Review
Ferulic acid: pharmaceutical functions, preparation and applications in foods

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Abstract: Ferulic acid (4-hydroxy-3-methoxycinnamic acid), an effective component of Chinese medicine herbs such as *Angelica sinensis, Cimicifuga heracleifolia* and *Lignsticum chuangxiong*, is a ubiquitous phenolic acid in the plant kingdom. It is mainly conjugated with mono- and oligosaccharides, polyamines, lipids and polysaccharides and seldom occurs in a free state in plants. Ferulic acid is a phenolic acid of low toxicity; it can be absorbed and easily metabolized in the human body. Ferulic acid has been reported to have many physiological functions, including antioxidant, antimicrobial, anti-inflammatory, anti-thrombosis, and anti-cancer activities. It also protects against coronary disease, lowers cholesterol and increases sperm viability. Because of these properties and its low toxicity, ferulic acid is now widely used in the food and cosmetic industries. It is used as the raw material for the production of vanillin and preservatives, as a cross-linking agent for the preparation of food gels and edible films, and as an ingredient in sports foods and skin protection agents. Ferulic acid can be prepared by chemical synthesis and through biological transformation. As polysaccharide ferulate is a natural and abundant source of ferulic acid, preparation of ferulic acid from plant cell wall materials will be a prospective pathway.
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INTRODUCTION
Ferulic acid (4-hydroxy-3-methoxycinnamic acid) has received much attention in the study of Chinese medicine since it was found to be one of the effective components in Chinese medicine herbs such as *Angelica sinensis*, *Cimicifuga heracleifolia* and *Lignsticum chuangxiong*.[1] It is a phenolic acid ubiquitously existing in the plant kingdom, which can be absorbed by the small intestine and excreted through the urine.[2] It is one of the most abundant phenolic acids in plants, varying from $5\,g\,kg^{-1}$ in wheat bran to $9\,g\,kg^{-1}$ in sugar-beet pulp and $50\,g\,kg^{-1}$ in corn kernel.[3,4] In plants, ferulic acid is rarely found in the free form. It is usually found as ester cross-links with polysaccharides in the cell wall, such as arabinoxylans in grasses, pectin in spinach and sugar beet and xyloglucans in bamboo.[5] It also can cross-link with proteins.[6] The cross-linking property of ferulic acid with both polysaccharides and proteins suggests that it can be used in the preparation of complex gels in food applications.

In recent years, there have been an increasing number of reports on the physiological functions of ferulic acid and its derivatives in human. Many applications of ferulic acid in the food industry have also been discovered. This article reviews the physiological role of ferulic acid, its metabolism in humans, its preparation and applications in the food industry.

PHARMACEUTICAL FUNCTIONS
Antioxidant activity
The human body is susceptible to the attack of free radicals and reactive oxygen species leading to a series of diseases, such as atherosclerosis, cancer, cataracts, macula lutea, etc.[7] The generation of free radicals in the human body is influenced by endogenous and exogenous factors. Superoxide and hydroxyl radicals, which are associated with many diseases, are formed by endogenous processes. Superoxide can be produced by oxidation of the molecules of adrenaline,

flavine nucleotides, thiol compounds and sugars in the presence of oxygen.[8] Exogenous factors such as ultraviolet light, air pollutants and cigarette smoke may also induce the production of free radicals that cause damage to our body. Since free radicals are constantly produced in the human body, a defensive system that can prevent the damage caused by free radicals is essential to human health.

Although endogenous antioxidant systems already exist in the human body, the intake of antioxidants is necessary to strengthen the defensive systems. In recent years, there has been an increasing awareness of the bioactivity and potential health benefits of hydroxycinnamates (eg ferulic, caffeic, *p*-coumaric and sinapic acid) and their conjugates. Free ferulic acid is a good antioxidant since it forms a resonance-stabilized phenoxy radical. Ferulic acid showed high scavenging activity for hydrogen peroxide, superoxide, hydroxyl radical and nitrogen dioxide free radicals. Ou *et al*[9] observed that ferulic acid, at a concentration of $250\,mg\,l^{-1}$, scavenged 92.5% of hydroxyl radicals in a Fenton reaction system. The nitrogen dioxide radical is known to be toxic agent produced in the metabolism of nitrates and nitrites. Zhang *et al*,[10] using the pulse radiolysis technique, showed that hydroxycinnamic acid derivatives, including ferulic acid, sinapic acid and caffeic acid, scavenged nitrogen dioxide radicals. Ferulic acid can prevent peroxynitrite-mediated nitration of protein-bound and free tyrosine and peroxynitrite-mediated oxidation of dihydrorhodamine 123 and DNA.[11] Ferulic acid not only scavenges free radicals, but also increases the activity of enzymes that are responsible for scavenging free radicals and inhibits enzymes that catalyze the production of free radicals. Kayahara *et al*[12] observed that ferulic acid, as well as its amino acid derivatives, showed strong tyrosinase-inhibitory activity and superoxide dismutase-like activity. Kawabata *et al*[13] found that feeding F334 rats with a dose of $0.1\,g\,kg^{-1}$ significantly elevated the activities of detoxifying enzymes, namely glutathione *S*-transferase in the liver and quinone reductase in the liver and colonic mucosa.

Antioxidant properties of hydroxycinnamates have been measured *in vitro*, and the potential health effects of hydroxycinnamates have been demonstrated in animal models. However, few studies have been undertaken concerning the extent to which these compounds are absorbed *in vivo* from the diet. Further studies are required to show the bioavailability of hydroxycinnamates and to demonstrate that particular ones are responsible for some of the health benefits in humans.

Cholesterol-lowering activity

Ferulic acid and γ-oryzanol have been shown to have cholesterol-lowering activity. γ-Oryzanol is a mixture of ferulic acid esters of sterol and triterpene alcohols. It occurs in rice bran oil at a level of 1–2%, where it serves as a natural antioxidant. Rong *et al*[14] found that γ-oryzanol treatment resulted in a significant reduction in plasma total cholesterol and non-high-density lipoprotein cholesterol in hamsters fed with diets containing 5% coconut oil and 0.1% cholesterol. In addition, the γ-oryzanol-treated animals also exhibited a reduction in cholesterol absorption versus control animals. Kamal-Eldin *et al*[15] studied the effects of the phenolic compounds butylated hydroxytoluene, sesamin, curcumin and ferulic acid on plasma, liver and lung concentrations of tocopherol and on plasma and liver cholesterol in male Sprague-Dawley rats. Ferulic acid had no effect on the level of tocopherol in the plasma, liver or lung, while the other substances showed different interactions with α- and γ-tocopherols. With the exception of butylated hydroxytoluene, all test compounds tended to decrease total cholesterol in plasma. Ferulic acid tended to lower plasma very-low-density lipoprotein + low-density lipoprotein cholesterol concentrations. It was also found that ferulic acid increased plasma high-density lipoprotein cholesterol while the other compounds reduced it numerically, but not statistically. The results suggest some *in vivo* interactions between the phenolic compounds and tocopherol that may increase the bioavailability of vitamin E and decrease cholesterol in rats. The cholesterol-lowering activity of ferulic acid was confirmed by Kim *et al*.[16] It was suggested that ferulic acid inhibited cholesterol synthesis by competitively inhibiting the activity of hydroxymethylglutaryl CoA reductase in the liver and increasing excretion of acidic sterol.[16,17]

Prevention against thrombosis and atherosclerosis

Ferulic acid-rich herbs have long been used in China for curing thrombosis. Platelet aggregation, one of the mechanisms involved in repair of blood vessel injury, is related to diseases such as thrombosis. Developing a compound capable of inhibiting platelet aggregation may thus provide a therapeutic means. Kayahara *et al*[12] synthesized three types of ferulic acid derivatives (feruloylaminoacid benzyl or methyl esters, feruloylaminoacids and 4-0-[*N*-(carbobenzyloxy)aminoacyl]ferulic acid). They reported that 4-0-[*N*-(carbobenzyloxy)aminoacyl] ferulic acid (amino acid components: isoleucine, praline) could maintain inhibition of collagen-induced platelet aggregation to the same level as ferulic acid, but showed stronger dissociation of ADP-induced aggregation. In other words, these compounds may not only prevent thrombosis but also dissolve thrombi. From the results of *in vitro* and clinical studies, ferulic acid has been shown to inhibit the activity of thromboxane A_2 (TXA_2) synthetase and blood platelet aggregation.[18–20] Eicosanoic acid is a precursor of TXA_2. This compound is released from cell membrane lipids by a hydrolysis reaction catalyzed by phospholipase A_2. Pan *et al*[21] reported that ferulic acid could prevent the release of eicosanoic acid by inhibiting

phosphoslipase A_2. On the basis of these reports, Ou et al[17] summarized that the anti-thrombosis effect of ferulic acid was attributed to its antagonistic effect on TXA_2 and inhibitory effects on TXA_2 synthetase and phosphoslipase A_2.

As atherosclerosis induced by peroxidation of lipids is a main cause of coronary heart disease, the effects of antioxidants on the development of atherosclerosis in experimental animals have been investigated by some researchers. Hiramatsu et al[22] tested the antioxidant action of γ-oryzanol in hypercholesterolemic rabbits to determine its effects on the development of atherosclerosis. They found that oleate incorporation into cholesteryl ester by macrophages was significantly reduced in the γ-oryzanol-treated group compared with the non-treated group. Sakamoto et al[23] also observed that atherogenic index was reduced by intravenous administration of ferulic acid in a high cholesterol diet fed to rats.

Owing to the antioxidant and cholesterol-lowering activities, as well as the preventive effects against thrombosis and atherosclerosis, ferulic acid is considered a potential chemopreventive agent against coronary heart disease.

Antimicrobial and anti-inflammatory activity

Ferulic acid has been shown to possess inhibitory activity on the growth and reproduction of viruses such as influenza virus, respiratory syncytial virus and AIDS. Ferulic acid and isoferulic acid are the active components of the rhizoma of *Cimicifuga* species, which is used frequently as anti-inflammatory drugs in Japanese Oriental medicines. Hirabayashi et al[24] investigated the effect of ferulic acid and isoferulic acid on murine interleukin-8 (IL-8) production in response to influenza virus infections *in vitro* and *in vivo* by antibody-sandwich enzyme-linked immunosorbent assay. In the *in vitro* study, they found that both ferulic acid and isoferulic acid reduced the IL-8 levels in the 20-h conditioned medium in comparison with control in a dose-dependent manner. In the *in vivo* study, mice were infected with 1000 PFU (plaque forming units) of the virus and received daily oral administrations of *Cimicifuga heracleifolia* extract (5 mg mouse^{-1} day^{-1}), ferulic acid (0.5 mg mouse^{-1} day^{-1}), or isoferulic acid (0.125 mg mouse^{-1} day^{-1}). The three drugs showed a tendency to reduce IL-8 levels in bronchoalveolar lavage (BAL) obtained 2 days after infection. Moreover, both ferulic acid and isoferulic acid significantly reduced the number of exuded neutrophils into BAL. Sakai et al[1] investigated the effect of ferulic acid and isoferulic acid on the production of macrophage inflammatory protein-2 (MIP-2) in a murine macrophage cell line, RAW264.7, in response to respiratory syncytial virus (RSV) infection. In the presence of either ferulic acid or isoferulic acid, RSV-infected cells reduced MIP-2 production in a dose-dependent manner. These results suggest that ferulic acid and isoferulic acid might be responsible, at least in part, for the anti-inflammatory drug effect of *Cimicifuga heracleifolia* extract through the inhibition of MIP-2 production. Edeas et al[25] reported that ferulic acid and its derivatives inhibited AIDS virus, suggesting it to be a potential chemopreventive agent for AIDS.

Ferulic acid possesses a wide spectrum of antimicrobial activity. It exhibited antimicrobial activity towards Gram-positive bacteria, Gram-negative bacteria and yeasts.[26] It also showed strong inhibitory effects on the growth of some human gastrointestinal microflora, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Citrobacter koseri*, *Pseudomonas aeruginosa*, *Helicobacter pylori* and *Shigella sonnei*.[27–29] The antimicrobial mechanism of ferulic acid was attributed to its inhibition of arylamine *N*-acetyltransferase in the bacteria.[29] Ferulates of triterpene alcohols and sterols, isolated from the methanol extract of rice bran, had anti-inflammatory activity against inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate in mice.[30]

Anti-cancer effect

Studies on the chemopreventive effects of ferulic acid on oral and large bowel carcinogenesis have been reported in recent years. Mori et al[31] studied the effects of ferulic acid on oral cancer in rats by feeding ferulic acid in the diet at a dose of 0.5 g kg^{-1} after exposure to 4-nitroquinoline-1-oxide (4NQO) for 5 weeks in drinking water at a dose of 0.02 g kg^{-1}. They found that the incidences of tongue carcinomas and preneoplastic lesions (severe dysplasia) were significantly lower on termination of the experiment (32 weeks) than the group with the carcinogen alone. The results suggest that ferulic acid has chemopreventive activity on oral cancer. Recently many researchers have focused their attention on the anti-cancer activity of ferulic acid on colon and rectal cancer.[13,31,32] Kawabata et al[13] examined the modifying effects of dietary administration of ferulic acid on azoxymethane (AOM)-induced colon carcinogenesis in rats. After 35 weeks, rats which were given ferulic acid during the initiation phase at doses of 0.25 and 0.5 g kg^{-1}, respectively, had lower incidences of colonic carcinomas than those which were given AOM alone. They also observed that ferulic acid could elevate the activities of phase II detoxifying enzymes, glutathione *S*-transferase (GST) and quinone reductase (QR) in liver and colon of rats induced by AOM. These results suggest that detoxifying enzymes are related to the blocking effect of ferulic acid on AOM-induced colon carcinogenesis. As free radicals play an important role in the development of cancer, the anti-cancer effects of some antioxidants is attributed to their ability in scavenging free radicals. Kaul and Khanduja[33] reported that topical application of polyphenols (ellagic acid, tannic acid, caffeic acid and ferulic acid) simultaneously with phorbol-12-myristate-13-acetate or mezerein resulted in significant protection against 7,12-dimethylbenz[a]anthracene-induced skin tumors

in mice. *In vivo* and *in vitro* treatment of murine peritoneal macrophages with the tumor promoters resulted in stimulation of superoxide anion radical formation. In their experiments, the polyphenols were strong inhibitors of the superoxide anion free radical.

Besides the functions mentioned above, ferulic acid has been reported to play important roles in scavenging nitrite,[34] as well as increasing sperm viability, transmembrane migration ratio (TMMR) and the levels of intracellular cAMP and cGMP in spermatozoa.[35]

Pharmacokinetics of ferulic acid in animals and human

Ferulic acid and other hydroxycinnamic acids occur in plant tissues mainly as low-molecular-weight, watersoluble conjugates present in the cytosol and in bound forms esterified or etherified to cell wall polymers. Water-soluble conjugates are more readily absorbed as ester or the aglycone in the upper digestive tract of non-ruminants. Bound acids are primarily released by microbial action in the hindgut of non-ruminants species, including humans.[36]

Bourne and Rice-Evans[37] investigated the bioavailability of ferulic acid in humans from tomato consumption through the monitoring of the pharmacokinetics of excretion in relation to intake. They found that the peak time for maximal urinary excretion was approximately 7 h and the recovery of ferulic acid in the urine, on the basis of total ferulic acid and feruloyl glucoronide excreted, was 11–25% of the amount ingested. In their subsequent research, no urinary excretion of ferulic acid was detected approximately 10 h after tomato ingestion.[38] Chang *et al*[39] used pure free ferulic acid to carry out a pharmacokinetic study in Wistar female rats. They concluded that free ferulic acid did not enter enterohepatic circulation. Hence, the chemopreventive effect of ferulic acid on colon carcinogenesis depends largely on the ingestion of fiber-bound ferulic acid in plant tissues, which can get to the colon and is partially released by colon microorganisms.

Absorbed ferulic acid and other flavonoids are present in the rat blood circulation in the form of glucuronide, sulfate and methylate conjugates and are excreted via urine or bile.[40,41] Piskula *et al*[41] proposed that the first step of conjugation of dietary flavonoids was glucuronidation, occurring in the intestinal mucosa in rats. The glucurinized form entered blood circulation and was sulfated in the liver and methylated in the liver and kidney. The presence of non-conjugated ferulic acid found in rat plasma might be due to overdosing of the animals, as discussed by Piskula and Terao[42] in their study of quercetin absorption in rats.

From the results mentioned above, it can be concluded that free ferulic acid is absorbed from the alimentary tract and is metabolized into various forms. The range of metabolites and their relative proportions depend on many factors, including dose, route of administration and animal species.

The vast proportion of ferulic acid in plants exists in its bound form in the cell wall cross-linking with polysaccharides and proteins by diferulic acids. The bound form of ferulic acid cannot be absorbed through the gastrointestinal tract wall. Hence, esterase activity is necessary to cleave the ester bonds and to release the free acids into the gut lumen where they then become available for absorption or for further metabolism. It has been demonstrated that microbial esterases present in the intestine of mammals (rats and humans) can release ferulic acid and *p*-coumaric acid into the lumen.[3,9] Free hydroxycinnamic acids (ferulic, caffeic, *p*-coumaric acids) released from colonic fermentation can be absorbed into the circulatory system.[3,37,43]

Andreasen *et al*[44] provided the evidence that diferulic acids could be absorbed via the gastrointestinal tract. The 5-5-, 8-*O*-4-, and 8-5-diferulic acids were identified in the plasma of rats after oral administration with a mixture of the three acids in oil. Their study also revealed that human and rat colonic microflora containing esterase activity were able to release 5-5-, 8-*O*-4- and 8-5-diferulic acids from model compounds and dietary cereal brans, hence providing a mechanism for the release of dietary diferulates prior to absorption of the free acids. In addition, cell-free extracts from human and rat small intestine mucosa exhibited esterase activity towards diferulate esters. Hence, esterified diferulates can be released from cereal brans by intestinal enzymes, and those free diferulic acids can be absorbed and enter the circulatory system. However, Kroon *et al*[3] showed that, in humans, over 95% of the total release of feruloyl groups took place during fermentation in the colon, and only a small portion was released by gastric and small intestinal treatment. This means that, although the small intestine mucosa secretes esterase, it contributes very little to the release of ferulic acid from the plant cell wall.

In summary, free ferulic acid, its soluble conjugates and bound ones can be absorbed from the human gastrointestinal tract. The first two types can be directly absorbed in the small intestine, but the bound ferulic acid must be first released by microbial esterases in the colon before it can be absorbed. The metabolism, physiological role and pharmacokinetic properties of the released free acid and feruloyl compounds need to be further elucidated in future studies.

PREPARATION OF FERULIC ACID
Preparation of ferulic acid by chemical synthesis

It is well-known that ferulic acid can be prepared by the condensation reaction of vanillin with malonic acid catalyzed by piperidine.[45] This method produces ferulic acid as a mixture of *trans*- and *cis*-isomers. The yield is high, but it takes as long as three weeks to complete the reaction. Da and Xu[46] improved this method by using benzylamine as the catalytic agent, methylbenzene as the solvent and a reaction temperature of 85–95 °C. The improved method

increased the yield and reduced the reaction time to 2 h.

Preparation of ferulic acid from natural sources

There are three pathways to prepare ferulic acid from natural resources: (1) from low-molecular-weight ferulic conjugates, (2) from plant cell walls, and (3) by tissue culture or microbial fermentation. Several feruloyl esters of triterpene alcohols and sterols were isolated from the methanol extract of rice bran, of which the main component is γ-oryzanol, accounting for about 1.5–2.8% of rice bran oil by weight.[47] Taniguchi et al[48] prepared ferulic acid in large quantities from rice bran pitch, a blackish brown waste oil discharged in the process of the production of rice bran oil. In this process, the bran oil waste material was hydrolyzed with sodium hydroxide or potassium hydroxide at 90–100 °C for 8 h under atmospheric pressure, producing crude ferulic acid with purity of 70–90%. The solution containing alkaline salt of ferulic acid was acidified with dilute sulfuric acid to precipitate ferulic acid.

There are many reports on the use of feruloyl esterases produced by microorganisms to release ferulic acid from plant cell walls. Feruloyl esterases are a subclass of the carboxylesterases that are able to release ferulic acid from a range of esterified substances including methyl ferulate, feruloylated oligosaccharides and polysaccharides.[49] These enzymes are secreted by fungal, bacterial and yeast microbes, such as *Aspergillus niger, Pycnoporus cinnabarinus, Streptomyces avermitilis, Clostridium thermocellum, Bacillus spp, Lactobacilli, Pseudomonas fluorescens* and *Brettanomyces anomalus*. Although feruloyl esterases are not yet commercially used to prepare ferulic acids, extensive research studies have been carried out. First, microorganisms that can secrete feruloyl esterases have been screened.[50–55] Second, some characteristics of the enzymes, such as structure, optimal temperature and pH, factors affecting their stability, and the effect of the substrate and polysaccharide-degrading enzymes on the release of ferulic acid were elucidated.[52,56,57] Third, the effect of some factors on the production of feruloyl esterases, such as carbon resources, nitrogen resources and ferulic acid were studied.[58] Fourth, the purification method of ferulic acid from fermentation liquids was established.[59,60] Future work will be focused on how to improve the production of feruloyl esterases by optimizing fermentation technology and genetic engineering.

Cell suspension cultures of *Beta vulgaris, Zea mays* and *Chenopodium rubrum* have been reported to accumulate ferulic acid.[61–63] Bokern et al[61] isolated five water-soluble ferulic conjugates by TLC from callus cultures of *Beta vulgaris*. They were identified as 1-O-feruloylglucose, 6-O-feruloylsucrose, 6-O-hydroxycinnamoylglucosides, 1-O-feruloylglucuronosylglycerol and feruloylaspartic acid. These water-soluble conjugates were accumulated in different amount between cell lines and conjugates. The most

frequent one, 1-O-feruloylglucose, was accumulated up to 20.0 μmol g^{-1} dry matter. This suggests that screening of cell line can increase the content of ferulic acid conjugates in *Beta vulgaris*.

In contrast to the plant cultures mentioned above, cell cultures of *Ajuga pyramidalis* accumulated free ferulic acid[64] and also conjugated to anthocyanins[65] up to 150 mg l^{-1} cell culture on the twelfth day. With the increasing demand for natural ingredients, production of ferulic acid by plant cell culture will become a prospective pathway.

APPLICATIONS IN FOODS

Ferulic acid is of low toxicity with LD$_{50}$ of 2445 mg kg^{-1} body weight in male and 2113 mg kg^{-1} body weight in female rat.[66] In Japan, ferulic acid has been approved as a food additive and used as a natural antioxidant in foods, beverages and cosmetics. Also, in the USA and most European countries, numerous medical essences and natural extracts of herbs, coffee, vanilla beans, spices and other botanicals are selected for their high content of ferulic acid and added to foods as an FDA-approved antioxidant concoction.[67] The main applications are summarized as follows.

Production of vanillin

Vanillin is an important aromatic flavor compound used in foods, beverages, perfume and pharmaceuticals. It is produced on a large scale in the industry through chemical synthesis. However, the vanillin obtained by chemical synthesis cannot be considered as natural. Thus, there are many attempts to produce vanillin based on bioconversion of natural sources such as lignin, phenolic stilbenes, isoeugenol, eugenol, ferulic acid or aromatic amino acids.[68] Ferulic acid can be used to produce vanillin through biotransformation in microorganisms by three major pathways. The first is decarboxylation of ferulic acid by decarboxylase to produce 4-vinylguaiacol and then vanillin. The second is the reduction of ferulic acid to dihydroferulic acid, from which vanillic acid and vanillin are formed. The third is to produce vanillic acid and vanillin by formation of coniferyl alcohol from ferulic acid. These biotransformations have been discovered in many bacteria, fungi and yeasts. Use of enzymes secreted by these microorganisms, rather than direct use of microorganisms, is the practical pathway to produce vanillin from ferulic acid, as vanillin is toxic to most microorganisms and the formed vanillin will be further oxidized to the less toxic vanillic acid.[68]

The cell suspension cultures of some plants, such as *Vanilla planifolia* and *Capsicum frutescens*, can also be used to transform ferulic acid to produce vanillin.[69–71] The pathways involved in the conversion of ferulic acid to vanillin in plant systems have not been investigated in detail, but a pathway analogous to the β-oxidation of fatty acid metabolism was supposed.[69]

Ferulic acid as a preservative

Ferulic acid can be used to preserve foods because of its antioxidant and antimicrobial activities. Ferulic acid was first used in Japan in 1975 to preserve oranges and to inhibit the autooxidation of linseed oil, lard and soybean oil. Mixtures of ferulic acid and amino acids or ferulic acid and dipeptides, such as glycylglycine or alanylalanine, exerted a synergistic inhibitory effect on the peroxidation of linoleic acid.[67] Ferulic acid is an effective antioxidant in some food-related system, such as lecithin-liposomes and aqueous emulsions.[72,73]

Compared with other phenolic substances, ferulic acid has two advantages. First, ferulic acid has strong antioxidant activity. Heinonen et al[74] tested the antioxidant activity of gallic acid, propyl gallate, caffeic acid, malvidin, delphinidin, catechin, epicatechin, rutin, quercetin and ferulic acid in lecithin-liposome oxidation systems at doses of 5 and $10 \, \mu mol \, l^{-1}$. They found that, on the basis of calculation of percentage inhibition values at the propagation phase of oxidation on day 2 for hydroperoxides and on day 3 for hexanal, ferulic acid was the most efficient in inhibiting lipid and protein oxidation. Another advantage is that ferulic acid is much less affected by pH changes than other phenolic compounds, such as chlorogenic acid, caffeic acid and gallic acid.[75] This is very important for foods subjected to alkali processing, which is commonly used to recover proteins from cereals and legumes, to induce the formation of fiber-forming meat analogue vegetable protein, and to prepare peeled fruits and vegetables. Furthermore, the glucoside esters of ferulic acid also have strong antioxidant activity. The antioxidant activity of some ferulic acid esters is even greater than that of ferulic acid.[76] This was confirmed by a recent study, in which Kikuzaki et al[77] found that esterification of ferulic acid resulted in increased antioxidant activity, and the activity was influenced by the chain length of the alcohol moiety. When the inhibitory effects of alkyl ferulates against oxidation of liposome induced by 1,1-diphenyl-2-picrylhydrazyl (DPPH) were tested, hexyl, octyl and 2-ethyl-1-hexyl ferulates were more active than the other alkyl ferulates. The results indicated that the affinity of ferulates with lipid substrates affected their antioxidant activity. Medina et al[78] reported that phenolic compounds showed synergistic properties in reinforcing the antioxidant activity of lactoferrin in lipid systems containing iron. However, ferulic acid also has shortcomings. It has been reported that ferulic acid formed 4-vinylguaiacol by decarboxylation during processing, contributing off-flavors in cooked foods, beer and orange juice.[79,80]

Another preservative function of ferulic acid comes from is its antimicrobial activity. Ferulic acid can inhibit the growth of bacteria, fungi and yeasts. Ferulic acid is an active ingredient of extracts of some plants showing antimicrobial activity. Lattanzio et al[81] tested the antifungal activity of 12 kinds of phenolic compounds against five fungi (*Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Alternia* sp, *Botrytis cinerea* and *Penicillium digitatum*) and found that ferulic acid showed the highest activity. It was reported that feruloyl oligosaccharide ester showed inhibitory effects against many kinds of Gram-positive and -negative bacteria.[82] Ferulic acid, at a concentration of $500 \, mg \, l^{-1}$, can also appreciably inhibit growth of yeasts such as *Pichia anomala, Debaryomyces hansenii* and *Saccharomyces cerevisiae*, but it is less effective than potassium sorbate.[83]

As a cross-linking agent

As ferulic acid is known to cross-link with polysaccharides, it is used to increase the viscosity and form gels from some polysaccharides such as pectin and arabinoxylans.[84–86] Gel formation can also be effected from feruloylated arabinoxylans and proteins using cross-linking agents such as ammonium sulfate,[6,87] hydrogen peroxide and peroxidase,[84] and laccase.[85] This property is very important, as ferulic acid can make it possible to use polysaccharides of lower molecular weight, which have low viscosity and poor gel formation capacity, to make new gels in food processing.[6]

Ferulic acid and its oxide, quinoid ferulic acid, can react with some amino acids in proteins such as tyrosine, lysine, cysteine[88,89] and cross-link protein molecules. Thus, it can be used as a cross-linking agent to improve the properties of protein-based edible films. Kwok and Ou[90] found that incorporation of ferulic acid into the film-forming solution made from soy protein isolate (SPI) increased the tensile strength, the percentage of elongation at break, and decreased the water vapor permeability and gas permeability of the SPI film. O' Connell and Fox[91] reported that ferulic acid at $5.5 \, mmol \, l^{-1}$ markedly enhanced the heat stability of milk at $140 \, °C$. The addition of caffeic acid resulted in a reduction of the reactive lysine and sulphydryl content and inhibited the dissociation of κ-casein-rich protein from the casein micelles in milk on heating. It was postulated that on heating in milk, caffeic acid was thermally oxidized to quinones which then interacted with nucleophilic amino acid residues to inhibit κ-casein dissociation from the casein micelle. These results suggest that caffeic acid and its related phenolic compounds, such as ferulic acid, may find their prospective applications in the processing of milk products.

As an ingredient in sport foods and skin lotions

As ferulic acid is a potent antioxidant and is believed to stimulate hormone secretion in humans, it is widely used as an ergogenic substance in sport foods.[92,93]

Ultraviolet light is an exogenous factor that may cause skin damage, resulting in both precancerous and cancerous skin lesions and acceleration of skin ageing.[94] Reactive oxygen species are believed to be largely responsible for some of the deleterious effects of UV light upon skin. Particularly, prolonged skin exposure to UV light results in a severe decrease of its antioxidant content.[95] Overproduction of nitric

oxide from keratinocytes seems to play a major role in the integrated response leading to erythema production and inflammation processes following UV radiation exposure.[96] Owing to the high degree of conjugated unsaturation (as a strong UV absorber) and its permeability to the skin,[97] ferulic acid constitutes an active ingredient in many skin lotions, subscreens and hair creams designed for photoprotection[68] and for skin tumor inhibition.[98]

Concluding remarks

Ferulic acid is beneficial to health due to its chemopreventive activities against coronary heart disease, thrombosis, carcinogenesis and mutagenesis. Many researchers have recently focused their attention on the anti-cancer activity of ferulic acid on colon and rectal cancer. As free ferulic acid does not enter enterohepatic circulation, oral or intravenous ferulic acid does not easily reach the colon. Although dietary fiber-bound ferulic acid can get to the colon and is partly released by colon microorganisms, the concentration of the released ferulic acid is too low to act as a chemoprevention agent.[9] An approach to solve this problem is to study the synthesis of enzyme-resistant derivatives of ferulic acid which can be delivered to the colon safely. In a recent study, Ou et al[17] used maize starch and ferulic acid to synthesize starch ferulate. They found that the starch ferulate was only partly hydrolyzed (less than 10%) by diastase and the bound ferulic acid was largely released by colon microorganisms. Some derivatives of ferulic acid showed even higher biological activities than the free form. For these reasons, synthesis of enzyme-resistant and high-biological-activity derivatives of ferulic acid will be a focused area of future studies. Extensive toxicological and biological experiments are needed to test this kind of product.

Ferulic acid is an abundant ingredient naturally present in the plant kingdom. It can be commercially produced from natural sources. Because of the many health benefits as well as the antioxidant and antimicrobial activity, more extensive uses of ferulic acid in food applications can be anticipated in the future.

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