L-tyrosine deamination, catalyzed by tyrosine ammonia lyase (TAL) directly produces *p*-coumaric acid (Castelluccio *et al*., 1995). *p*-Coumaric acid is then esterified to coenzyme A by the enzyme 4-coenzyme A ligase (4CL), transesterified with shikimate or quinate by hydroxycinnamoyl CoA: quinate/shikimate hydroxycinnamoyl transferase (HCT) and further hydroxylated in carbon 3 to produce cafeoyl-shikimate/quinate ester by the enzyme coumaroyl-3-hydroxylase (C3H). Caffeoyl-shikimate/quinate is transesterified with CoA and the hydroxyl in C3 is methylated by cinnamoyl-coenzyme A orthomethyl transferase to produce feruloyl-CoA. The ester may be exported to feruloylate polysaccharides in Golgi apparatus by action of a putative feruloyl transferase or released as coniferaldehyde in a reaction mediated by cinnamoyl-coenzyme A reductase (CCR). The free FA is produced by the subsequent oxidation of coniferaldehyde by the enzyme coniferyl aldehyde dehydrogenase (CALDH) (Chen, 2006).

High concentrations of FA may occur in common foods, such as corn bran (2610-3300 mg/100 g), wheat bran (1358-2293 mg/100 g), maize bran (3000 mg/100 g), banana (5.4 mg/100 g), bamboo shoots (243.6 mg/100 g), eggplant (25 mg/100 g), orange (9.2-9.9 mg/100 g), beets (800 mg/100 mg) as well as in broccoli, spinach, cabbage, potatoes, carrots, tomatoes, coffee, natural extracts of herbs and a range of fruits and vegetables (Kroon *et al*.,

1997; Zhao *et al*., 2005; Mattila *et al*., 2005; Matilla *et al*., 2006; Liyana, Shahidi, 2006; Mattila *et al*., 2007).

The esters of hydroxycinnamic acids and quinic acid produced by HCT (Figure 2) are also generically named chlorogenic acids of which the most common is 5-*O*-caffeoyl quinic acid (Clifford, 1999). It is present in particularly high concentrations in numerous foods and beverages such as coffee, pears, potato tubers and apple, and as a consequence in derived by-products. Analysis of the coffee pulp (the solid residue from coffee processing) indicated that chlorogenic acid (around 40%) is the main phenolic compounds (Pandey *et al*., 2000).

The industrial use of hydroxycinnamates has attracted growing interest for several years ever since they and their conjugates were shown to be bioactive molecules, possessing potential antioxidant activities and

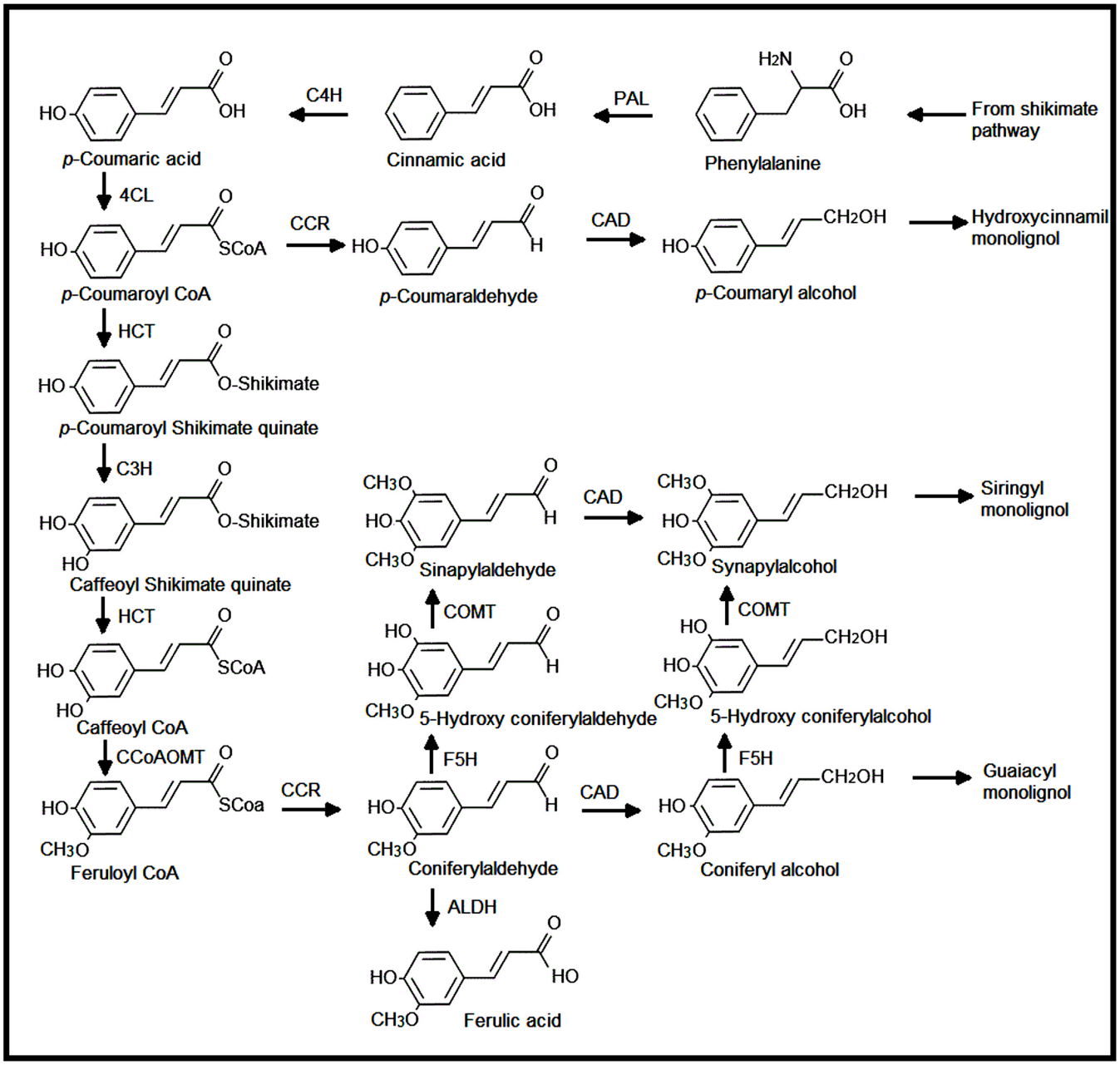


**FIGURE 2** – Simplified phenylpropanoid pathway**.** PAL, phenylalanine ammonia-lyase; C4H, cinnamate-4-hydroxylase; 4CL, 4-coumarate:CoA ligase; HCT, hydroxycinnamoyl CoA: quinate/shikimate hydroxycinnamoyl transferase; C3H, coumarate-3-hydroxylase; CCoAOMT, caffeoyl coenzyme A 3-*O*-methyltransferase; CCR, cinnamoyl CoA reductase; F5H, ferulate 5-hydroxylase; COMT, caffeic acid 3-*O*-methyltransferase; CAD, cinnamyl alcohol dehydrogenase; ALDH, aldehyde dehydrogenase (Santos *et al*., 2008).

health benefits. Extraction of these phenolic compounds from biomass through the breakdown of the ester linkages with polymers has allowed the exploitation of such compounds for pharmaceutical, industrial and food applications (Benoit *et al*., 2006).

Huang *et al.* (2011) obtained high concentrations of FA from lignocellulolytic agricultural waste (rice bran, wheat bran, corncob) employing an extracellular esterase (AXE) and xylanase (Tfx) from *Thermobifida fusca* NTU22. Corncob exhibited the best ferulic acid yield, where 396 µM accumulated in the culture broth. However, FA with purity greater than 98% was obtained from extracts of *Radix Angelicae sinensis* after microwave-assisted extraction (MAE) followed by high-speed counter-current chromatography (HSCCC) (Liu *et al.,* 2006).

## PRECLINICAL PHARMACOKINETIC

A person can ingest from 80-165 mg of FA in a meal. FA is present in food in both conjugated and free forms (Rondini *et al*., 2004), and presents a very low toxicity. The acute oral $LD_{50}$ of FA in male and female F344 rats was 2445 $mg.kg^{-1}$ and 2133 $mg.kg^{-1}$, respectively (Tada *et al*., 1999). Both free and linked FA are quickly absorbed from the stomach without modification due to acid pH, according to studies carried out *in situ* in the rat stomach, but it was verified that only the free form of the acid was absorbed by the intestine after administration of 8 µmol FA / kg body weight (Zhao *et al*., 2004).

Digestion of bound FA involves xylanases (EC 3.2.1.8), feruloyl (EC 3.1.1.73) and cinnamoyl (EC 3.1.1.1) esterases present in the gastro-intestinal tract of ruminants (Kroon *et al*., 1997). The absorption of FA occurs mainly in the colon by passive diffusion (*c.* 90%), or by active transport via the monocarboxylic acid transporter (MCT) (Poquet *et al*., 2008). Studies have shown a high FA absorption rate, with peak plasma concentration attained within 15-30 min after administration of FA. Only 0.5-0.8% is found in feces of mice (Zhao *et al*., 2003). After absorption, about 50% of FA reaches the liver, and the remainder is distributed in the bloodstream, gastric mucosa and peripheral tissues (Adam *et al*., 2002; Zhao *et al*., 2004; Silberberg *et al*., 2006).

Chang *et al*. (1993) administered pure FA in Wistar rats and found that the free acid did not enter the enterohepatic circulation. Conjugation was required for its distribution in the organism. The conjugation reactions of FA occur mainly in the liver but may also occur in the intestinal mucosa or kidney, catalyzed by sulfotransferases (EC 2.8.2.1) and UDP glucuronosyl transferases (EC 2.4.1.17) (Piskula, Terao, 1998; Kern *et al*., 2003; Zhao *et al*., 2004). Studies in humans and rats showed that after oral intake of FA, the most abundant metabolites generated in plasma were FA-glucuronide (FA conjugate with glucuronic acid) and FA-sulfoglucuronide (FA conjugate with sulfate and glucuronide) in addition to unmodified FA. The studies indicated that concentrations of metabolites derived from FA ingestion are a function of several factors such as the dose and route administered, as well as the animal species (Zhao *et al*., 2003, 2004).

Free phenolic acids can be absorbed via paracellular transport and active transport mediated by monocarboxylic acids transporters (MCT) in the gastrointestinal mucosa. According to Konishi *et al*. (2006) the absorption efficiency of each phenolic acid depends on its affinity for the MCT. To elucidate the different affinities, different phenolic acids were administered in the rats' stomach at concentration of 2.25 mmol $L^{-1}$, after which plasma concentrations were measured. The plasma concentration rate increased in the following order: gallic acid = chlorogenic acid <caffeic acid <*p*-coumaric acid = FA, which corresponds to their affinities to MCT. Peak levels of FA occur within 5 min after administration.

In rats, FA and its metabolites are predominantly excreted in urine, but about 4-6% of the ingested dose may be excreted through bile (Adam *et al*., 2002). Excretion may occur 1.5 h after administration of the acid (Rondini *et al*., 2002), while in humans only 7-9 h after consumption (Bourne, Rice-Evans, 1998). However, in both rats and humans the rate of unmodified FA recovered in urine is only 4-5% of the ingested acid (Bourne, Rice-Evans, 1998; Rondini *et al*., 2002). Urinary excretion of FA is influenced by its combination, where the elimination rate of the acid after consumption of wheat bran was 15 times slower than after the consumption of the free molecule (Rondini *et al*., 2002). Conclusive studies on pharmacokinetics and bioavailability of FA and its conjugated forms in humans are necessary so that it may be utilized as a nutrient supplement administered orally in its free form or bound to sugars in order to improve its absorption and interaction with target tissues, increasing its efficiency in preventing or treating chronic diseases.

## RADICAL SCAVENGER PROPERTIES

Free radicals may be defined as organic and inorganic molecules or atoms which contain one or more unpaired, independently existing electrons (Halliwell, 1994). They present short half-life and are very reactive. Found in all biological systems, they are continuously generated by several physiological processes from

either endogenous or exogenous sources. The activity of oxidases, dehydrogenases, peroxidases and the presence of transition metals in the cell give rise to free radicals and are considered to be endogenous sources. Tobacco, air pollution, organic solvents, anesthetics, pesticides, gamma and ultraviolet rays are examples of exogenous sources (Soares, 2002).

The uneven balance between oxidant and antioxidant molecules, which results in the induction of cell damage by free radicals, is referred to as oxidative stress (Sies, 1993) and can trigger a series of chronic degenerative diseases such as arthritis, atherosclerosis, diabetes, cataracts, chronic inflammations, brain dysfunction, aging, cancer and others (Bianchi, Antunes, 1999). An antioxidant is defined as "any substance that when present in low concentrations compared to the oxidizable substrate effectively delays or inhibits the oxidation of the substrate". In organisms, antioxidants are the agents responsible for inhibition and reduction of injuries caused by free radicals in cells (Sies, 1993; Sies, Stahl, 1995).

The antioxidant potential of FA can be attributed to the formation of a phenoxy radical from the phenolic nucleus. Due to its potential displacement in resonance structures, such a radical has low energy which generates a more stable hybrid resonance structure (Figure 3). In the reactive collision of FA with a free radical, the hydrogen atom of the acid is easily transferred to the radical, forming a phenoxy radical that is highly stabilized since the unpaired electron may be present not only on the oxygen but it can be delocalized across the entire molecule. This phenoxy radical is unable to initiate or propagate a radical chain reaction and its most probable fate is a collision and condensation with another radical, including another ferulate radical to yield the dimer curcumin and other dimers. The presence of the extended side chain enhances stabilization of the conjugated methoxy radical, because it is an unsaturated chain with the function of a carboxylic acid, but dimers and oligomers are still able to stop radical chain reactions. Additionally, this carboxylic acid group also acts as an anchor of FA by which it binds to the lipid bilayer, protecting against lipid peroxidation. In other words, the stable resonance structure of the phenoxy radical is responsible to cease propagation of any chain reaction initiated by free radicals, making FA especially able to scavenge and stop free radical chain reactions (Kanski *et al*., 2002; Graf, 1992). FA also presents "indirect" free radical scavenging activity, namely the ability of this phenolic acid to up-regulate the heme oxygenase-biliverdin reductase system (Calabrese *et al*., 2008; Barone *et al*., 2009; Fetoni *et al*., 2010), which in turn generates bilirubin, an endogenous free radical scavenger (Mancuso *et al*., 2006; Mancuso, Barone, 2009b).

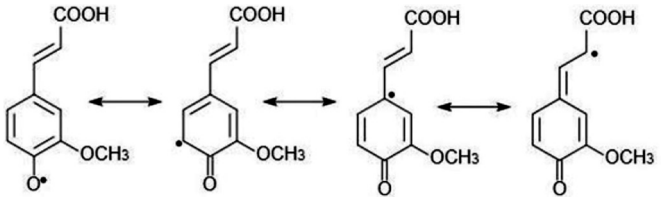


**FIGURE 3 -** Resonance stabilization mechanism of the FA radical.

## PHARMACOLOGICAL APPLICATIONS

### Antioxidant agent

Intestinal ischemia is a disease that occurs in the absence or reduction of arterial blood flow and/or bowel venous malformation by acute or chronic obstruction of the arteries and/or visceral veins. It may be caused by a thrombus, stenosis - derived (or not) from atherosclerosis, a trauma or vasospasm induced by vasoactive drugs (Simi, 2002). Among the various mechanisms involved in causing intestinal lesions that result from ischemia and subsequent reperfusion, the generation of reactive oxygen species (ROS) through the hypoxanthine/xanthine oxidase system is a major factor causing intestinal damage. The free radicals generated act mainly in peroxidation of cellular membranes, inactivation of disulfide bond dependent enzymes, inhibition of ATP synthesis through DNA changes and the formation of several oxygen-derived residues, which have great reducing potential (Horton, Walker, 1993; Schoenberg, Beger, 1993; Yoshida, 1996). In order to investigate the protective effects of FA in intestine injuries resulting from ischemia-reperfusion, Itagaki *et al*. (2009) conducted *in vivo* assays using male Wistar rats to compare the antioxidant activity of ferulic acid with ascorbic acid and epigallocatechin gallate (EGCG).

Ascorbic acid and EGCG are compounds with high activity for elimination of the superoxide anion and inhibition xanthine oxidase. Mancuso and Barone (2009a) report the possibility that EGCG inhibits several drug metabolizing enzyme, thus increasing the potential toxic effects of xenobiotics. Previous studies have demonstrated that EGCG inhibits the growth of tumors of the liver and intestine (Nishida *et al*., 1994; Fujita *et al*., 1989). In these studies it was found that EGCG and ascorbic acid have protective effects on intestinal ischaemia–reperfusion injury in the small intestine of rats. Although combined antioxidant activity from radical scavenging and xanthine oxidase

inhibition of FA was much weaker than the combined antioxidant activities of EGCG and ascorbic acid, treatment with FA also prevented an increase in vascular permeability caused by intestinal ischaemia-reperfusion, suggesting that it can be used as an ingredient in functional foods to enhance the effect of other protective compounds.

Kawata *et al*. (2000) investigated the protective effects of FA on rat colon carcinogenesis induced by azoxymethane (AOM). In one experiment it was verified that the group receiving FA doses of 250 and 500 ppm presented a lower incidence of colon carcinomas (23 and 27% respectively) compared to group that received only AOM (59%). In another experiment, it was found that the FA influenced the activities of glutathione S-transferase and quinone reductase in the liver and colon when utilizing doses of 25, 50 and 100 mg FA/kg body weight. The higher dose significantly increased activity of both enzymes, suggesting that their detoxifying activities are related to the effect of FA on colon carcinogenesis induced by AOM.

## Antimicrobial and anti-inflammatory agent

Studies performed *in vitro* for FA and ethyl ferulate (EF) activity on HIV revealed that these compounds reduced the release and activity of the p24 antigen, an essential protein from the virus capsid, after chronically infected cells were treated with 1, 5 and 10 μmol $L^{-1}$ of FA or EF. FA and FE at 5 μmol $L^{-1}$ inhibited the replication of the virus without cytotoxicity, suggesting that the FA and derivatives are potentially useful molecules for antiviral therapy (Edeas *et al*., 1995).

FA also inhibits growth of both Gram-positive and negative bacteria *(Escherichia coli)* and is already present in the composition of anti-inflammatory drugs used in Oriental Medicine (Jeong *et al*., 2000).

Hirabayashi *et al.* (1995) investigated the effects of FA and isoferulic acid (IFA), active components of the rhizome of *Cimicifuga* species (plants used as anti-inflammatory agents in Japanese medicines) on murine interleukin-8 (IL-8) production in response to influenza virus infections *in vitro* and *in vivo* using the antibody-sandwich enzyme-linked immunosorbent assay. IL-8 is a protein of the cytokine family which acts as a mediator in the inflammatory process which is also expressed in tumor cells. In the *in vitro* study, the murine macrophage cell line RAW 264.7 was infected with 10 PFU (plaque forming units) of the influenza virus and cultured in the presence or absence of phenolic acids. Levels of IL-8 were reduced after 20 h in the conditioned medium when compared with the control, but the effect of IFA was greater than that of FA: IL-8 levels were reduced to 43% and 56% (compared with control) in the presence of 100 mg/mL of IFA and FA, respectively. In the *in vivo* study, mice were infected with 1 PFU of the virus and received daily oral administrations of the *Cimicifuga heracleifolia* extract (5 mg/mouse/day), FA (0.5 mg/mouse/day), IFA (0.125 mg/mouse/day), or phosphate buffered saline. All drugs presented a tendency to reduce IL-8 levels observed via bronchoalveolar lavage (BAL) two days after infection, and both acids significantly reduced the number of neutrophils exuded in BAL. Data indicates that these two compounds are the most active principles of the anti-inflammatory species obtained from *Cimicifuga*.

## Hepatoprotective agent

The liver plays a key role in the detoxification and elimination of various harmful agents that can enter the organism through environmental or occupational exposure (Vander *et al*., 1994). But it also can suffer damage from a variety of hepatotoxins, such as excessive alcohol intake, heavy metals, and organic and inorganic solvents, resulting in excessive generation of free radicals which cause hepatotoxic lesions including acute hepatitis, cirrhosis, portal fibrosis and hepatic carcinoma (Vander *et al*., 1994; Tolman, Sirrine, 1998; Nakagiri *et al*., 2003). Rukkumani *et al*. (2004) evaluated the hepatoprotective effect of FA on the toxicity induced by alcohol and poly-unsaturated fatty acids in female Wistar rats by administering (orally) ethanol and sunflower oil at the level of 40 mg FA/kg body weight for 45 days. The enzymes alkaline phosphatase, glutamyl transferase, alanine aminotransferase and aspartate aminotransferase presented significantly decreased activities after treatment with FA. Enzymes with antioxidant activity, such as superoxide dismutase, catalase, and glutathione peroxidase presented significantly lower activity in rat livers receiving pure ethanol, pure sunflower oil and both. However, in the liver of rats given FA doses, the activities of these enzymes were increased and the reduction of oxidative stress was most significant in the lowest dose (20 mg FA/kg body weight). These positive results suggest that FA is a hepatoprotective agent against toxins commonly ingested in the diet and it has the advantage of showing no side effects. Therefore it may be considered a potential molecule for alternative treatments of liver damage. Shanmugarajan *et al*. (2008) further evaluated the protective effects of FA on D-galactosamine, a hepatotoxin employed in studies involving liver disease, because it causes damage (necrosis) similar to the injury resultant of viral hepatitis in humans (Shi *et al*., 2008). The results showed that the group of male Wistar rats that received pre-treatment (20 mg FA/kg body weight) had

increased activity of antioxidant enzymes in liver tissue, significant inhibition of lipid peroxidation and decreased levels of cholesterol, triglycerides and free fatty acids in relation to the control group.

FA also has a hepatoprotective effect against toxicity induced *in vivo* by carbon tetrachloride, as reported by Srinivasan *et al.* (2005). Treatment with the acid significantly decreased the index of lipid peroxidation in the liver and significantly increased the activities of superoxide dismutase, catalase and glutathione peroxidase.

Yeh and Yen (2006) investigated the modulatory effects of FA in the *in vivo* system, where mice received a dose of 100 mg FA/kg body weight for 14 days. The activities of hepatic superoxide dismutase, glutathione peroxidase and catalase were higher after administration of FA when compared with the control group ($P<0.05$), and liver homogenates of rats treated with FA had a greater oxygen radical absorption capacity than the control group.

Kim *et al*. (2011) also investigated the hepatoprotective effect of FA against carbon tetrachloride ($CCl_4$)-induced acute liver injury. Mice were treated intraperitoneally with the vehicle or FA (20, 40, and 80 mg/kg) 1 h before and 2 h after $CCl_4$ injection (20 μL/kg), followed by serum analysis. Pretreatment with FA attenuated the increase in aminotransferase activities, hepatic level of malondialdehyde, serum level and mRNA expression of tumor necrosis factor-α, the levels of inducible nitric oxide synthase and cyclooxygenase-2 proteins, as well as mRNA expression. FA significantly attenuated the increase in levels of phosphorylated JNK and p38 mitogen-activated protein (MAP) kinase, as well as nuclear translocation of activated c-Jun. While acute $CCl_4$ challenge induced the TLR4, TLR2, and TLR9 proteins and mRNA expression, FA significantly inhibited TLR4 expression. This study provides evidence that FA may offer an alternative for prevention of acute liver diseases, because it prevents $CCl_4$-induced hepatotoxicity by suppression of oxidative stress and inflammatory signaling pathways. These studies show that FA can also be used for protection and treatment of liver damage caused by drugs, viruses or metabolic disorders.

Recently, Ramar *et al*. (2012) investigated the effect of FA and resveratrol on alloxan-induced diabetic mice, through analysis of basic biochemical parameters, enzyme activities, lipid peroxidation and immunohistochemical studies. In this study FA was administrated orally to alloxan-induced diabetic mice at the concentration of 10 mg FA/kg body weight and 20 mg resveratrol/kg body weight. The diabetic mice treated with FA and resveratrol exhibited smaller levels of lipid peroxidation, higher levels of antioxidants in the liver, kidney and serum, and a marked decrease in the immunoreactivity of the nuclear transcription factor (NF-κB) compared to untreated diabetic mice. These results showed that FA and resveratrol exerted antioxidant and anti-diabetic effects, probably through inhibition of the proinflammatory and NF-κB factors, reducing liver, kidney and pancreas damage caused by alloxan-induced diabetes.

## Anti-diabetic agent

The metabolic disease Diabetes Mellitus (DM) which presents a multifactorial origin and increased oxidative stress has been indicated as playing a central role in these disorders (Reis *et al*., 2008; Sharma *et al*., 2005). Evidence suggests that oxidative cell injury caused by free radicals contributes to the development of complications in type 1 diabetes (T1DM) and reduces enzymatic and non-enzymatic antioxidant defenses (Reis *et al*., 2008).

*In vivo* studies have shown that FA has the ability to neutralize free radicals present in the pancreas induced by streptozotocin. Female Wistar rats received 10 and 40 mg of FA/kg body weight for 45 days. The result was an increase in body weight of 61% in the group given the lowest dose and 52% in the group receiving the highest dose. Furthermore, blood glucose levels decreased 60% for the high dose compared to the group of diabetic rats that did not receive FA. Activities of the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase were higher in the liver of the diabetic rats which received FA doses compared to the untreated diabetic group. This study shows that the elimination of free radicals facilitates the proliferation of β-cells that secrete insulin, which in turn enhance the use of glucose by extra hepatic tissues, thus reducing blood glucose levels (Balasubashini *et al*., 2004).

Noumura *et al.* (2003) reported that amides derived from FA also influence the increase in insulin secretion by pancreatic β-cells. Studies performed in rats have shown that administration of the derivatives at a dose of 0.01% to 0.1% of the base diet decreased levels of glucose in diabetic rats induced by streptozotocin. In a study performed by Ohnishi *et al*. (2004) with KK-Ay mice, the dose of 0.05% FA effectively suppressed blood glucose levels and reduced lipid peroxidation in adipose tissue, indicating that FA may be useful in the reduction of oxidative stress and hyperglycemia in individuals suffering from DM. Subsequently, Jung *et al.* (2007) demonstrated in studies using diabetic mice that FA increases the activity of the enzyme glucokinase, a key enzyme in the regulation of blood glucose levels.

Adisakwattana *et al*. (2009) investigated the inhibitory activity of cinnamic acid derivatives against rat

intestinal α-glucosidase and porcine pancreatic α-amylase *in vitro* in order to find effective inhibitors from natural sources that could be used in prevention and treatment of DM. Inhibition of α-glucosidase and α-amylase delays the digestion of starch and disaccharides to absorbable monosaccharides, resulting in a reduction of postprandial hyperglycemia. Among the cinnamic acids tested, caffeic acid, FA and IFA were the most potent inhibitors against intestinal maltase, while IFA and FA were effective inhibitors of intestinal sucrase. However, all cinnamic acid derivatives were found to be inactive with respect to pancreatic α-amylase inhibition. Such studies are useful in developing treatments for diabetes as well as prevention.

## Anti-cholesterolemic agent

Kim *et al.* (2003) showed that FA has the ability to reduce the level of low density lipoproteins in rats. It was suggested that synthesis of cholesterol was decreased by competitive inhibition of hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase) by FA. This enzyme is the most important regulatory step in the biosynthesis of cholesterol in the organism catalyzing the synthesis of mevalonic acid. In another *in vivo* study, conducted by Yogeeta *et al*. (2006), it was reported that pretreatment with FA at a dose of 20 mg/kg body weight and ascorbic acid at a dose of 80 mg/kg body weight in rats intoxicated with isoproterenol significantly reduced levels of triglycerides, total cholesterol, cholesterol esters and free fatty acids in serum and heart tissues. Also observed was a decrease in the levels of phospholipids, lipid peroxides and low density lipoproteins. This study confirmed the action of two antioxidants in lipid metabolism and the synergistic effect between them.

Recently, Kwon *et al*. (2010) studied the anti-atherogenic effects of FA by administering 0.02% FA (w/w) compared to clofibrate (0.02%, w/w) in apolipoprotein E-deficient [apo E(-/-)] mice. Clofibrate reduces cholesterol and triglycerides in the blood. The results revealed that concentrations of total cholesterol (total-C) and apolipoprotein B (apo B) in plasma and adipose tissue were significantly lower in the group that received FA or clofibrate, and that there was no formation of fatty plaques in the aorta compared to the control group. The activities of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and paraoxonase) in the hepatocyte and erythrocyte were significantly higher in the FA group than in the control group, and the hepatic TBARS level was only slightly lower in the FA group. This study demonstrated that FA is as effective as clofibrate for reducing cholesterol and deserves attention due to its anti-atherogenic property in apo E(-/-) mice fed with a Western diet.

## Neuroprotective agent

In another study performed by Kanski *et al*. (2002), the presence of FA in neuronal cell systems exposed to peroxyl and hydroxyl radicals reduced damage in the cells without causing its death, proving to be more potent than vanillic acid, coumaric acid and cinnamic acid. Analysis using the electron paramagnetic resonance technique in synaptosomal membrane proteins indicated that the protection provided by FA against free radicals is mediated by conformational changes in these proteins.

Parkinson's disease (PA) and Alzheimer's disease (AD) are neurodegenerative diseases associated with chronic inflammation caused by oxidative stress resulting from ROS and reactive nitrogen species. These oxidative species affect activity of essential proteins, injure RNA and DNA, and induce lipid peroxidation resulting in neuronal dysfunction (Barnham *et al*., 2006; Joshi *et al*., 2006). AD is characterized by neuronal loss, diffuse cortical atrophy, the presence of large numbers of senile plaques and neurofibrillary tangles, bead-vacuolar degeneration, neuronal loss, accumulation of β-amyloid proteins in senile plaques and disorders of the transmission of acetylcholine and acetyltransferases (Katzman, 1986; Mancuso *et al*., 2007). The production of free radicals and neuroinflammation contribute to the destruction of some brain regions such as the cortex (Mancuso *et al*., 2007). Thus, FA can have a favorable effect on AD due to its anti-inflammatory and antioxidant properties (Graf, 1992; Kanski *et al*., 2002).

Ono *et al*. (2005) evaluated the ability of FA to inhibit formation of β-amyloid fibrils (fAβ) and the destabilization of existing fibrils when compared with the results obtained *in vitro* in previous studies with curcumin, rifampicin and tetracycline. Using fluorescence spectroscopic analysis with thioflavin T and electron microscopy, fAβ at pH 7.5 and 37 °C was analyzed. FA dose-dependently inhibited the formation of fAβ and destabilized fAβs already formed. The activity of all the molecules examined was curcumin (a diferulate) >FA>rifampicin=tetracycline. Inhibition of fAβ and destabilization of preformed fAβ in the central nervous system are attractive therapeutic targets for the treatment of AD, making FA an interesting molecule in studies toward development of a therapeutic treatment. In studies performed *in vivo* by Yan *et al*. (2001), mice were pretreated by ingesting pure water or that containing FA (0.006%). After 4 weeks, 410 pmol of β-amyloid peptide (Aβ1-42) was administered via

intracerebroventricular injection. Pretreatment with FA significantly reduced neuroinflammation, which was assessed using the glial fibrillary acidic protein (GFAP) as a biochemical marker for gliosis and interleukin-1 β (IL-1β) in the hippocampus, indicating that the prolonged delivery of FA induces resistance to toxicity caused by Aβ1-42 in the brain and may be a useful chemopreventive agent against AD. Sultana *et al*. (2005) also found that ethyl ferulate (eFA) has a protective effect against neurotoxicity induced by Aβ1-42. In the pretreatment of primary hippocampal cultures with 10-50 mmol $L^{-1}$ eFA, cytotoxicity, intracellular accumulation of ROS, protein oxidation and lipid peroxidation induced by Aβ1-42 were decreased. The study shows that the derivative of FA, eFA, may be a key molecule in the therapeutic treatment of AD and other diseases related to oxidative stress.

## Anticarcinogenic agent

Reactive oxygen species are considered a significant class of carcinogens, participating in the initiation, progression and metastasis of neoplasm. ROS generated in the intracellular environment can directly produce alterations in simple or double stranded DNA, leading to mutagenesis (Ames, 1983). Large amounts of hydrogen peroxide are produced and secreted by tumor cells, confirming its importance in spreading and invasion of the tumor (Szatrowski, Nathan, 1991). Anti-cancer activity of FA is related to its antioxidant property to eliminate ROS and stimulate the activity of antioxidant enzymes (Hirose *et al*., 1999).

Mori *et al*. (1999) studied the effects of FA on oral cancer after causing chemically induced carcinogenesis in rats using 4-nitroquinoline 1-oxide (4NQO), exposing them to drinking water containing 0.02 g 4NQO/kg for 5 weeks and after this period subjecting them to 0.5 g FA/kg body weight. It was found that the incidence of carcinomas on the tongue and preneoplastic lesions were significantly lower in the group receiving the dose of FA than the control group, suggesting that the FA possess chemopreventive activity against oral cancer. In another study performed by Kawabata *et al*. (2000), the effects of FA administered to the mice diets were examined after induced carcinogenesis in the colon by azoxymethane (AOM). After 35 weeks, the group that received doses of 0.25 and 5 g FA/kg body weight presented a lower incidence of colon carcinomas in relation to the group that received merely AOM. It was also observed that the enzymes responsible for detoxification of the liver and colon, glutathione S-transferase and quinone reductase, showed increased activities in mice treated with FA, suggesting these enzymes are directly related to the blocking effect caused by FA in carcinogenesis induced by AOM.

Alias *et al*. (2009) evaluated and compared the chemopreventive potential of topically applied and orally administered FA against 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin carcinogenesis, estimating the status of phase I and phase II detoxification agents, lipid peroxidation byproducts and antioxidants. Skin squamous cell carcinoma was induced on the shaved back of mice, by painting with DMBA (25 μg in 0.1 mL acetone) twice weekly for 8 weeks. Oral administration of FA completely prevented the formation of skin tumors and reverted the status of phase I and phase II detoxification agents, lipid peroxidation byproducts and antioxidants to near-normal range in DMBA-treated mice. However, when topically applied, FA did not show significant chemopreventive activity during DMBA-induced skin carcinogenesis in the mice. The results demonstrate that orally administered FA has a potent suppressing effect on cell proliferation during DMBA-induced skin carcinogenesis, probably due to its modulating effect on the status of lipid peroxidation, antioxidants and detoxification agents during DMBA-induced skin carcinogenesis.

Another recent study using Sprague–Dawley rats evaluated the FA chemopreventive potential by monitoring the incidence of tumors as well as analyzing phase II detoxification enzymes during mammary carcinogenesis induced by DMBA. Oral administration of FA at a dose of 40 mg/kg body weight prevented tumor formation in 80% of the rats (Baskaran *et al*., 2010). Although there is no detailed mechanism of the process, the modulatory effect of FA on the phase II detoxification cascade could play a possible role and it deserves attention due to its therapeutic potential in preventing mammary cancer.

## UV protection agent

Saija *et al.* (2000) conducted *in vitro* and *in vivo* studies which proved the effectiveness of FA in combating skin damage caused by ultraviolet rays. They also showed that absorption of FA through the skin is not influenced by the pH of the lotion formulation, suggesting that FA can be used in the composition of lotions to combat photoaging. Murakami *et al*. 2002 further demonstrated that a derivative from FA, FA15 (2-methyl-1-butyl ferulic acid) is also a chemopreventive agent. In tests performed *in vitro*, FA15 markedly suppressed the combined lipopolysaccharide and interferon-gamma-induced protein expressions of inducible nitric oxide synthase and cyclooxygenase-2, and also inhibited the release of tumor necrosis factor-α accompanied by suppression of I-κappa

B degradation in RAW264.7, a murine macrophage cell line. In tests conducted *in vivo* on mouse skin, topical application of FA15 caused a decrease in the production of hydrogen peroxide and edema formation caused by ultraviolet radiation while application of FA did not. These results suggest that FA15 is a novel chemopreventive agent, both structurally and functionally.

FA can be used as an additive in sunscreens available on the market to increase photoprotection of the skin, hair and combat premature and natural aging according to studies conducted by Lin *et al.* (2008). Pig skin was treated with five well-known isoflavone compounds (genistein, equol, daidzein, biochanin A, and formononetin) and one antioxidant combination solution of 15% vitamin C, 1% vitamin E and 0.5% FA daily for 4 days. Skin was irradiated with solar-simulated UV irradiation, 1 to 5 minimal erythema dose (MED) at 1-MED intervals. Topical application of 0.5% solutions of the three individual phytoestrogens – genistein, daidzein and biochanin A, showed less protection than that provided by the antioxidant mixture as measured by sunburn cell formation and/or erythema. With the objective of determining if a stable topical formulation of 15% L-ascorbic acid, 1% α-tocopherol, and 0.5% FA could protect human skin *in vivo* from substantial amounts of solar-simulated UV radiation, this mixture and its vehicle were applied to separate patches of normal-appearing human skin for 4 days. Each patch was irradiated with solar-simulated UV irradiation, 2 to 10 MED, at 2-MED intervals, and one day later the skin was evaluated for erythema and sunburn cells, as well as immunohistochemically for thymine dimers and p53. UV-induced cytokine formation and tumor necrosis factor-α were evaluated by real-time PCR. The results showed that the antioxidant mixture lotion provided significant photoprotection for skin according to all evaluation methods and its mechanism of action is different from sunscreens, suggesting that they can be used as a supplement to conventional sun protectors (Murray *et al*., 2008).

Oresajo *et al*. (2008) evaluated the protective effects of a topical antioxidant mixture containing vitamin C, FA and phloretin against ultraviolet-induced photodamage in human skin using biomarkers of skin damage. Ten human subjects (18-60 years old; Fitzpatrick skin types II and III) were randomized and treated with the antioxidant product or vehicle control on the lower back for four consecutive days. On day 4, the two test sites received solar-simulated UV irradiation, and on day 5 digital images were taken and biopsies collected from the two test sites, as well as a control site from each subject for morphology and immunohistochemical studies. Pretreatment of skin with the antioxidant composition limited the increase of the erythema, sunburn cell formation and p53 protein expression. As in the above mentioned case, this study confirmed the protective role of a unique mixture of antioxidants containing vitamin C, FA, and phloretin on human skin from the harmful effects of UV irradiation and may be proposed as a sunscreen complement for providing photoprotection to human skin.

## Radioprotective agent

Radioprotectors are antioxidants that have the ability to balance the free radicals produced by incidence of ionizing radiation offering some degree of protection for living tissues (Aruoma *et al*., 1989). Today a number of radioprotective substances have been researched that reduce the negative effects caused by exposure to ionizing radiation. Even with a mechanism of action that has not yet been fully elucidated, several authors reported in the literature that their protective role is related to chemical bonding with certain enzymes that are activated by these substances and free radicals (Malinda, Kleinman, 1996). The ranges of molecules that can act as radioprotectors, with the exception of synthetic substances, are commonly found in foods such as fruits, vegetables and meat (Aruoma *et al.*, 1989). Thus, FA may be included among potentially radioprotective molecules (Kanski *et al*., 2002; Graf, 1992).

Srinivasan *et al*. (2006) evaluated the protective effects of FA in hepatocytes isolated from the liver of rats exposed to gamma radiation. Pretreatment of cells with 1, 5 and 10 mg FA/mL significantly decreased DNA damage, the generation of ROS and increased levels of antioxidant enzymes, suggesting that FA has potential for use in radiotherapy as a radioprotective agent.

Studies in rats have shown that intraperitoneal administration of 50, 75 and 100 mg FA/kg body weight 1 h before exposure to gamma radiation (4 Gy) found a decrease in yield of DNA strand breaks in murine peripheral blood leukocytes and bone marrow cells (Maurya *et al*., 2006). The dose of 50 mg of FA/kg body weight resulted in faster disappearance of DNA strand breaks than the group of mice that received no FA. Janakiraman *et al*. (2012) repeated the same experiment, supplying 50 mg FA/kg body weight once daily for five consecutive days. One hour after the last administration of FA on the sixth day, the whole body of the animals was exposed to gamma radiation of 8 Gy and the effects of FA pretreatment on radiation-induced changes in antioxidant enzymes and lipid peroxidation status in spleen, liver and intestine were analyzed. Pretreatment with FA significantly increased activity of antioxidant enzymes, including the superoxide dismutase, catalase and glutathione peroxidase

at 24 h post irradiation. Using the comet assay, it was observed that FA pretreatment significantly decreased the percentage of tail DNA, tail length, tail moment and Olive tail moment in the peripheral blood of mice whose entire body was submitted to radiation. The histological observations indicated a decline in the villus height and crypt number with an increase in goblet and dead cell population in the irradiated group, which was normalized by FA pretreatment. These studies indicated that FA treatment prevents radiation-induced lipid peroxidation, DNA damage and restored antioxidant status and histopathological changes in experimental animals, suggesting that it may be adjuvant in radiotherapy to protect normal tissues from gamma-radiation damage.

## CONCLUSIONS

Ferulic acid and some derivatives have been proven to be effective antioxidant, anti-microbial, anti-inflammatory, hepatoprotective, neuroprotective, anticarcinogenic, anti-diabetic, anti-cholesterolemic, UV-protective and radioprotective compounds. Most of the diverse pharmacological properties of FA may be associated with its ability of break free radical chain reactions, but not all. The positive effects of FA on HMG-CoA reductase, glucokinase and antioxidant and detoxification gene expression suggest additional properties whose mechanisms deserve further investigation. The noteworthy pharmacological properties of FA – wide array of therapeutic applications and lack of side known effects – make it an interesting compound for use as a functional food as well as a substitute to synthetic drugs. However, the large number of *in vitro* and animal tests contrasts with the lack of clinical trials, preventing the use of FA in human health both as a nutrient supplement as well as a therapeutic drug against human diseases.

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## REFERENCES

ADAM, A.; CRESPY, V.; LEVRAT-VERNY, M.A.; LEENHARDT, F.; LEUILLET, M.; DEMIGNE, C. The bioavailability of ferulic acid is governed primarily by the food matrix rather than its metabolism in intestine and liver in rats. *J. Nutr.,* v.132, n.7, p.1962-1968, 2002.

ADISAKWATTANA, S.; CHANTARASINLAPIN, P.; THAMMARAT, H.; YIBCHOK-ANUN, S. A series of cinnamic acid derivatives and their inhibitory activity on intestinal alpha-glucosidase. *J. Enzyme Inhib. Med. Chem.,* v.24, n.5, p.1194-1200, 2009.

ALIAS, L.M.; MANOHARAN, S.; VELLAICHAMY, L.; BALAKRISHNAN, S.; RAMACHANDRAN, C.R. Protective effect of ferulic acid on 7, 12-dimethylbenz[a] anthracene induced skin carcinogenesis in Swiss albino mice. *Exp. Toxicol. Pathol*., v.61, n.3, p.205-214, 2009.

AMES, B.N. Dietary carcinogens and anticarcinogens. *Science*, v.221, n.4617, p.1256-1264, 1983.

ARUOMA, O.T.; LAUGHTON, M.J.; HALLIWELL, B. Carnosine, homocarnosine and anserine: could they act as antioxidants in vivo? *Biochem. J*., v.264, n.3, p.863-869, 1989.

BALASUBASHINI, M.S.; RUKKUMANI, R.; VISWANATHAN, P.; MENON, V.P. Ferulic acid alleviates lipid peroxidation in diabetic rats. *Phytother. Res.,* v.18, n.4, p.310-314, 2004.

BARNHAM, K.J.; CAPPAI, R.; BEYREUTHER, K. Delineating common molecular mechanisms in Alzheimer's and prion diseases. *Trends Biochem. Sci*., v.31, n.8, p.465-472, 2006.

BARONE, E.; CALABRESE, V.; MANCUSO, C. Ferulic acid and its therapeutic potential as a hormetin for age-related diseases. *Biogerontology*, v.10, n.2, p.97-108, 2009.

BASKARAN, N.; MANOHARAN, S.; BALAKRISHNAN, S.; PUGALENDHI, P. Chemopreventive potential of ferulic acid in 7, 12- dimethylbenz[a]anthracene-induced mammary carcinogenesis in Sprague-Dawley rats. *Eur. J. Pharmacol.,* v.637, n.1-3, p.22-29, 2010.

BENOIT, I.; NAVARRO, D.; MARNET, N.; RAKOTOMANOMANA, N.; LESAGE-MEESEN, L.; SIGOILLOT, J.C.; ASTHER, M.; ASTHER, M. Feruloyl esterases as a tool for the release of phenolic compounds from agro-industrial by-products. *Carbohydr. Res.*, v.341, n.11, p.1820-1827, 2006.

BIANCHI, M.L.P.; ANTUNES, L.M.G. Radicais livres e os principais antioxidantes da dieta. *Rev. Nutr.,* v.12, n.2, p.123-130, 1999.

BOURNE, L.C.; RICE-EVANS, C. Bioavailability of ferulic acid. *Biochem. Biophys. Res. Commun.,* v.253, n.2, p.222-277, 1998.

CALABRESE, V.; CALAFATO, S.; PULEO, E.; CORNELIUS, C.; SAPIENZA, M.; MORGANTI, P.; MANCUSO, C. Redox regulation of cellular stress response by ferulic acid ethyl ester in human dermal fibroblast: role of vitagenes. *Clin. Dermatol.,* v.24, n.4, p.358-363, 2008.

CASTELLUCCIO, C.; PAGANGA, G.; MELIKIAN, N.; PRIDHAM, J.; SAMPSON, J.; RICE-EVANS, C. Antioxidant potential of intermediates in phenylpropanoid metabolism in higher plants. *FEBS Lett.,* v.368, n.1, p.188-192, 1995.

CHANG, M.X.; XU, L.Y.; CHEN, J.S.; FENG, Y. Pharmacokinetic study of ferulic acid in rats. *J. Chinese Med. Mater.,* v.18, p.300-304, 1993.

CHOUDHURY, R.; SRAI, S.K.; DEBNAM, E.; RICE-EVANS, C.A. Urine excretion of hydroxycinnamates and flavonoids after oral and intravenous administration. *Free Radic. Biol. Med*., v.27, n.3-4, p.278-286, 1999.

CLIFFORD, M.N. Chlorogenic acids and other cinnamates-nature, occurrence and dietary burden. *J. Sci. Food Agric.,* v.79, n.3, p.362-372, 1999.

D'ARCHIVIO, M.; FILESI, C.; DI BENEDETTO, R.; GARGIULO, R.; GIOVANNINI, C.; MASELLA, R. Polyphenols, dietary sources and bioavailability. *Ann. Ist. Super Sanita*., v.43, n.4, p.348-361, 2007.

DE VRIES, R.P.; VAN KUYK, P.A.; KESTER, H.C.M.; VISSER, J. The *Aspergillus niger* faeB gene encodes a second feruloyl esterase involved in pectin and xylan degradation, and is specifically induced on aromatic compounds. *Biochem. J.*, v.363, n.2, p.377-386, 2002.

DURÁN, R.M.; PADILLA, R.B. Actividad antioxidante de los compuestos fenólicos. Grasas y Aceites. *Sevilla*, v.44, n.2, p.101-106, 1993.

EDEAS, M.; KHALFOUN, Y.; LAZIZI, Y.; VERGNE, L.; LABIDALLE, S.; POSTAIRE, E.; LINDENBAUM, A. Effect of the liposolubility of free radical scavengers on the production of antigen P24 from a HIV infected monocytic cell line. *C R Seances Soc. Biol. Fil*., v.189, n.3, p.367-373,1995.

FAULDS, C.B.; BARTOLOMÉ, B.; WILLIIAMSON, G. Novel biotransformations of agro-industrial cereal waste by ferulic acid esterases. *Ind. Crop. Prod.*, v.6, n.3-4, p.367-374, 1997.

FAULDS, C.B.; RALET, M.C.; WILLIAMSON, G.; HAZLEWOOL, G.P.; GILBERT, H.J. Specificity of an esterase (XYLC) from *Pseudomonas fluorescens* subsp. Cellulose. *Biochim. Biophys. Acta*, v.1243, n.2, p.265-269, 1995.

FETONI, A.R.; MANCUSO, C.; ERAMO, S.L.M.; RALLI, M.; PIACENTINI, R.; BARONE, E.; PALODETTI, G.; TROIANE, D. *In vivo* protective effect of ferulic acid against noise-induced hearing loss in the guinea-pig. *Neuroscience*, v.169, n.4, p.1575-1588, 2010.

FAZARY, A.E.; JU, Y.H. Feruloyl esterases as biotechnological tools: current and future perspectives. *Acta Biochim. Biophys. Sin.,* v.39, n.11, p.811-828, 2007.

FUJITA, Y.; YAMANE, T.; TANAKA, M.; KUWATA, K.; OKUZUMI, J.; TAKAHASHI, T.; FUJIKI, H.; OKUDA, T. Inhibitory effect of (-)-epigallocateshin gallate on carcinogenesis with N-ethyl-N'-nitro-N-nitrosoguanidine in mouse duodenum. *Jpn. J. Cancer Res.,* v.80, n.6, p.503-505, 1989.

FULCHER, R.G. *Fluorescence microscopy of cereals in new frontiers in food microstructure*. Otawa: American Association of cereal chemists, 1983. p.167-175.

GRAF, E. Antioxidant potential of ferulic acid. *Free Radic. Biol. Med.,* v.13, n.4, p.435-448, 1992.

HALLIWELl, B. Free radicals and antioxidants: a personal view. *Nutr. Rev.,* v.52, n.8, p.253-265, 1994.

HIRABAYASHI, T.; OCHIAI, H.; SAKAI, S.; NAKAJIMA, K.; TERASAWA, K. Inhibitory effect of ferulic acid and isoferulic acid on murine interleukin-8 production in response to influenza virus infections in-vitro and in-vivo. *Planta Med.*, v.61, n.3, p.221-226, 1995.

HIROSI, M.; TAKAHASHI, S.; OGAWA, K.; FUTAKUCHI, M.; SHIRAI, T. Phenolics: blocking agents for heterocyclic amine-induced carcinogenesis. *Food. Chem. Toxicol.,* v.37, n.9-10, p.985-992, 1999.

HOLLMAN, P.C.; KATAN, M.B. Bioavailability and health effects of dietary flavonols in man. *Arch. Toxicol. Suppl.,* v.20, p.237-248, 1998.

HORTON, J.W.; WALKER, P.B. Oxygen Radicals lipid peroxidation, and permeability changes after intestinal ischemia and reperfusion. *J. Appl. Physiol.*, v.74, n.4, p.1515-1520, 1993.

HUANG, Y.C.; CHEN, H.F.; CHEN, C.Y., CHEN W.L.; CIOU, Y.P.; LIU, W.H.; YANG, C.H. Production of ferulic acid from lignocellulolytic agricultural biomass by *Thermobifida fusca* thermostable esterase produced in Yarrowia lipolytica transformant. *Bioresour. Technol.*, v.102, n.17, p.8117-8122, 2011.

IIYAMA, K.; LAM, T.B.T.; STONE, B.A. Covalent cross-links in the cell wall. *Plant Physiol.,* v.104, n.2, p.315-320, 1994.

ITAGAKI, S.; KUROKAWA, T.; NAKATA, C.; SAITO, Y.; OIKAWA, S.; KOBAYASHI, M. *In vitro* and *in vivo* antioxidant properties of ferulic acid: a comparative study with other natural oxidation inhibitors. *Food Chem.,* v.114, n.2, p.466-471, 2009.

ITO, N.; FUKUSHIMA, S.; HASEGAWA, A.; SHIBATA, M.; OGISO, T. Carcinogenicity of butylated hydroxyanisole in F344 rats. *J. Natl. Cancer Inst.*, v.70, n.2, p.343-347, 1983.

JANAKIRAMAN, S.; ARUMUGAM, K.; REDDY, V.B.; NAGARAJAN, R.P. Ferulic acid, a dietary phenolic acid, modulates radiation effects in swiss albino mice. *Eur. J. Pharmacol.,* v.691, n.1-3, p.268-274, 2012.

JEONG, Y.C.; JAE, H.M.; KEUN, H.P. Isolation and identification of 3-methoxy-4 hydroxybenzoic acid and 3-methoxy-4- hydroxycinnamic acid from hot water extracts of *Hovenia dulcis* Thumb and confirmation of their antioxidative and antimicrobial activity. *Korean J. Food Sci. Technol.*, v.32, n.6, p.1403-1408, 2000.

JOSHI, G.; PERLUIGI, M.; SULTANA, R.; AGRIPPINO, R.; CALABRESE, V.; BUTTERFIELD, D.A. *In vivo* protection of synaptosomes by FA ethylester from oxidative stress mediated by 2, 2-azo bis (2-amido-propane) dihydrochloride (AAPH) or Fe2+/H2O2: Insight into mechanisms of neuroprotection and relevance to oxidative stress-related neurodegenerative disorders. *Neurochem. Int.*, v.48, n.4, p.318-327, 2006.

JUNG, E.H.; KIM, S.R.; HWANG, I.K.; HA, T.Y. Hypoglycemic effects of a phenolic acid fraction of rice bran and ferulic acid in C57BL/KsJ-db/db mice. *J. Agric. Food. Chem.*, v.55, n.24, p.9800-9804, 2007.

KANSKI, J.; AKSENOVA, M.; STOYANOVA, A.; BUTTERFIELD, D.A. 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.*, v.13, n.5, p.273-281, 2002.

KATZMAN, R. Alzheimer's disease. *N. Engl. J. Med.*, v.314, n.15, p.964-973, 1986.

KAWABATA, K.; YAMAMOTO, T.; HARA, A.; SHIMIZU, M.; YAMADA, Y.; MATSUNAGA, K.; TANAKA, T; KAYAHARA, H.; MIAO, Z.; FUJIWARA, G. Synthesis and biological activities of ferulic acid derivatives. *Anticancer Res.*, v.19, n.5-A, p.3763-3768, 1999.

KERN, S.M.; BENNETT, R.N.; NEEDS, P.W.; MELLON, F.A.; KROON, P.A.; GARCIA-CONESA, M.T. Characterization of metabolites of hydroxycinnamates in the in vitro model of human small intestinal epithelium caco-2 cells. *J. Agric. Food Chem.,* v.51, n.27, p.7884-7891, 2003.

KIM, H.K.; JEONG, T.S.; LEE, M.K.; PARK, Y.B.; CHOI, M.S. Lipid lowering efficacy of hesperidin metabolites in high-cholesterol fed rats. *Clin. Chim. Acta,* v.327, n.1-2, p.129-137, 2003.

KIM, H.Y.; PARK, J.; LEE, K.H.; LEE, D.U.; JONG, H.K.; YEONG, S.K.; LEE, S.-M. Ferulic acid protects against carbon tetrachloride-induced liver injury in mice. *Toxicology,* v.282, n.3, p.104-111, 2011.

KONISHI, Y.; ZHAO, Z.; SHIMIZU, M. Phenolic acids are absorbed from rat stomach with different absorption rates. *J. Agric. Food Chem.,* v.54, n.20, p.7539-7543, 2006.

KROON, P.A.; FAULDS, C.B.; RYDEN, P.; ROBERTSON, J.A.; WILLIAMSON, G. Release of covalently bound ferulic acid from fiber in the human colon. *J. Agric. Food Chem.*, v.45, n.3, p.661-667, 1997.

KROON, P.A.; GARCIA CONES, M.T.; FILLINGHAM, I.J.; WILLIAMSON, G. Release of ferulic acid dehydrodimers from plant cell walls by feruloyl esterases. *J. Sci. Food Agric.,* v.79, n.3, p.428-434, 1999.

KWON, E.Y.; DO, G. M.; CHO, Y.Y.; PARK, Y.B.; JEON, S.M.; CHOI, M.S. Anti-atherogenic property of ferulic acid in apolipoprotein E deficient mice fed Western diet: Comparison with clofibrate. *Food Chem. Toxicol.,* v.48, n.8-9, p.2298-3303, 2010.

LIN, J-K.; TOURNAS, J.A.; BURCH, J.A.; MONTEIRO-RIVIERE, N.A.; ZIELINSKI, J. Topical isoflavones provide effective photoprotection to skin. *Photodermatol. Photoimmunol. Photomed.,* v.24, n.2, p.61-66, 2008.

LIU, Z.; WANG, J.; SHEN, P.; WANG, C.; SHEN, Y. Microwave-assisted extraction and high-speed counter-current chromatography purification of ferulic acid from *Radix Angelicae sinensis*. *Sep. Purif. Technol.*, v.52, n.1, p.18-21, 2006.

LIYANA-PATHIRANA, C.M.; SHAHIDI, F. Importance of insoluble-bound phenolics to antioxidant properties of wheat. *J. Agric. Food Chem.,* v.54, n.4, p.1256-1264, 2006.

MALINDA, K.M.; KLEINMAN, H.K. The Laminins. *Int. J. Biochem. Cell Biol*., v.28, n.9, p.957-959, 1996.

MANCUSO, C.; BARONE, E. The heme oxygenase/biliverdin reductase pathway in drug research and development. *Curr. Drug Metab.,* v.10, n.6, p.579-594, 2009a.

MANCUSO, C.; BARONE, E. Therapeutic use of tea derivatives: all that glitters is not gold. *Blood*, v.114, n.11, p.2359-236, 2009b.

MANCUSO, C.; BONSIGNORE, A.; CAPONE, C.; DI STASIO, E.; PANI, G. Albumin-bound bilirubin interacts with nitric oxide by a redox mechanism. *Antioxid. Redox Signal*, v.8, n.3-4, p.487-494, 2006.

MANCUSO, C.; SCAPAGINI, G.; CURRÒ, D.; BUTTERFIELD, D.A.; CALABRESE, V. Mitochondrial dysfunction, free radical generation and cellular stress response in neurodegenerative disorders. *Front Biosci*., v.12, p.1107-1123, 2007.

MATTILA, P.; HELLSTROM, J. Phenolic acids in potatoes, vegetables, and some of their products. *J. Food Comp. Anal.,* v.20, n.3-4, p.152-160, 2007.

MATTILA, P.; HELLSTROM, J.; TORRONEN, R. Phenolic acids in berries, fruits, and beverages. *J. Agric. Food Chem.,* v.54, n.19, p.7193-7199, 2006.

MATTILA, P.; PIHLAVA, J.M.; HELLSTROM, J. Contents of phenolic acids,alkyl- and alkenylresorcinols, and avenanthramides in commercial grain products. *J. Agric. Food Chem.,* v.53, n.21, p.8290-8295, 2005.

MAURYA, D.K.; SALVI, V.P.; NAIR, C.K. Radiation protection of DNA by ferulic acid under *in vitro* and *in vivo* conditions. *Mol. Cell. Biochem*., v.280, n.1-2, p.209-217, 2005.

MORI, H. Modifying effects of ferulic acid on azoxymethane-induced colon carcinogenesis in F344 rats. *Cancer Lett.,* v.157, n.1, p.15-21, 2000.

MORI, H.; KAWABATA, K.; YOSHIMI, N.; TANAKA, T.; MURAKAMI, T.; OKADA, T.; MURAI, H. Chemopreventive effects of ferulic acid on oral and rice germ on large bowel carcinogenesis. *Anticancer Res.,* v.19, n.5A, p.3775-3778, 1999.

MURAKAMI, A.; NAKAMURA, Y.; KOSHIMIZU, K.; TAKAHASHI, D.; MATSUMOTO, K.; HAGIHARA, K.; TANIGUCHI, H.; NOMURA, E.; HOSODA, A.; TSUNO, T.; MARUTA, Y.; KIM, H.W.; KAWABATA, K.; OHIGASHI, H. FA15, a hydrophobic derivative of ferulic acid, suppresses inflammatory responses and skin tumor promotion: comparison with ferulic acid. *Cancer Lett.,* v.180, v.2, p.121-129, 2002.

MURRAY, J.C.; BURCH, J.A.; STREILEIN, R.D.; IANNACCHIONE, M.A.; HALL, R.P.; PINNELL, S.R. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. *J. Am. Acad. Dermatol.,* v.59, n.3, p.418-425, 2008.

NAKAGIRI, R.; HASHIZUME, E.; KAYAHASHI, S.; SAKAI, Y.; KAMIYA, T. Suppression by Hydrangeae Dulcis Folium of D-galactosamine-induced liver injury *in vitro* and *in vivo*. *Biosci. Biotechnol. Biochem.,* v.67, n.12, p.2641-2643, 2003.

NISHIDA, H.; OMORI, M.; FUKUTOMI, Y.; NINOMIYA, M.; NISHIWAKI, S.; SUGANUMA, M.; MORIWAKI, H.; MUTO, Y. Inhibitory effects of (-)-epigallocatechin gallate on spontaneous hepatoma in C3H/HeNCrj mice and human hepatoma-derived PLC/PRF/5 cells. *Jpn. J. Cancer Res*., v.85, n.3, p.221-225, 1994.

NOUMURA, E.; KASHIWADA, A.; HOSODA, A.; NAKAMURA, K.; MORISHITA, H.; TSUNO, T.; TANIGUSHI, H. Synthesis of amide compounds of ferulic acid and their stimulatory effects on insulin secretion *in vitro*. *Bioorg. Med. Chem*., v.11, n.17, p.3807-3813, 2003.

OHNISHI, M.; MATUO, T.; TSUNO, T.; HOSODA, A.; NOMURA, E.; TANIGUCHI, H.; SASAKI, H.; MORISHITA, H. Antioxidant activity and hypoglycemic effect of ferulic acid in STZ-induced diabetic mice and KK-Ay mice. *Biofactors.*, v.21, n.1-4, p.315-319, 2004.

ONO, K.; HIROHATA, M.; YAMADA, M. Ferulic acid destabilizes preformed b-amyloid fibrils *in vitro*. *Biochem. Biophys. Res. Commun.,* v.336, n.2, p.444-449, 2005.

ORESAJO, C.; STEPHENS, T.; HINO, P.D.; LAW, R.M.; YATSKAYER, M.; FOLTIS, P.; PILLAI, S.; PINNELL, S.R. Protective effects of a topical antioxidant mixture containing vitamin C, ferulic acid, and phloretin against ultraviolet-induced photodamage in human skin. *J. Cosmet. Dermatol*., v.7, n.4, p.290-297, 2008.

OSAWA, T.; NAMIKI, M.; KAWAKISHI, S. Role of dietary antioxidants in protection against oxidative damage. *Basic Life Sci.,* v.52, p.139-153, 1990.

PANDEY, A.; SOCCOL, C.R.; NIGAM, P.; BRAND, D.; MOHAN, R.; ROUSSOUS, S. Biotechnological potential of coffee pulp and coffee husk for bioprocesses. *Biochem. Eng. J.*, v.6, n.2, p.153-162, 2000.

PIMENTEL, C.V.M.B.; FRANCKI, V.M.; GOLLÜCKE, A.P.B. *Alimentos funcionais*: introdução às principais substâncias bioativas em alimentos. São Paulo: Ed. Varela, 2005. 100 p.

PISKULA, M.K.; TERAO, J. Accumulation of *(−)*-epicatechin metabolites in rat plasma after oral administration and distribution of conjugation enzymes in rat tissues. *J. Nutr.,* v.128, n.7, p.1172-1178, 1998.

POQUET, L.; CLIFFORD, M.N.; WILLIAMSON, G. Transport and metabolism of ferulic acid through the colonic epithelium. *Drug Metab. Dispos*., v.36, n.1, p.190-197, 2008.

PRIOR, R.L.; CAO, G.; MARTIN, A.; LISCHNER, N.; EHLENFELDT, M.; KALT, W.; KREWER, G.; MAINLAND, C.M. Antioxidant capacity as influenced by total phenolics and anthocyanin content, maturity, and variety of *Vaccinum* species. *J. Agric. Food Chem.,* v.46, n.7, p.2686-2693, 1998.

RAMAR, M.; MANIKANDAN, B.; RAMAN, T.; PRIYADARSINI, A.; PALANISAMY, S.; VELAYUDAM, M.; MUNUSAMY, A.; MARIMUTHU PRABHU, N.; VASEEHARAN, B. Protective effect of ferulic acid and resveratrol against alloxan-induced diabetes in mice. *Eur. J. Pharmacol.,* v.690, n.1-3, p.226-235, 2012.

RECHNER, A.R.; PANNALA, A.S.; RICE-EVANS, C.A. Caffeic acid derivatives in artichoke extract are metabolised to phenolic acids *in vivo*. *Free Radic Res*., v.35, n.2, p.195-202, 2001.

REIS, J.S.; VELOSO, C.A.; MATTOS, R.T.; PURISH, S.; MACHADO, J.A.N. Oxidative stress: a review on metabolic signaling in type 1 diabetes. *Arq. Bras. Endocrinol. Metab*., v.52, n.7, p.1096-1105, 2008.

RONDINI, L.; PEYRAT-MAILLARD, M.N.; MARSSET-BAGLIERI, A.; BERSET, C. Sulfated ferulic acid is the main in vivo metabolite found after short-term ingestion of free ferulic acid in rats. *J. Agric. Food Chem*., v.50, n.10, p.3037-3041, 2002.

RONDINI, L.; PEYRAT-MAILLARD, M.N.; MARSSET-BAGLIERI, A.; FROMENTIN, G.; DURAND, P.; TOMÉ, D.; PROST, M.; BERSET, C. Bound ferulic acid from bran is more bioavailable than the free compound in rat. *J. Agric. Food Chem*., v.52, n.13, p.4338-4343, 2004.

ROSAZZA, J.P.N.; HUANG, Z.; DOSTAL, L.; VOLM, T.; ROUSSEAU, B. Review: biocatalytic transformations of ferulic acid: an abundant aromatic natural product. *J. Ind. Microbiol.,* v.15, n.6, p.457-471, 1995.

RUKKUMANI, R.; ARUNA, K.; VARMA, P.S.; MENON, V.P. Influence of ferulic acid on circulatory prooxidant-antioxidant status during alcohol and PUFA induced toxicity. *J. Physiol. Pharmacol.,* v.55, n.3, p.551-561, 2004.

RUMBOLD, K.; BIELY, P.; MASTIHUBOVA, M.; GUDEL, J.; GUBITZ, G.; ROBRA, K.H.; PRIOR, B.A. Purification and properties of a feruloyl esterase involved in lignocellulose degradation by *Aureobasidium pullulans*. *Appl. Environ. Microbiol.,* v.69, n.9, p.5622-5626, 2003.

SAIJA, A.; TOMAINO, A.; TROMBETTA, D.; DE PASQUALE, A.; UCCELLA, N.; BARBUZZI, T.; PAOLINO, D.; BONINA, F. *In vitro* and *in vivo* evaluation of caffeic and ferulic acids as topical photoprotective agents. *Int. J. Pharm.,* v.199, n.1, p.39-47, 2000.

SAKAI, S.; KAWAMATA, H.; KOGURE, T.; MANTANI, N.; TERASAWA, K.; UMATAKE MAND OCHIAI, H. Inhibitory effect of ferulic acid and isoferulic acid on the production of macrophage inflammatory protein-2 in response to respiratory syncytial virus infection in RAW264.7 cells. *Mediators Inflamm.,* v.8, n.3, p.173-175, 1999.

SÁNCHEZ, M.; QUEIJEIRO, E.; REVILLA, G.; ZARRA, I. Changes in ascorbic acid levels in apoplastic fluid during growth of pine Hypocotyls. Effect on peroxidase activities associated with cell walls. *Physiol. Plant.,* v.101, n.4, p.815-820, 1996.

SANTOS, W.D.; FERRARESE, M.L.L.; NAKAMURA, C.V.; MOURÃO, K.S.M.; MANGOLIN, C.A.; FERRARESE-FILHO, O. Soybean (Glycine max) root lignification induced by Ferulic Acid. The possible mode of action. *J. Chem. Ecol.*, v.34, n.9, p.1230-1241, 2008.

SCHOENBERG, M.H.; BEGER, H.G. Reperfusion injury after intestinal ischemia. *Crit. Care Med*., v.21, n.9, p.1376-1386, 1993.

SHANMUGARAJAN, T.S.; KRISHNAKUMAR, E.; SOMASUNDARAM, I.; SIVARAMAN, D.; ARUNSUNDAR, M.; BALAJI, R.; SIVAKUMAR, S.M. Salutary effect of ferulic acid against D-galactosamine challenged liver damage. *J. Biol. Sci.,* v.8, n.8, p.1271-1279, 2008.

SHARMA, P.; MISHRA, S.; AJMERA, P.; MATHUR, S. Oxidative stress in metabolic syndrome. *Indian J. Clinical. Biochem.,* v.20, n.1, p.145-149, 2005.

SHI, Y.; SUN, J.; HE, H.; GUO, H.; ZHANG, S. Hepatoprotective effects of ganoderma lucidum peptides against D-galactosamine-induced liver injury in mice. *J. Ethnopharmacol.*, v.117, n.3, p.415-419, 2008.

SIES, H. Strategies of antioxidant defence. Review. *Eur. J. Biochem.*, v.215, n.2, p.213-219, 1993.

SIES, H.; STAHL, W. Vitamins E and C, beta-carotene, and other carotenoids as antioxidants. *Am. J. Clin. Nutr.,* v.62, n.6, p.1315-1321, 1995.

SILBERBERG, M.; MORAND, C.; MATHEVON, T.; BESSON, C.; MANACH, C.; SCALBERT, A.; REMESY, C. The bioavailability of polyphenols is highly governed by the capacity of the intestine and of the liver to secrete conjugated metabolites. *Eur. J. Nutr.,* v.45, n.2, p.88-96, 2006.

SIMI, A.C. *Isquemia intestinal*. Maffei FHA. Doenças vasculares periféricas. Rio de Janeiro: MEDSI, 2002. p.123912-123957.

SOARES, S.E. Ácidos fenólicos como antioxidantes. *Rev. Nutr.*, v.15, n.1, p.71-81, 2002.

SOOBRATTEE, M.A.; NEERGHEEN, V.S.; LUXIMON-RAMMA, A.; ARUOMA, O.I.; BAHORUN, T. Phenolics as potential antioxidant therapeutic agents: mechanism and actions. *Mutat. Res.,* v.579, n.1-2, p.200-213, 2005.

SRINIVASAN, M.; RUKKUMANI, R.; RAM SUDHEER, A.; MENON, V.P. Ferulic acid, a natural protector against carbon tetrachloride induced toxicity. *Fundam. Clin. Pharmacol.,* v.19, n.4, p.491-496, 2005.

SRINIVASAN, M.; SUDHEER, A.R.; PILLAI, K.R.; KUMAR, P.R.; SUDHAKARAN, P.R.; MENON, V.P. Influence of ferulic acid on γ-radiation induced DNA damage, lipid peroxidation and antioxidant status in primary culture of isolated rat hepatocytes. *Toxicology,* v.228, n.2-3, p.249-258, 2006.

SULTANA, R.; RAVAGNA, A.; MOHMMAD ABDUL, H.; CALABRESE, V.; BUTTERFIELD, D.A. Ferulic acid ethyl ester protects neurons against amyloid beta-peptide (1-42) induced oxidative stress and neurotoxicity: relationship to antioxidant activity. *J. Neurochem*., v.92, n.4, p.749-758, 2005.

SZATROWSK, T.P.; NATHAN, C.F. Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Res*., v.51, n.3, p.794-798, 1991.

TADA, Y.; TAYAMA, K.; AOKI, N. Acute oral toxicity of ferulic acid, natural food additive, in rats. *Ann. Rep. Tokyo Metr. Res. Lab. P. H.*, v.50, p.311-313, 1999.

TANIGUCHI, H.; HOSODA, A.; TSUNO, T.; MARUTA, Y.; NOMURA, E. Preparation of ferulic acid and its application for the synthesis of cancer chemopreventive agents. *Anticancer Res.,* v.19, n.5A, p.3757-3761, 1999.

TOLMAN, K.; SIRRINE, R. Drug-induced liver disease. Occupational hepatotoxicity. *Clin. Liver Dis.*, v.2, n.3, p.563-581, 1998.

VANDER, A.J.; SHERMAN, J.H.; LUCIANO, D.S. (Eds.). Nonimmune metabolism of foreign chemicals. In: _____ *Human physiology*: the mechanisms of body function. Toronto: Mc Graw Hill, 1994. p.738-740.

WANG, S.Y.; LIN, H.S. Antioxidant activity in fruits and leaves of blackberry, raspberry, and strawberry varies with cultivar and developmental stage. *J. Agric. Food Chem.*, v.48, n.2, p.140-146, 2000.

WONG, D.S.W. Feruloyl esterase: a key enzyme in biomass degradation. *Appl. Biochem. Biotechnol.,* v.133, n.2, p.87-112, 2005.

WÜRTZEN, G. Shortcomings of current strategy for toxicity testing of food chemicals: antioxidants. *Food Chem. Toxicol.,* v.28, n.11, p.743-745, 1990.

YAN, J.J.; CHO, J.Y.; KIM, H.S.; JUNG, J.S.; HUH, S.O.; SUH, H.W.; KIM, Y.H.; SONG, D.K. Protection against beta amyloid peptide toxicity in vivo with long-term administration of ferulic acid. *Br. J. Pharmacol*., v.133, n.1, p.89-96, 2001.

YEH, C.T.; YEN, G.C. Induction of hepatic antioxidant enzymes by phenolic acids in rats is accompanied by increased levels of multidrug resistance – associated protein 3 mRNA expression. *J. Nutr.,* v.136, n.1, p.11-15, 2006.

YOGEETA, S.K.; HANUMANTRA, R.B.; GNANAPRAGASAM, A.; SUBRAMANIAN, S.; RAJAKANNU, S.; DEVAKI, T. Attenuation of abnormalities in the lipid metabolism during experimental myocardial infarction induced by isoproterenol in rats: beneficial effects of ferulic acid and ascorbic acid. *Basic Clin. Pharmacol. Toxicol.,* v.98, n.5, p.467-472, 2006.

YOSHIDA, W.B. Radicais livres na síndrome de isquemia e reperfusão. *Cir. Vasc. Angiol.*, v.12, p.82-95, 1996.

ZHAO, Z.; EGASHIRA, Y.; SANADA, H. Digestion and absorption of ferulic acid sugar esters in rat gastrointestinal tract. *J. Agric. Food Chem.,* v.51, n.18, p.5534-5539, 2003.

ZHAO, Z.; EGASHIRA, Y.; SANADA, H. Ferulic acid is quickly absorbed from rat stomach as the free form and then conjugated mainly in liver. *J. Nutr*., v.134, n.11, p.3083-3088, 2004.

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