The effect of Ferulic acid asFree Radical Scavenger, Hepatoprotective, Neuroprotective, Radioprotective, as potential in Cancer, Diabetes, Cardiovascular, and Autoimmunity Treatment and Prevention(Part One)

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Abstract: Ferulic acid (FA), a ubiquitous natural phenolic phytochemical present in seeds, leaves, both in its free form and covalently conjugated to the plant cell wall polysaccharides, glycoproteins, polyamines, lignin and hydroxy fatty acids.

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.

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.

Ferulic acid, like many natural phenols, is an antioxidant in vitro in the sense that it is reactive toward free radicals such as reactive oxygen species.

In this article, I discuss Ferulic acid, Chemistry and Biochemistry of Ferulic Acid, Metabolism of ferulic acid, Radical Scavenger Properties, Pharmacological Applications

Key Word: Ferulic acid, Free Radical Scavenger, Hepatoprotective, Neuroprotective, Anticarcinogenic ,Radioprotective, Cancer, and Autoimmunity

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Introduction

Ferulic acid 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 (1),(2),(3),(4). In 1925, FA was chemically synthesized and structurally confirmed by spectroscopic techniques, depicted the presence of an unsaturated side chain in FA, and also existence of both cis and trans isomeric forms (5),(6). The double bond present in the side chain is subjected to cis–trans isomerization, and the resonance stabilized phenoxy radical accounts for its effective antioxidant activity. It catalyzes the stable phenoxy radical formation upon absorption of ultra-violet light, which gives the strength to FA for terminating free radical chain reactions. Collectively with dihydroferulic acid, it is the component of lignocelluloses, where it confers rigidity to the cell wall by making the crosslink between polysaccharides and lignin. It makes esters by binding with a variety of molecules such as polysaccharides, long chain alcohols,-various-sterols-of-plant,-tetra-hydroisoquinoline-monoterpene-glucoside,-a cyanogenetic glycoside and an amino-hydroxy-cyclopentenone, flavonoids and different types of hydroxycarboxylic acids including gluconic, tartaric, malic, hydroxycitric, tartronic, quinic, and hydroxy fatty acids. Natural antioxidants exhibit therapeutic potential for a variety of diseases such as cancer, diabetes, and cardiovascular and neurodegenerative diseases (7),(8),(9), where free radicals play a key role in development (10). 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 (11),(12),(13). Antioxidants found in vegetables can act as sequesters, reducing agents, enzyme inhibitors, metal chelators or free radical scavengers (14). Phenols are widely distributed in the plant kingdom and diet vegetables. There are found in significant concentrations in fruits, vegetables and beverages andhave been indicated as effective antioxidants (15),(16). In vivo

experiments on rats have shown that the metabolism of esterified FA occurs first with a de-esterification reaction done by the enzymes produced by the lactic acid bacteria present in the gastrointestinal tract (17). Then, FA is converted into a variety of metabolites, predominantly containing glucuronic or sulphate molecules (18),(19),(20). Jacobson et al. (21), identified FA, vanillic acid, and caffeic acid in human urine after ingestion of 1 g of FA. It has also been evidenced that free FA or FA linked to simple sugars had a higher absorption rate when compared to FA bound with more complex matrices: in humans, the urinary recovery of FA was 74% after drinking beer while it was in the range of 11%–25% after tomato consumption (22),(23). This significant difference is due to the fact that in the beer FA is found as free, while in tomato it is present as FA-O-glucoside(24). The conjugation of FA mainly occurs in liver through the enzymes sulfotransferases and a Uridine 51-diphospho glucuronosyltransferase (UDP-glucuronosyltransferases) (25), although the kidney (19), and the intestinal mucosa (26), can participate in the process. The present article updates the therapeutic properties of FA, reviewing its sources, mechanisms of action pharmacokinetics, and pharmacodynamics, in order to to provide a basis for understanding its as well as its pharmaceutical potential.

Nature, Chemistry and Biochemistry of Ferulic Acid

Ferulic acid (C10H10O4) is the most abundant, ubiquitous hydroxyl cinnamic acid derived from phytochemical phenolic compounds, distributed widely throughout the plant kingdom (spices, vegetables, grains, pulses, legumes, cereals, and fruits), their by-products (tea, cider oil, and beverages) and medicinal plants. It is a renewable resource for the bio-catalytic or chemical conversion to other useful aromatic chemicals from agricultural by-products in nature. Ferulic acid is a phenyl propenoid derived from the cinnamic Acid,3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid, 4-hydroxy-3-methoxycinnamic acid, or coniferic acid. It shows two isomers: *Cis*(a yellow oily liquid) and *Trans* (crystalline). Its nomenclature comes from Umbelliferae, *Ferula foetida*from which this active compound was isolated for the first time in 1866. It is said that ferulic acid supplies hydrogens to free radicals with phenolic-OH groups to provide the antioxidant effect.

3. Metabolism of Ferulic Acid

The formation of FA in plants occurs through the metabolic route of shikimate pathway starting with aromatic amino acids, L-phenylalanine and L-tyrosine as key entities. Initially, phenylalanine and tyrosine are converted into cinnamic and p-coumaric acid with the help of phenylalanine ammonia lyase and tyrosine ammonia lyase, respectively(27).The p-coumaric acid gets converted into FA by hydroxylation and methylation reaction(28).Oxidation and methylation of FA and other aromatic compounds give di- and tri-hydroxy derivatives of cinnamic acid, which takes part in the lignin formation together with FA. The conversion reactions occur during the formation of FA and other aromaticcompounds. In vivo studies on FA metabolism suggests that it gets converted into a variety of metabolites such as ferulic acid-sulfate, ferulic acid-glucuronide, ferulic acid-sulfoglucuronide (major metabolites in the plasma and urine of rats), ferulic acid-diglucuronide, feruloylglycine, m-hydroxyphenylpropionic acid, dihydroferulic acid, vanillic acid and vanilloylglycine(19),(29).The data obtained from these outcomes recommends that the major pathway of FA metabolism is the conjugation reaction with glucuronic acid and/or sulfate. The conjugation of FA takes place mainly in the liver

through the activities of sulfotransferases and uridinediphosphate (UDP) glucuronosyltransferases, while small amount of conjugation reaction also takes place in the intestinal mucosa and kidney(30),(26),(19).A small portion of free FA possibly metabolized through
b-oxidation in the liver(31).A study was carried out by Overhage et al. with the help of Pseudomonas sp. strain HR199 at the end of twentieth century which revealed that the genes involved in the catabolic mechanism of FA were present on a DNA region, which was covered by two EcoRI fragments, E230 and E94, respectively. These genes were fcs,ech, and aat encoding for feruloyl coenzyme A synthetase, enoyl-CoA hydratase/aldolase, and b-ketothiolase, respectively(32).Report on the degradation of FA into vanillin and other useful organic compounds through protocatechuate 4,5-cleavage (PCA) pathway in Sphingomonaspaucimobilis SYK-6 confirmed that FA got converted into feruloyl-CoA by feruloyl-CoA synthetase (FerA), and further into HMPMP-CoA (4-hydroxy-3-methoxyphenylb-hydroxypropionyl-coenzyme A) with the help of feruloyl-CoA hydratases/lyases (FerB and FerB2). It subsequently resulted intovanillin with the removal of CH3COSCoA (acetyl coenzyme A), andfinally vanillin transformed into pyruvate and oxaloacetatethrough the PCA pathway(33).The end products of FA catabolismenter into the TCA (tricarboxylic acid cycle), and produce energy inthe biological system.

Radical Scavenger Properties

Free radicals may be defined as organic and inorganic molecules or atoms which contain one or more unpaired, independently existing electrons(34).They present short half-life and are very reactive. Found in all biological systems, they are continuously generated by several physiological processes fromeither 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(35).

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(36),and can trigger a series of chronic degenerative diseases such as arthritis, atherosclerosis, diabetes, cataracts, chronic inflammations, brain dysfunction, aging, cancer and others(36).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. 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. 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(36),(37),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(38),(27).FA also presents "indirect" free radical scavenging activity, namely the ability of this phenolic acid to up-regulate the hemeoxygenase-biliverdinreductase system(39),(40),(41),which in turn generates bilirubin, an endogenous free radical scavenger(42),(43).

5. Pharmacological Applications

5.1. 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(44).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(45),(46),(47).In order to investigate the protective effects of FA in intestine injuries resulting from ischemia-reperfusion,(48),conducted *in vivo* assays using male Wistar rats to compare the antioxidant activity of ferulic acid with ascorbic acid and epigallocatechingallate (EGCG).

Ascorbic acid and EGCG are compounds with high activity for elimination of the superoxide anion and inhibition xanthine oxidase Mancuso and Barone(49), 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(50),(51).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*. (7), 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 quinonereductase 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.

5.2. 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(52).

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(53).

Hirabayashi*et al.*(54), 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 (54)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 *Cimicifugaheracleifolia*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*.

5.3. 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(7),(55),(56),(57),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, glutamyltransferase, 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 (58), 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(59).The results showed that the group of male Wistar rats that received pre-treatment (20 mg FA/kg body weight) hadincreased 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(60).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 (61), 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*.(62), also investigated the hepatoprotective effect of FA against carbon tetrachloride (CCl4)-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 CCl4 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 CCl4 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 CCl4-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.* (63), 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.

5.4. 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(64),(7).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(64).*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(65).Noumura*et al.*(66), 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(67),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,(68),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.*(69), investigated the inhibitory activity of cinnamic acid derivatives against ratintestinal 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.

5.5. Anti-cholesterolemic Agent

Kim *et al.* (8), 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(70),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.* (71), 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 apoE(-/-) mice fed with a Western diet.

5.6. NeuroprotectiveAgent

In another study performed by(38),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(72),(73),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(7),(74).The production of free radicals and neuroinflammation contribute to the destruction of some brain regions such as the cortex(74).Thus, FA can have a favorable effect on AD due to its anti-inflammatory and antioxidant properties(27),(38).

Ono *et al*. (75), 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(76),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 viaintracerebroventricular 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*. (71), 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.

5.7. 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(77).Large amounts of hydrogen peroxide are produced and secreted by tumor cells, confirming its importance in spreading and invasion of the tumor(78).Anti-cancer activity of FA is related to its antioxidant property to eliminate ROS and stimulate the activity of antioxidant enzymes(79).

Mori *et al*. (80), 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(7),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 quinonereductase, 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*.(81),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(82).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.

5.8. 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(83).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(7). 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(83).Thus, FA may be included among potentially radioprotective molecules(38),(27), 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(84).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*. (85), 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 peroxidaseat 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.

5.8. Pulmonary protection and cardiovascular effect of ferulic acid

Nicotine is one of themajor hazardous compounds of cigarette smoke(86).It causes the oxidative cellular injury by increasing the lipid peroxidation, which is supposed to play a key role in the pathogenesis of several smoking related diseases(87).Due to the administration of FA, a reverse reaction occurs in the damage, which was induced by nicotine. FA causes a significant increase in the endogenous antioxidant defense, which protect the cells from oxidative damage. FA protects the membrane by successfully quenching of free radicals from attacking the membrane. It alsoinhibits the leakage of marker enzymes into circulation, andincrease the antioxidant status in circulation(88).It has been shown that the blood pressure was decreased in both SHRSP (stroke-prone spontaneously hypertensive) rats and SHR (spontaneously hypertensive rats) with a maximumeffect (34mmHg) after 2 h of oral intake of FA (1–100mg/kg body

weight)(89),(90).Studies also showed that sodium salt of FA decreases the serum lipids, inhibits platelet aggregation and prevents thrombus formation(91).

6. 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.The positive effects of FA on HMG-CoA reductase, glucokinase and antioxidant and detoxification gene expression suggest additional properties whose mechanisms deserve further investigation.FA has given positive results in the inhibition of neurotoxic A-aggregation in vitro and in vivo in animal models. Furthermore, FA is able to interfere with the biological pathways involved in apoptotic programmed cell death induced by oxidative stress and inflammation due to A-aggregation. Most of the activities as shown by FA can be attributed to its potent antioxidant capacity because of conjugation in its nucleus and side chain.Ferulic acid, reducing the risk of serious diseases such as diabetes, cholesterol, heart diseases, and cancer, is a useful phenolic acid for the human health. It is both a good antioxidant and a good antimicrobialHowever, 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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