

Review

Ferulic Acid—A Brief Review of Its Extraction, Bioavailability and Biological Activity

Krystyna Pyrzynska 

Department of Chemistry, University of Warsaw, Pasteur Str. 1, 02-093 Warsaw, Poland;
kryspyrz@chem.uw.edu.pl

Abstract: Ferulic acid is a widespread phenolic compound that occurs in seeds and leaves, both in its free form and conjugated to polysaccharides, carbohydrates, glycoproteins and lignins in the plant cell walls. It exhibits various biological activities, like antioxidant, anticarcinogenic, anti-inflammatory, hepatoprotective, antimicrobial, and antiviral activity, and it modulates enzyme activity. Given these wide potential health benefits, ferulic acid has attracted considerable research interest and may be considered a biomolecule with strong prospects as a functional food ingredient. Great attempts have been made to enhance its extraction process and recovery from natural matrices and agro-industrial wastes for its various applications relating to human health and nutrition. This review presents the recently available information on the extraction methods for quantifying ferulic acid in different samples, along with its bioavailability and stability in processing foods and biological activities.

Keywords: ferulic acid; extraction; bioavailability; biological activity



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1. Introduction

Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA) belongs to the group of hydroxycinnamic acids, the class of phenolic compounds. Its name is derived from the genus *Ferula*, referring to the giant fennel (*Ferula communis*). As a by-product of the metabolism of phenylalanine and tyrosine, it is found in all plants. FA is abundant in numerous cereals and grains (such as rice, barley, wheat, and maize), fruits and vegetables (bananas, citrus fruits, eggplant, and cabbage), some beverages (coffee and beer) as well as in monocot plants [1–5]. It is a component of plant cell walls and forms a three-dimensional structure with cellulose, hemicellulose, and lignin [6]. The contents of FA (101.99–884.68 µg/g dry weight) determined in commonly consumed vegetables in China were mainly found in leafy vegetables [7].

Ferulic acid has low toxicity and exerts a wide range of biological functions. It presents potential therapeutic effects useful in treating cancer, diabetes, and lung cardiovascular diseases, and it is an important active component of many traditional Chinese medicines [8–12]. Its antioxidant properties are mainly manifested through the effective scavenging of oxygen-reactive species by phenolic hydroxyl groups and this effect is much stronger than vanillic, coumaric, and cinnamic acids [6,13,14]. FA is quickly absorbed by the organism and remains for longer in the blood compared to other phenolic acids [15].

In addition to being widely used in medicine, some countries have approved it as a food additive to prevent lipid peroxidation [14]. Ferulic acid is also used for the production of vanillin [16,17] and preservatives [18] and as a cross-linking agent for the preparation of gels and edible films used in food industries [19,20]. It is widely applied in the cosmetic industry to protect skin from UV-induced damage [21,22]. Adding FA to the mixture containing ascorbic acid and tocopherol improved the chemical stability of these vitamins and enhanced skin photoprotection under solar-simulated irradiation [23].

Given its potential health benefits and several applications, ferulic acid has attracted considerable research interest and may be considered a biomolecule with strong prospects

as a functional food ingredient. Great attention is paid to its extraction from natural matrices and agro-industrial wastes for its various applications relating to human health and nutrition, particularly to achieve greater efficiency in the isolation of the free-form FA from plant materials and to increase its bioavailability. This review presents the recently available information on the extraction methods for quantifying ferulic acid in different samples, along with its bioavailability and stability in processing foods. The biological activities of FA are also described.

2. Extraction and Preconcentration of Ferulic Acid

In plant materials, ferulic acid is present in three forms: as soluble-free, soluble-conjugated (esterified to sugars and other low molecular mass compounds), and insoluble-bound FA as a constituent of arabinoxylan and lignocellulosic complexes (Figure 1) [24]. The FA content and distribution can vary a lot between the different varieties of plants, but most of this phenolic acid exists in the insoluble-bound form. Recovery of FA from natural sources requires the use of the appropriate extraction conditions with high quality and purity of the final product. Moreover, a detailed knowledge of the ferulic acid content in foods and pharmaceuticals is important to understand its potential for human health. The methods used for its determination have some limitations due to both spectral and background interferences, and often the low content of FA. To improve the detection capability and selectivity of analytical methods, the separation and preconcentration of FA from matrix samples are usually necessary before the final quantification.

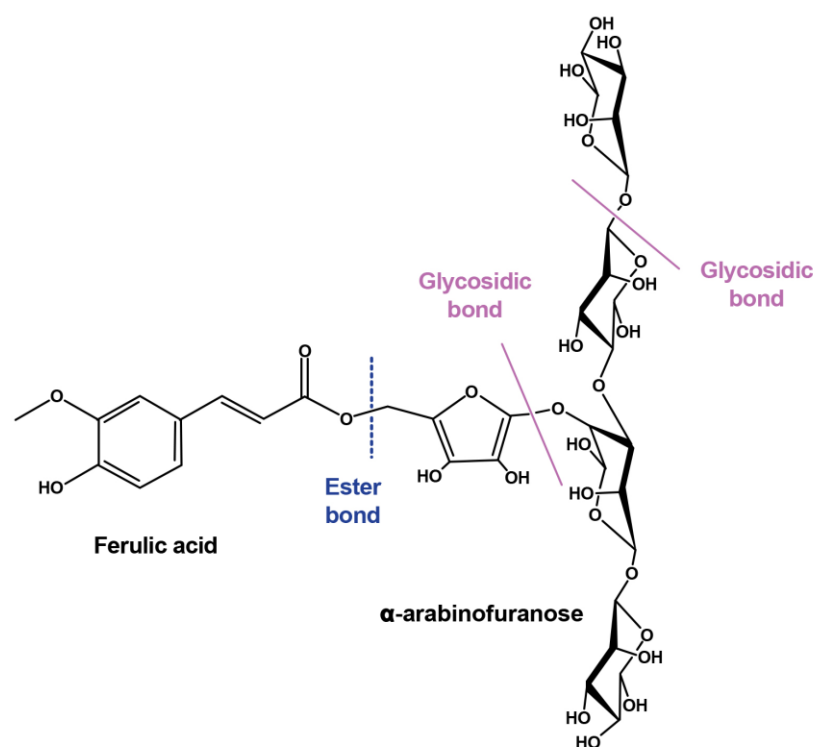


Figure 1. The structure of ferulic acid linked to arabinoxylans. Reprinted with permission from Ref. [24] 2021 Elsevier.

2.1. Recovery of Ferulic Acid from Natural Sources

Typical Soxhlet extraction is increasingly being replaced by advanced techniques to enhance its efficiency and selectivity. These techniques are generally faster and have higher automation levels. Several methodologies based on accelerated solvent extraction (ASE), microwave-assisted extraction (MAE), ultrasound-assisted extraction (USE), subcritical water extraction (SWE), and pressurized liquid extraction (PLE) have been used for the isolation of FA from plant materials, particularly from wheat-based foods [25–30]. Ap-

plication of mathematical and statistical methods to the analysis of chemical data, like experimental design, response surface analysis and principal component analysis, has often been used for determining the optimum extraction conditions as this process is influenced by several factors, such as the solvent type, temperature, extraction time, and liquid–solid ratio [29,30].

Free ferulic acid and its ester forms can be directly extracted using pressurized hot water or aqueous ethanol solution [25,31–33]. Pressurized water at 200 °C for 3.5 min extracted 17% of FA-free form from destarched wheat bran and the rest was covalent ester-bounded to arabinoxylans [25]. In terms of the extraction yield, no significant effect was observed with microwave heating used to intensify this process. However, it was stated that microwave power enhanced the FA extraction from tomatoes using 80% methanol [31]. Buranov et al. reported that using the SWE method resulted in higher amounts of FA being extracted from corn bran (432 ± 3 mg/100 g) compared to wheat bran (115 ± 5 mg/100 g) and flax shives (7.9 ± 3 mg/100 g) [32]. Papadaki et al. investigated the release and recovery of FA from wheat bran using hydrothermal treatment [34]. The best results were obtained when 10% of either citric acid or sodium carbonate (90 °C for 24 h) was applied. Based on chromatographic analysis, it was found that Na_2CO_3 extraction afforded products enriched in free ferulic acid, but the use of citric acid gave extracts enriched in a ferulate pentose ester [34].

Conjugated ferulic acid bound to the cell wall via an ester bond can be extracted using alkaline hydrolysis [17,27,32–36]. This process can cleave the lignin/phenolic-carbohydrate complexes structure, resulting in a phenolic portion, soluble sugars, insoluble lignin, and carbohydrates. Similar results were reported for pressurized and non-pressurized alkaline extractions using 0.5 M NaOH solution for wheat and corn bran [32]. The purification of FA from alkaline extracts was usually performed by its adsorption on a surface of a different solid material [17,33,37–39]. Ren et al. found that among the four tested carbon adsorbents, mesoporous carbon showed the highest adsorption capacity (238.5 mg/g of carbon) due to its high mesopore volume in comparison with powdered active charcoal (220 mg/g) and XAD-4 resin (49.98 mg/g) [38]. However, the purification methods using solid sorbents are expensive for industrial use; thus, purification of extracted FA by precipitation method is recommended where oily substances and hemicelluloses can be precipitated after ethanol addition [32].

Harsh chemicals and high temperatures are usually used for alkaline hydrolysis, thus representing the main limitation of its use in the pharmaceutical, cosmetic, and food industries. For this reason, enzymatic processes as alternative hydrolysis methods for the extraction of FA (in the free and conjugated forms) were applied [33]. The enzymes used differ in their specification in the degradation of plant cells. Feruloyl esterases, the most commonly used enzyme for the release of ferulic acid from agro-industrial by-products, cause the hydrolysis of the ester bond between FA and α -L-arabinofuranose in hemicellulose [40–43]. Commercial enzyme preparations are also used [42,44,45]. For instance, the enzymatic hydrolysis was performed by sequential biorefining, applying four hydrolytic enzymes under optimal conditions for each enzyme [44]. Among the enzymes tested, the superiority of multi-enzyme complex Viscozyme[®] L has been highlighted, as the maximal yield of 11.3 and 8.6 g/kg from rye and wheat bran was obtained, respectively [43]. To increase the accessibility of the enzymes and increase the dissolution of the plant structure, some preliminary steps before enzymatic hydrolysis have been explored, mostly by applying high temperatures and pressures (hydrothermal pretreatment) [41–43,46,47]. However, the main disadvantages of enzymatic hydrolysis are the cost of the enzymes and/or the reaction time. Additionally, for the process to be efficient, control of the reaction temperature and pH is required [48]. Table 1 presents recent examples of the extraction conditions for the isolation of ferulic acid from different natural sources.

Table 1. Recent examples of the extraction of ferulic acid from natural sources.

Sample	Extraction Conditions	FA Yields	Ref.
Wheat bran	SWE; 200 °C, 3.5 min	Total FA 78%	[24]
Wheat bran	Pressurized 20% (<i>v/v</i>) ethanol, 110 °C, 40 min SWE; 160 °C, 8 MPa, 74 min	226.8 ± 1.4 µg/g 381.6 µg/g	[25]
Brewery spent grain	Alkaline hydrolysis; 120 °C, 90 min, 2% (<i>w/v</i>) NaOH	46.17 mg/100 g	[28]
Corn bran Wheat bran Flax shives	SWE; 220 °C, 8 MPa, 57 min	432 ± 3 mg/100 g 115 ± 5 mg/100 g 7.9 ± 3 mg/100 g	[32]
Corn bran Wheat bran Flax shives	Alkaline hydrolysis; 0.5 M NaOH, 180 °C, 5.2 MPa, 57 min	2500 ± 50 mg/100 g 391 ± 50 mg/100 g 18 ± 1.0 mg/100 g	[32]
Wheat bran	Alkaline hydrolysis; 2M NaOH, 40 °C, 4 h 60% (<i>v/v</i>) ethanol, 90 °C, 24 h 10% (<i>w/v</i>) Na ₂ CO ₃ , 90 °C, 24 h 10% (<i>w/v</i>) citric acid, 90 °C, 24 h	2158.61 ± 112.02 µg/g 32.62 ± 2.52 µg/g 1822.97 ± 16.66 µg/g 344.52 ± 3.55 µg/g	[34]
Corn fiber	Ultraflo [®] X enzyme, pH 5, 55 °C Hydrothermal pretreatment 140 °C for 40 min + Ultraflo [®] X enzyme	0.13 ± 0.02% 4.9 ± 0.3%	[41]
Wheat bran	Hydrothermal and enzymatic pretreatment (Ac + Term), then enzymatic treatment with Dris and FAE (pH 6.4, 60 min)	0.528 ± 0.041 g/kg	[42]
Rye bran	Enzymatic treatment with multi-enzyme complex Viscozyme [®] L (citric buffer, 44 °C, 24 h)	11.3 g/kg	[44]
Palm pressed fiber	Deep eutectic solvent (CHCl-AA); MAE, 60 °C, 9 min	1.123 mg/g	[49]

SWE, subcritical water extraction; MAE, microwave assisted extraction; Ac, alcalase; Term, termamyl; Dris, driselase; FAE, feruloyl esterase; CHCl-AA, choline chloride-acetic acid solvent.

2.2. Preconcentration of Ferulic Acid for Analytical Determination

Among the different techniques that can be used for the determination of ferulic acid, solid-phase extraction (SPE) using various solid sorbents has been developed [38,50–52]. Besides the preconcentration, it can also be used for the matrix removal necessary in some procedures. SPE methods are considered to be superior to liquid–liquid extraction in terms of the simplicity, rapid phase separation, high enrichment factor, and the ability to combine them with different detection techniques. Moreover, they offer the possibility of direct combination with the final chromatographic analysis. The imprinted polymer coupled with HPLC was used for the selective enrichment and determination of ferulic acid in traditional Chinese medicine and biological samples [50] and in orange peels [51]. Dil et al. applied also molecularly imprinted polymer, albeit based on syringe-to-syringe magnetic solid-phase microextraction for FA preconcentration from pomegranate, grape, and orange samples [52].

Recently, room temperature ionic liquids (ILs) and deep eutectic solvents (DESs) were introduced as a new kind of alternative solvents for the preconcentration and/or purification of bioactive compounds [53–55]. ILs represent organic salts with a melting point generally below 100 °C, that consist entirely of ions, relatively bulky organic cations (imidazolium, pyridinium) with different tailorable characteristics, and small inorganic anions (Cl[−], Br[−], BF₄[−], PF₆[−]). DESs, formed from Lewis or Brönsted acids and bases,

exhibit physicochemical properties similar to ILs, such as negligible volatility and high thermal and chemical stabilities, but they are less toxic and more biodegradable. In a study by Wang et al., four hydrophobic ionic liquids with a PF_6^- anion and different cations based on imidazolium derivatives were examined [56]. The experimental results showed that the extraction efficiency of FA increased with the increase in the alkyl chain length from butyl to hexyl. The DES of choline chloride-acetic acid was used for ferulic acid isolation and preconcentration from palm-pressed fiber with microwave assistance [56].

3. Bioavailability of Ferulic Acid

The bioavailability of nutrients is an important factor as it is directly proportional to the positive effects they have on overall health. The bioavailable fraction is defined as the amount of ingested nutrients that are absorbed, distributed to organs and tissues, and then transformed into a biochemically active form that is effectively used by the organism [57–60]. For assessing the bioavailability, most science researchers investigated the main factors that affect bioavailability, such as the bioaccessibility, absorption, and potential transformation of a provides biomolecules. The term bioaccessibility refers the fraction of an ingested biocomponent that is potentially available for absorption and used for storage and metabolic function. As bioaccessibility falls within the scope of bioavailability and both concepts are similar, it has been suggested that. they could be grouped in a broader definition as bioefficiency [60].

Several procedures were applied for the evaluation of the nutrients' bioavailability, including in vitro methodologies (simulated gastrointestinal digestion, Caco-2 cell assay) and in vivo approaches such as measuring their levels in the blood or tissues [59,60]. Only compounds that are released from the food matrix by the action of digestive enzymes (small intestine) and bacterial microflora (large intestine) are available for absorption, e.g., potentially bioavailable [59,61].

Ferulic acid is mostly bound to arabinoxylans and other indigestible polysaccharides and its bioavailability is limited due to the poor intrinsic distribution rate [15,62,63]. Anson et al. investigated the bioaccessibility of ferulic acid from different wheat fractions and bread using a dynamic system that simulates the upper gastrointestinal transit [62]. The results showed the low bioaccessibility of FA from the wheat fractions and bread (<1%). However, the bioaccessibility was high (~60%) when free FA was added to flour. Raj and Singh reported that the presence of lipids had a considerable effect on the bioavailability of drugs containing FA due to their pH-dependent solubility profile [63]. Simulated in vitro upper gastrointestinal digestion increased the percentage of free FA for bread (3.12% to 15.44%), cookies (6.00% to 17.55%), and pasta (1.78% to 8.62%) [64]. This increase in the potential bioaccessibility was noticeable within the first hour of this process.

The bioavailability of the bioactive compounds is also influenced by food processing, such as mechanical or thermal treatment, extrusion cooking, and bioprocessing, which alters the matrix [65–71]. The thermal action of boiling increased the extractability of FA, possibly through the loosening of the food matrix and breaking the bonds between phenolic acid and the cell wall components. The content of free FA in whole-grain, hullless raw barley varieties in the range of 5.39–8.16 $\mu\text{g/g}$ dry weight, while after boiling for 40 min the range of 7.94–12.58 $\mu\text{g/g}$ was determined [65]. After simulated gastric digestion (with α -amylase, pepsin, and pancreatin), the major bioaccessible phenolic was ferulic acid. Its bioaccessibility (calculated as the amount of FA in the digested samples divided by its amount in boiled samples) ranged from 131 to 173%. Thus, boiling enhanced the extractability of bound phenolic acid, while digestion increased its free-form content.

Pumpkin leaves were subjected to different household cooking methods (boiling, microwaving, steaming, and stir-frying) to evaluate their effect on the phenolic compounds, antinutrients (tannins, phytates, and oxalates), and antioxidant properties [66]. All the used cooking methods significantly reduced the antinutrients (oxalates by more than 50%, tannins by 47%, and phytates by 79%) and antioxidant activities, whilst the content of

ferulic acid was significantly increased. Steaming (91.8 mg/kg) and boiling (103.90 mg/kg) resulted in the highest concentrations of FA compared to the other cooking methods.

Kongkachuichai et al. studied the effect of different processing conditions such as germination, parboiling, and polishing on the ferulic acid content in various landrace brown rice varieties from Thailand [67]. The ferulic content ranged from 9.94 to 14.98 mg/100 g for raw rice, 10.35 to 16.30 mg/100 g for parboiled rice, 10.24 to 17.77 mg/100 g for germinated parboiled rice, and 3.06 to 5.19 mg/100 g for polished samples, respectively. According to this study, the polishing process strongly removed 65–73% of ferulic acid as it is mostly located in the outer layer of rice grain. The effect of the parboiling hydrothermal process on the ferulic acid content was not significant, but together with germination, it reduced the glycemic index (GI); thus, it could be beneficial for health promotion. The changes in the FA contents were also not significant during the whole wheat bread-making process [68]. The use of low temperatures during the fluidized bed-drying process of paddy black rice is essential for obtaining a low glycemic index, but this process does not favor the bioaccessibility of ferulic acid in the rice grains [70].

Generally, food-processing treatment under high temperature and pressure increased the content of the bound form of ferulic acid and free FA, but to a much lesser extent due to the partial decomposition of the plant matrix. The degree of this effect depends on the cell wall structure and its chemical composition [69,70]. During these processes, the content of other compounds is also changing. It has an impact on the antioxidant activity of the obtained hydrolysate. On one side, food processing could liberate more compounds with significant antioxidant activity, but on the other side, it is well known that polyphenolic compounds can be degraded under these treatments. Mashitoa et al. reported that all household cooking methods reduced the total antioxidant activities of pumpkin extracts [66], while opposite results were obtained for cooking rice under high pressure [71]. Although some research has been conducted on the effects of different kinds of processing methods on the contents of phenolic compounds, including FA, little work has described the impacts of its bioavailability. Even with a high content of FA being determined in raw or cooked cereal and rice grains, only a small fraction was available for absorption in the gut [61,69].

4. Biological Activity

The biological and pharmacological properties of ferulic acid have been extensively studied to reveal its antioxidant, anti-inflammatory, anticancer, antiallergic, and antiviral effects, protective properties against cardiovascular disorders, and neurodegenerative properties, among others [4,72,73]. This wide range of biological activities has strong beneficial effects on the human body and is mostly attributed to the powerful free radical scavenging activity of FA. Examples of its main biological activities are presented in Figure 2. Interested readers can find more specific information regarding the biological activities of ferulic acid and the results of the preclinical studies in the recent review papers [9,15,74].

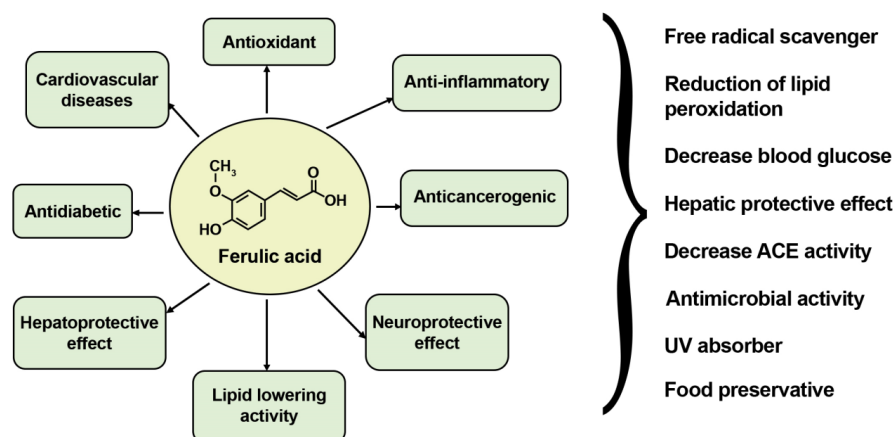


Figure 2. Main biological activities of ferulic acid.

4.1. Free Radical Scavenging

Several researchers have examined the antioxidant activity of FA using various assays [6,13–15,75,76]. Its antioxidant properties are mainly expressed by direct free radical scavenging or indirectly by increasing the activity of antioxidant enzymes, such as superoxide dismutase, catalase, or glutathione peroxidase [77]. In a living organism, reactive oxygen species (ROS) can contribute to oxidative stress, i.e., an imbalance between ROS production and the ability of cells to detoxify the reactive intermediates [78]. The increase in ROS is positively related to the pathology of many diseases. As a secondary antioxidant, ferulic acid and its derivatives can also bind transition metal ions, such as iron and copper, preventing the formation of toxic hydroxyl radicals, which lead to cell membrane peroxidation. Thus, some methods that are used to study the antioxidant activity of a given compound or a natural sample are concerned with electron or radical screening, whereas others are focused on their reducing ability [79]. Zhang et al. reported that the presence of different ester derivatives does not greatly change the antioxidant capacity of ferulic acid [80]. The extracts after hydrothermal treatment in the presence of citric acid (enriched in the ferulate pentose ester) were more active in antiradical activity than water or 60% ethanol extracts [34].

Das et al. evaluated the properties of FA for free radical scavenging, reducing activity, and iron chelation using different assays (Figure 3) [81]. FA at low concentrations had much higher DPPH radical-scavenging power than ascorbic acid (as control), while at concentrations below 200 μM , both compounds showed similar effects (Figure 3A). The reducing activities of FA and ascorbic acid were comparable (Figure 3B). The hydroxyl radical-scavenging activity of ferulic acid at a concentration of up to 150 μM was higher than quercetin, which was reversed at higher concentrations (Figure 3C). FA had fairly higher NO scavenging activity as compared to quercetin (Figure 3D) and also higher iron chelating ability in comparison to EDTA (Figure 3E).

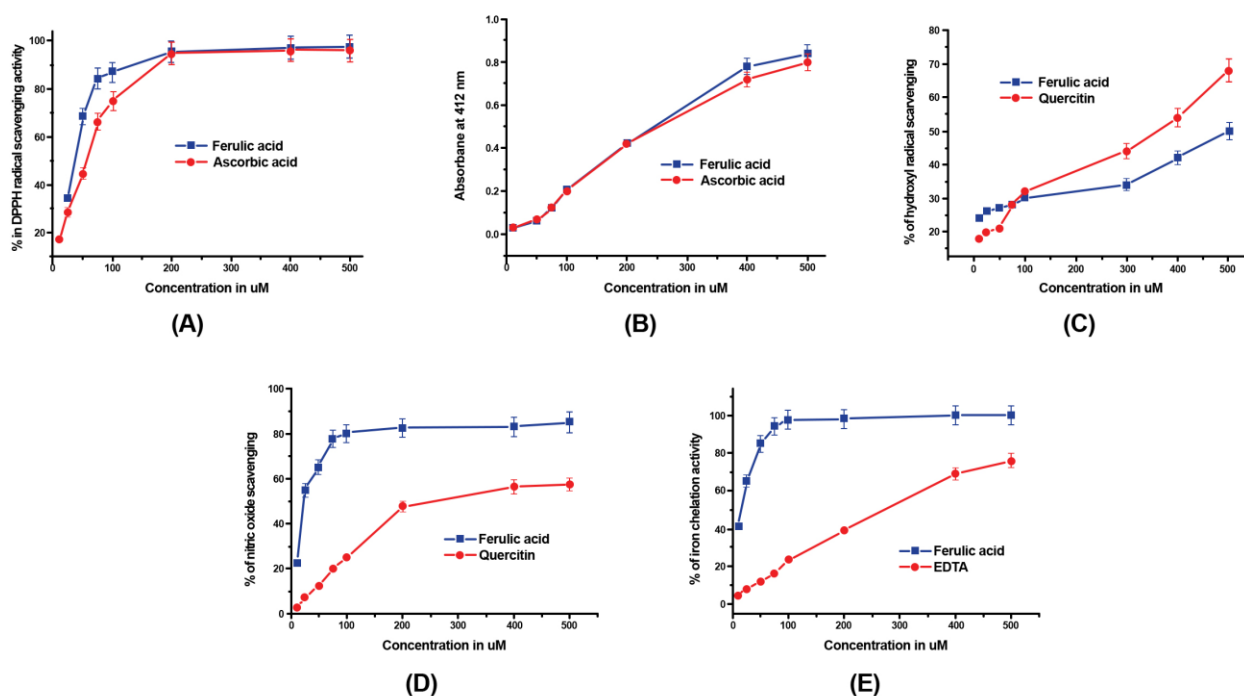


Figure 3. In vitro antioxidant activity of ferulic acid. (A) DPPH radical-scavenging activity of FA in comparison to ascorbic acid control. (B) Reducing activity of FA in comparison to ascorbic acid control. (C) Hydroxyl radical-scavenging activity of FA compared to quercetin control. (D) NO-scavenging activity of FA in comparison to quercetin. (E) Iron chelation activity of FA compared to the EDTA control. $p < 0.05$ was considered significant (error bars represent the SEM values of four independent experiments) [81]. Reprinted with permission from ref. [81]. 2016 Taylor & Francis.

However, while the antioxidant capacity of ferulic acid is limited by its relatively low solubility in hydrophobic media, several research efforts are being made to enhance the therapeutic benefits of ferulic acid. Adeyemi et al. synthesized ester and amide derivatives of ferulic acid, showing that these compounds had excellent antioxidant capacity and demonstrated strong inhibitory potential [82]. Another approach is to entrap ferulic acid in solid lipid nanoparticles or bind it to other therapeutic agents through organic moieties, which serve as carriers [74,83–86].

4.2. Anticancer Activity

Ferulic acid shows anticancer activity by inhibiting the proliferation and migration of various malignant tumors [87–89]. FA can cause mitochondrial apoptosis by inducing the generation of intracellular reactive oxygen species, acting on a series of intracellular and extracellular targets, and being involved in the regulation of tumor cell signaling pathways. Gao et al. found that FA can significantly inhibit proliferation and invasion in Hela and Caski cervical cancer cells in a concentration-dependent manner [90]. The combination of ferulic acid and some known chemotherapeutic drugs exhibits maximum therapeutic efficiency, minimal side effects, and overcomes drug resistance [91,92].

The administration of FA to male adult rats showed a dose-dependent protective effect against cisplatin-induced ototoxicity, indicating a biphasic response (hormetic effect), where being pro-oxidant at lower concentrations and antioxidant at higher concentrations promoted chemoresistance [93]. The lowest dose of 75 mg/kg had no protective effect, whereas starting from the dose of 150 mg/kg, FA attenuated cisplatin-induced hearing loss. The evidence of an FA-induced hormetic dose response in the treatment of inflammation was also discussed by Barreiro-Sisto et al. [94].

Nanocarriers can overcome the restriction of anticancer drug action by body barriers (such as the blood-brain barrier and blood–eye barriers), reduce drug doses, and improve availability [11,84,86,95]. Lipids, polysaccharides, polymers, dendrimers, and certain enzymes are the most common base materials used for the production of novel formulations with FA [96]. Sweed et al. obtained polymeric mixed micelles loaded with FA and investigated their potential concerning colon cancer [86]. The results reported by El-Gregory et al. revealed that both polymeric and lipidic nanocapsules of FA showed favorable anticancer properties [97]. The lipidic nanomaterial was smaller in size and presented a higher cumulative percent release of FA on the cellular level.

4.3. Cardiovascular Diseases

Cardiovascular disease (CVD) is a global term used for the group of diseases affecting the heart and/or blood vessels, such as coronary artery disease, cerebrovascular disease, peripheral artery disease, congenital heart disease, hypertension, heart failure, and stroke [98]. Consumption of various plant infusions rich in hydroxycinnamic acids has been associated with a lower risk of CVD due to their anti-hypertensive effect, capacity to reduce blood viscosity, and modulation of platelet function [98,99].

The cardioprotective effects of ferulic acid against various drugs and toxic agents (such as isoproterenol, cyclophosphamide, doxorubicin, streptozotocin, and arsenic species) demonstrated in animals and cell-line models have recently been summarized by Pandi et al. [100]. For example, the modulatory role of FA against arsenic-induced cardiotoxicity could be due to its ability to improve antioxidants, adenosine triphosphate (ATP) levels, and modulation of the AMP-activated protein kinase signaling pathway. Modulation of oxidative stress, together with inflammation, endoplasmic reticulum stress, calcium homeostasis, and renin, also played a major role in the cardioprotective efficacy of FA against doxorubicin.

4.4. Diabetes

Diabetes mellitus (DM) is a multisystem disease mainly characterized by high glucose levels in the blood (termed hyperglycemia), deficiency of insulin secretion, or insulin re-

sistance. Too high a level of sugar in the blood can lead to serious health problems, such as heart disease, stroke, high blood pressure, atherosclerosis, and other diabetic complications [101]. Thus, the multisystem pathophysiology of diabetes requires a multifaceted approach to treatment that combines therapies with complementary mechanisms of action [102,103]. New therapeutics as well as medicinal natural products with high efficiency and negligible toxic effects are constantly in demand [104]. As ferulic acid defends against free radical damage and inflammation, it was also suggested that it plays a crucial role in controlling DM and its complications [101,104,105].

Ferulic acid could be used as a potential therapeutic drug in diabetic nephropathy (denotes disease or damage of the kidney) [106], neuropathy (when nerve damage leads to pain, numbness and tingling in the feet or hands) [107], cardiomyopathy that affects the heart muscle [108], retinopathy (involves the growth of abnormal blood vessels in the retina) [109] and hypertension [13].

4.5. Other Activities

Ferulic acid also has neuropharmacological applications due to its antioxidant, anti-inflammatory, neuroprotective and antiapoptotic effects, among others [110]. The neuroprotective effect of ferulic acid has been studied in many diseases, like epilepsy, Alzheimer's and Parkinson's diseases. Sgarbossa et al. presented the role of ferulic acid as an inhibitor or disaggregating agent of amyloid structures, which play a central role in the development and progress of Alzheimer's disease, both in oligomer and fibril forms [111].

Ferulic acid has a protective role in relation to the main skin structures, such as keratinocytes, fibroblasts, collagen, and elastin. It inhibits melanogenesis, enhances angiogenesis, and accelerates wound healing. The applications of FA on the skin mainly aim for protection from aging, sun damage, and skin cancer [112].

5. Conclusions

Ferulic acid is a widespread phenolic phytochemical present in the seeds, leaves, and fruits, both in its free form and conjugated to the plant cell wall polysaccharides, carbohydrates, glycoproteins and lignins. The amount of ingested FA that is potentially available for adsorption is greatly dependent on its release from the food matrix. Bound forms of ferulic acid are converted by the intestinal microflora for adsorption and further metabolized in the liver. Similarly, the effective recovery of free ferulic acid from natural sources and agro-industrial waste requires the use of hydrothermal treatment, alkaline or enzymatic hydrolysis, and probiotic fermentation due to its covalently linking to lignins and other biopolymers. The intensification of these processes in terms of the extraction yields needs further investigation. The combination of treatment methods under optimized conditions seems to have great potential in the extraction of ferulic acid from natural sources.

The regular intake of whole grains of cereals, maize or rice, which are rich in FA, can reduce the risk of many chronic diseases. Ferulic acid has demonstrated antioxidant, anticarcinogenic, antidiabetic, anti-inflammatory, hepatoprotective, neuroprotective, and antibacterial activities according to several cited studies. Its ability to remove free radicals by balancing unpaired electrons, reduce substances by giving either an electron or a hydrogen atom, and interfere with numerous oxidative reactions are examples of its health-promoting properties. Although a variety of reported studies have confirmed the efficacy of FA in the management of several human disorders, only a few studies were carried out in humans, mostly using foods containing this compound [113,114]. Thus, the clinical effects of ferulic acid need to be tested in the future for the complete evaluation of its therapeutic potential in chronic diseases.

The still limited therapeutic use of FA is a result of its poor pharmacokinetic properties after oral administration, such as the short resistance duration, quick renal clearance, low plasma levels and low bioavailability. The strategies proposed to overcome this problem mostly apply to the inclusion of FA in a nanocarrier, which improves its stability and controls release. A wide range of nano-formulations with lipids, polymers or chi-

tosan conjugate have been investigated and developed, trying to maximize the effects of ferulic acid [75].

As ferulic acid is a naturally occurring potent antioxidant, dietary supplementation seems to be an effective strategy to delay ageing, for example. Many such products are commercially available without a prescription. However, taking into consideration the potential of FA as a diet supplement, attention should be paid to its dose as its excessive and uncontrolled consumption may induce negative effects. Truzzi et al. reported high FA contents in two supplements as 1.3695 ± 0.140 mg/g and 1.8494 ± 0.180 mg/g, which contain dry blueberry extract and dry extract from an apple, respectively [115]. They were higher than the relative contents found in fruit and flour. In addition, it was shown using three different cell lines in an in vitro cell model that ingestion of ferulic acid at the dose of ≥ 40 mg/L could induce negative effects on the intestinal wall's integrity.

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