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Review

Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: A review

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Abstract

Ferulic acid (FA) is an abundant dietary antioxidant which may offer beneficial effects against cancer, cardiovascular disease, diabetes and Alzheimer's disease. The impact of FA on health depends on its intake and pharmacokinetic properties. In this article, the literature pertaining to chemistry, natural sources, dietary intake and pharmacokinetic properties of FA is critically reviewed. High levels of FA are found in both free and bound forms in vegetables, fruits, cereals, and coffee. We have estimated that consumption of these foods may result in approximately 150–250 mg/day of FA intake. FA can be absorbed along the entire gastrointestinal tract and metabolized mainly by the liver. The absorption and metabolism of FA seem to be dose dependent at least in experimental settings. Further pharmacokinetic and pharmacodynamic studies are required to characterize the impact of FA on human health.

Keyword: Ferulic acid; Phenolic acids; Pharmacokinetics; Dietary intake; Absorption; Metabolism; Bioavailability; Antioxidant

Contents

1. Introduction

Ferulic acid (4-hydroxy-3-methoxycinnamic acid, Fig. 1) is a ubiquitous phenolic compound in plant tissues, therefore, it constitutes a bioactive ingredient of many foods. Many staple foods such as grain bran, whole grain foods,

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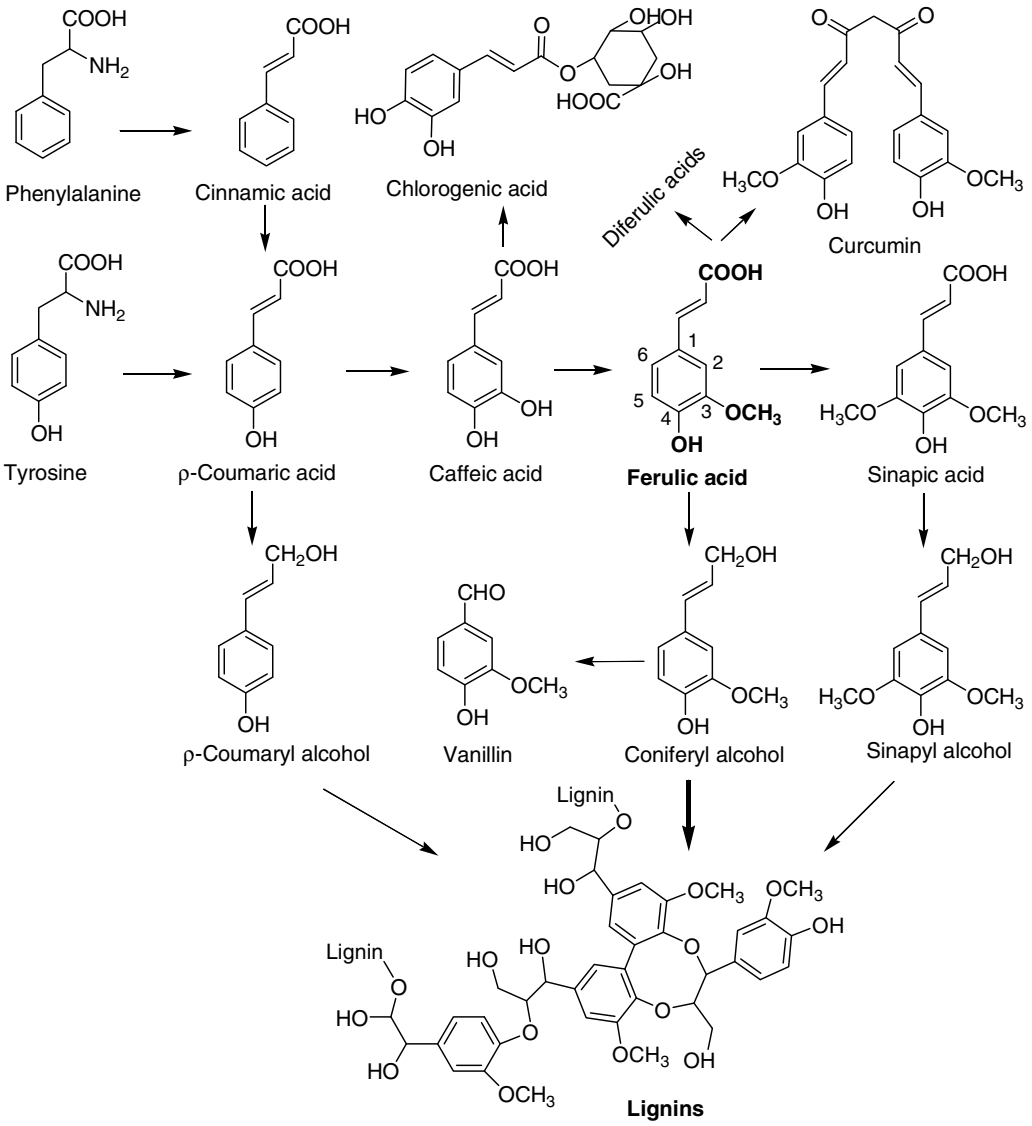

Fig. 1. Chemical structure and synthesis of ferulic acid and related compounds in plants (Fukuda & Komamine, 1982; Graf, 1992; Kroon & Williamson, 1999; Whetten & Sederoff, 1995).

citrus fruits, banana, coffee, orange juice, eggplant, bamboo shoots, beetroot, cabbage, spinach and broccoli are among the rich sources of FA (Clifford, 1999; Graf, 1992; Mattila & Hellstrom, 2007; Mattila, Hellstrom, & Torronen, 2006; Mattila, Pihlava, & Hellstrom, 2005; Nishizawa, Ohta, Egashira, & Sanada, 1998; Sakakibara, Honda, Nakagawa, Ashida, & Kanazawa, 2003). In addition to dietary intakes, natural extracts of herbs, spices, and coffee are other major sources of FA intake in Western countries (Graf, 1992; Virgili et al., 2000). Furthermore, FA has been approved as an additive antioxidant and food preservative in Japan (Graf, 1992; JFCRF, 1996). Sodium ferulate, a salt of ferulic acid, is used in China for treatment of cardiovascular and cerebrovascular diseases (Wang & Ou-Yang, 2005).

FA was first isolated from a commercial resin in 1866 and chemically synthesized in 1925 (Graf, 1992). However, its biological effects started to be noticed in 1970s when Japanese researchers discovered the antioxidant properties of FA steryl esters extracted from rice oil (Yagi & Ohishi, 1979). This property of FA was one of the main reasons that Chinese researchers investigated the potential anti-atherosclerotic effects of FA (Yin & Xu, 1980; Zhang, 1990). Promising data from these early studies resulted in significant increases in the investigations of understanding of FA biological effects over the past 10 years.

One of the best documented biological activities of FA is its antioxidant properties. Due to its phenolic nucleus and an extended side chain (Fig. 1), FA readily forms a resonance stabilized phenoxy radical which accounts for its free radical-scavenging effect (Graf, 1992; Palacios, 1990). This enables FA to protect DNA and lipids against oxidation through reactive oxygen species (ROS) (Andreasen, Landbo, Christensen, Hansen, & Meyer, 2001b; Anselmi et al., 2004; Bourne & Rice-Evans, 1997; Dinis, Santosa, & Almeida, 2002; Kanski, Aksenova, Stoyanova, & Butterfield, 2002; Kuenzig et al., 1984; Maurya & Nair, 2006; Nar-

Table 1
The levels of ferulic acid in grains, fruits, vegetables, and commercial foods[a]

	FA contents[b] (mg/100 g)	Serving size(g)	Mg/serving	References
Grains				
Refined corn bran	2610–3300	5	130–151	Saulnier and Thibault (1999), Zhao et al. (2005)
Barley extract	1358–2293	5	68–115	Madhujith and Shahidi (2006)
Soft and hard wheat bran	1351–1456	5	68–73	Liyana-Pathirana and Shahidi (2006)
Rice endosperm cell wall	910	5	45	Shibuya (1984)
Fine wheat bran	530–540	5	26–27	Kroon et al. (1997), Andreasen et al. (2001a)
Rye bran	280	5	14	Mattila et al. (2005), Andreasen et al. (2001a)
Corn, dehulled kernels	174	30	52.2	Adom and Liu (2002)
Whole wheat kernels	64–127	30	19–38	Nishizawa et al. (1998), Adom and Liu (2002)
Whole-wheat flour	89	30	26.7	Mattila et al. (2005)
Whole grain rye flour	86	30	25.8	Mattila et al. (2005)
Whole brown rice	42	30	8.7–12.6	Nishizawa et al. (1998), Adom and Liu (2002)
Corn flour	38	30	11.4	Mattila et al. (2005)
Whole oats	25–35	30	10.5	Adom and Liu (2002), Mattila et al. (2005)
Whole grain barley flour	25–34	30	7.5–10	Nishizawa et al. (1998), Mattila et al. (2005)
Oat bran	33			Mattila et al. (2005)
Fruits				
Grapefruit	10.7–11.6	125	13.4–14.6	Mattila et al. (2006)
Orange	9.2–9.9	125	11.5–12.5	Mattila et al. (2006)
Banana	5.4	125	6.75	Mattila et al. (2006)
Berries	0.25–2.7	125	0.6–3.4	Mattila et al. (2006)
Rhubarb	2	125	2.5	Mattila et al. (2006)
Plum, dark	1.47	125	1.8	Mattila et al. (2006)
Apples	0.27–0.85	125	0.3–1	Mattila et al. (2006)
Vegetables				
Bamboo shoots	243.6	50	122	Nishizawa et al. (1998)
Water dropwort	7.3–34	200	14.6–68	Sakakibara et al. (2003)
Eggplant	7.3–35	200	14.6–70	Sakakibara et al. (2003)
Redbeet	25	100	25	Mattila and Hellstrom (2007)
Burdock	7.3–19	100	7.3–19	Sakakibara et al. (2003)
Soyabean	12	125	15	Mattila and Hellstrom (2007)
Peanut	8.7	60	5.22	Mattila and Hellstrom (2007)
Spinach/frozen	7.4	200	14.8	Mattila and Hellstrom (2007)
Redcabbages	6.3–6.5	200	12.6–13	Mattila and Hellstrom (2007)
Tomato	0.29–6	200	0.6–12	Bourne and Rice-Evans (1998), Mattila and Hellstrom (2007)
Radish	4.6	100	4.6	Mattila and Hellstrom (2007)
Broccoli	4.1	200	8.2	Mattila and Hellstrom (2007)
Carrot	1.2–2.8	100	1.2–2.8	Mattila and Hellstrom (2007)
Parsnip	2.2	200	4.4	Mattila and Hellstrom (2007)
Mizuna	1.4–1.8	200	2.8–3.6	Sakakibara et al. (2003)
Pot grown basil	1.5	200	3	Mattila and Hellstrom (2007)
Chinese cabbage	1.4	200	2.8	Mattila and Hellstrom (2007)
Pot grown lettuces	0.19–1.4	200	0.4–2.8	Mattila and Hellstrom (2007)
Green bean/fresh	1.2	200	2.4	Mattila and Hellstrom (2007)
Avocado	1.1	200	2.2	Mattila and Hellstrom (2007)
Commercial foods and beverages				
Sugar-beet pulp	800	10	80	Micard, Grabber, Ralph, Renard, and Thibault, (1997)
Popcorn	313	60	187.8	Nishizawa et al. (1998)
Whole grain rye bread	54	35	18.9	Mattila et al. (2005)
Whole grain oat flakes	25–52	35	8.75–18	Mattila et al. (2005), Nishizawa et al. (1998)
Sweet corn	42	60	24	Nishizawa et al. (1998)
Pickled red beet	39	25	9.75	Mattila and Hellstrom (2007)
Rice, brown, long grain parboiled	24	125	30	Mattila et al. (2005)
Coffee	9.1–14.3	200	18.2–28.6	Mattila et al. (2006), Nardini, Cirillo, Natella, and Scaccini (2002)
Boiled spaghetti	13.6	100	13.6	Nishizawa et al. (1998)
Pasta	12	100	12	Mattila et al. (2005)
White wheat bread	8.2	35	2.87	Mattila et al. (2005)

(*continued on next page*)

Table 1 (*continued*)

	FA contents[b] (mg/100 g)	Serving size(g)	Mg/serving	References
Orange juice	3–6.4	200	6–13.4	Mattila et al. (2006), Rapisarda, Carollo, Fallico, Tomaselli, and Maccarone (1998)
Pickled red cabbage	1.5	50	0.5	Mattila and Hellstrom (2007)
Bear	0.24–0.9	500	1–4.5	Bourne and Rice-Evans (1998), Mattila et al. (2006)

[a] The data are mean or a range of mean values reported. The data are total FA except for Sakakibara et al. (2003) which reported free FA. Total FA in the materials was detected by HPLC after absolute alkaline hydrolysis except for Madhujith and Shahidi (2006) and Liyana-Pathirana and Shahidi (2006), which reported that total FA was detected by Folin–Ciocalteu's reagent. Free FA was detected by HPLC without hydrolysis.

[b] The contents were calculated by 100 g fresh edible part of foods except that Nishizawa et al. (1998), reported by 100 g dry matter.

dini et al., 1995; Ogiwara et al., 2002; Ohta, Semboku, Kuchii, Egashira, & Sanada, 1997; Srinivasan et al., 2006). Thus, FA may be beneficial in prevention and/or treatment of disorders linked to oxidative stress, including Alzheimer's disease (Jin et al., 2005; Kim et al., 2004; Ono, Hirohata, & Yamada, 2005; Perluigi et al., 2006; Sultana, Ravagna, Mohmmad-Abdul, Calabrese, & Butterfield, 2005; Yan et al., 2001), diabetes (Balasubashini, Rukkumani, & Menon, 2003; Balasubashini, Rukkumani, Viswanathan, & Menon, 2004; Ohnishi et al., 2004), cancers (Asanoma et al., 1994; Chang et al., 2006; Kampa et al., 2004; Kawabata et al., 2000; Mori et al, 1999; Tanaka et al., 1993; Taniguchi, Hosoda, Tsuno, Maruta, & Nomura, 1999), hypertension (Suzuki et al., 2002; Suzuki et al., 2007), and atherosclerosis (Dinis et al., 2002; Hiramatsu, Tani, Kimura, Izumi, & Nakane, 1990; Ohta et al., 1997; Wang & Ou-Yang, 2005; Wang et al., 2004). The strong link between inflammation and oxidative stress suggests that FA may also be effective against inflammatory diseases (Chawla, Singh, Murthy, Gupta, & Singh, 1987; Fernandez, Saenz, & Garcia, 1998; Murakami et al., 2002; Ozaki, 1992; Sakai, Ochiai, Nakajima, & Terasawa, 1997). Furthermore, the special structure of FA also endows its strong UV absorptive ability, making it an important skin protecting agent (Chan et al., 2004; Lin et al., 2005; Saija et al., 1999).

The preventive/therapeutic efficacy of FA is dependent on its physiological concentrations, which is predominated by its pharmacokinetic properties (absorption, metabolism, distribution and elimination). Thus, the aim of this study was to critically review and summarize available information on chemistry, dietary sources and pharmacokinetic characteristics of FA for a better understanding of its potential applications in health and disease.

2. Natural sources

FA is one of the metabolites of the biosynthesis of lignin from phenylalanine and tyrosine in plants (Fig. 1) (Fukuda & Komamine, 1982; Graf, 1992; Kroon & Williamson, 1999; Whetten & Sederoff, 1995). It is found in plant tissues in two forms: free and conjugate; the sum of these two forms indicates total FA. FA is usually concentrated in the bran of grains, peel of fruits, and roots and peel of vegetables (Clifford, 1999; Herrmann, 1989). Similarly, measurable concentrations of FA were detected in edible parts of all of 8 grain types, 44 out of 45 vegetable types, all of 14 potato types, 22 out of 24 fruit types, and in 25 out of 29 berry types tested (Mattila & Hellstrom, 2007; Mattila et al., 2005, 2006). The levels of FA in a number of these foods are summarized in Table 1.

In most vegetables and fruits, FA is found in a conjugated form of hydroxyl acids like quinic acid (in coffee, cabbage, celery and carrots), glucaric and galataric acids (in citrus), tartaric acid (in grape), and malic acid (in radish), or with mono/disaccharides like glucose (in apple and cabbage), digalactose (in spinach) and gentiobiose (in broccoli) (Buchanan, Wallace, Fry, & Eastwood, 1996; Clifford, 1999; Herrmann, 1989). In root vegetables and grains, FA mainly occurs in pectic or hemicellulosic polysaccharides through its dimers (di-ferulic acid), and/or esterified with arabinose and galactose residues (Mathew & Abraham, 2004; Saulnier & Thibault, 1999). In grains, FA may also be esterified with sterols; one well-known example is FA-oryzanol. It consists primarily of cycloartenol and 24-methylenecycloartanol. In some vegetables such as burdock, water dropwort, and eggplant, free FA accounts for 50–90% of total of FA (Sakakibara et al., 2003). However, the percentage of free FA in cereals only accounts for 0.1–0.5% (Adom & Liu, 2002).

3. Dietary intake

Accurate information on the intake of FA is lacking. Scalbert and Williamson (2000) estimated the daily intake of total polyphenols to be about 1000 mg in subjects who consume fruits, vegetables, and phenolic acid-containing beverages. Clifford (1999) reported that people with a habit of consuming coffee, cereal bran, citrus fruits and beer may ingest daily 500–1000 mg caffeic acid and FA. Consumption of whole grains significantly contributes to daily intake of FA up to 167 mg (35–89 mg total FA/100 g grain, Table 1). Other dietary sources of FA may include coffee, orange juice, eggplant, water dropwort, cabbage, broccoli, spinach, radish, potato, tomato, banana, orange, grapefruit, soy bean, and peanut supplying 5–70 mg FA/100 g (Table 1, data not shown when FA < 1 mg/100 g). Therefore, one can estimate that the sum of FA intake through consumption of cereals, vegetables, fruits, coffee, and juices may reach 150–250 mg/d.

4. Pharmacokinetic properties of FA

4.1. Absorption

In situ or *ex vivo* absorption models suggest that FA can be absorbed from the stomach (Zhao, Egashira, & Sanada, 2004), jejunum (Spencer et al., 1999; Wolffram, Weber, Grenacher, & Scharrer, 1995), and ileum (Spencer et al., 1999). After a 25-min incubation of FA in the rat stomach, >70% of the FA disappeared from the stomach and it was recovered in the gastric mucosa, blood, bile and urine, suggesting a fast gastric absorption of FA (Zhao et al., 2004). Similarly, FA quickly disappeared from the jejunum and to a significantly lesser extent from the ileum when it was perfused in an isolated rat intestine model (Spencer et al., 1999). Only 0.5–0.8% of ingested FA was found in feces of rats, indicating very efficient absorption rate for FA (Adam et al., 2002; Jung & Fahey, 1983; Zhao, Egashira, & Sanada, 2003a).

The exact mechanism for this high absorption rate is not known. The fact that FA could move into the gastric mucosa even at 0 °C suggests that FA might diffuse across the stomach mucosa (Zhao et al., 2004). The suggested pK_a of 4 for FA indicates that low gastric pH facilitates the transportation of FA in an undissociated form via a passive diffusion mechanism (Tsuji & Tamai, 1996). However, this mechanism may not be true for intestinal absorption of FA, mainly because FA does not maintain its unassociated form in a natural or weak acidic environment of the intestine (pH > 5). One *in situ* study reported that FA absorption in the rat intestine was directly proportional to the perfused concentrations up to 50 μmol/L (Adam et al., 2002). Other *in vitro* or *ex vivo* studies have suggested an H^+-driven transport system for the uptake of cinnamic acid and structurally related substances such as ferulic acid and ρ-coumaric acid (Itagaki et al., 2005; Konishi & Shimizu, 2003; Wolffram et al., 1995). However, such transporters have not been identified. Wolffram showed the involvement of an Na^+-dependent, carrier-mediated transport process in the uptake of cinnamic acid and ferulic acid across the brush border membrane of rat jejunum (Wolffram et al., 1995). On the other hand, such mechanisms were not observed in Caco-2 cell monolayers (Konishi & Shimizu, 2003). Instead, Konishi showed that FA might be transported across the intestinal epithelial cells by monocarboxylic acid transporters (MCTs). In contrary, their recent study showed that MCT1, one of the best characterized subtypes of MCTs, was not involved in the absorption of FA in Caco-2 (Watanabe, Yashiro, Tohjo, & Konishi, 2006).

4.2. Metabolism

Metabolic studies (Adam et al., 2002; Booth, Emerson, Jones, & Deeds, 1957; Chang, Xu, Tao, & Feng, 1993; Choudhury, Srai, Debnam, & Rice-Evans, 1999; Rondini, Peyrat-Maillard, Marsset-Baglieri, & Berset, 2002; Teuchy & Van Sumere, 1971; Zhang, Zhang, & Zhou, 2005; Zhao, Egashira, & Sanada, 2003b; Zhao et al., 2004) have shown that FA can be metabolized *in vivo* into a number of metabolites including FA-glucuronide, FA-sulfate, FA-diglucuronide, FA-sulfoglucuronide (FA-diconjugate with sulfate and glucuronide), *m*-hydroxyphenylpropionic acid, feruloylglycine, dihydroferulic acid, vanillic acid and vanilloylglycine (Fig 2). Conjugated FA including FA-glucuronide, FA-sulfate and FA-sulfoglucuronide are the major metabolites in the plasma and urine of rats (Rondini et al., 2002; Zhao et al., 2003b). These results suggest that the conjugation reaction with glucuronic acid and/or sulfate is the principal pathway of *in vivo* FA metabolism. The conjugation of FA takes place mainly in the liver (Zhao et al., 2004) through the activities of sulfotransferases (EC 2.8.2.1) and UDP glucuronosyl transferases (EC 2.4.1.17). Intestinal mucosa (Kern et al., 2003b; Spencer et al., 1999) and kidney (Chang et al., 1993; Zhao et al., 2003b) may also, at least in part, contribute to this conjugation process. Conjugation of FA may be dose dependent as very high doses of FA may saturate the conjugation enzymes, leading to accumulation of free FA in plasma. This was evidenced by recovery of free FA in the plasma of rats after higher doses of FA (up to 70 μmol/kg), but not after lower doses (up to 7 μmol/kg) (Adam et al., 2002; Rondini et al., 2002; Zhao et al., 2003b). Similarly, the urinary excretion of free FA was found to be dose dependent after oral administration of a relative lower dose (70 μmol/kg) (Zhao et al., 2003b) and a higher dose (462 μmol/kg) (Chang et al., 1993) in rats; 2.9% of the lower dose and 14.3% of the higher dose was detected as free FA in the urine samples. More free FA was found in the urine after an i.p. injection (Teuchy & Van Sumere, 1971) than the oral administration (Zhao et al., 2003b). Furthermore, an i.v. administration of FA was associated with very high levels of free FA in the urine (Choudhury et al., 1999), suggesting a rapid filtration of free FA by the kidneys.

A small portion of free FA may be metabolized through β-oxidation in the liver (Chesson et al., 1999; Teuchy & Van Sumere, 1971); 1.95% of activity of ^{14}C-FA administered i.p. was recovered in exhaled CO_2 (Teuchy & Van Sumere, 1971). Intraperitoneally or orally administered FA was also recovered as urinary 4-hydroxy derivatives of FA like dihydroferulic acid, vanillic acid and vanilloylglycine in rats (Booth et al., 1957; Teuchy & Van Sumere, 1971). Furthermore, FA is also metabolized into *m*-hydroxyphenylpropionic acid by the intestinal microflora through reduction, demethylation, and dehydroxylation at C4 (Chesson et al., 1999; Scheline, 1968; Scheline & Midtvedt, 1970).

FA is found mostly in esterified forms with saccharides and sterols and/or in etherified forms with lignin. Esterases in the lumen of the intestine hydrolyze the bound FA to generate free FA; free FA then can be absorbed and undergoes further metabolism as explained above (Zhao et al., 2003a, 2003b). Feruloyl mono-, di-, and oligosaccharides

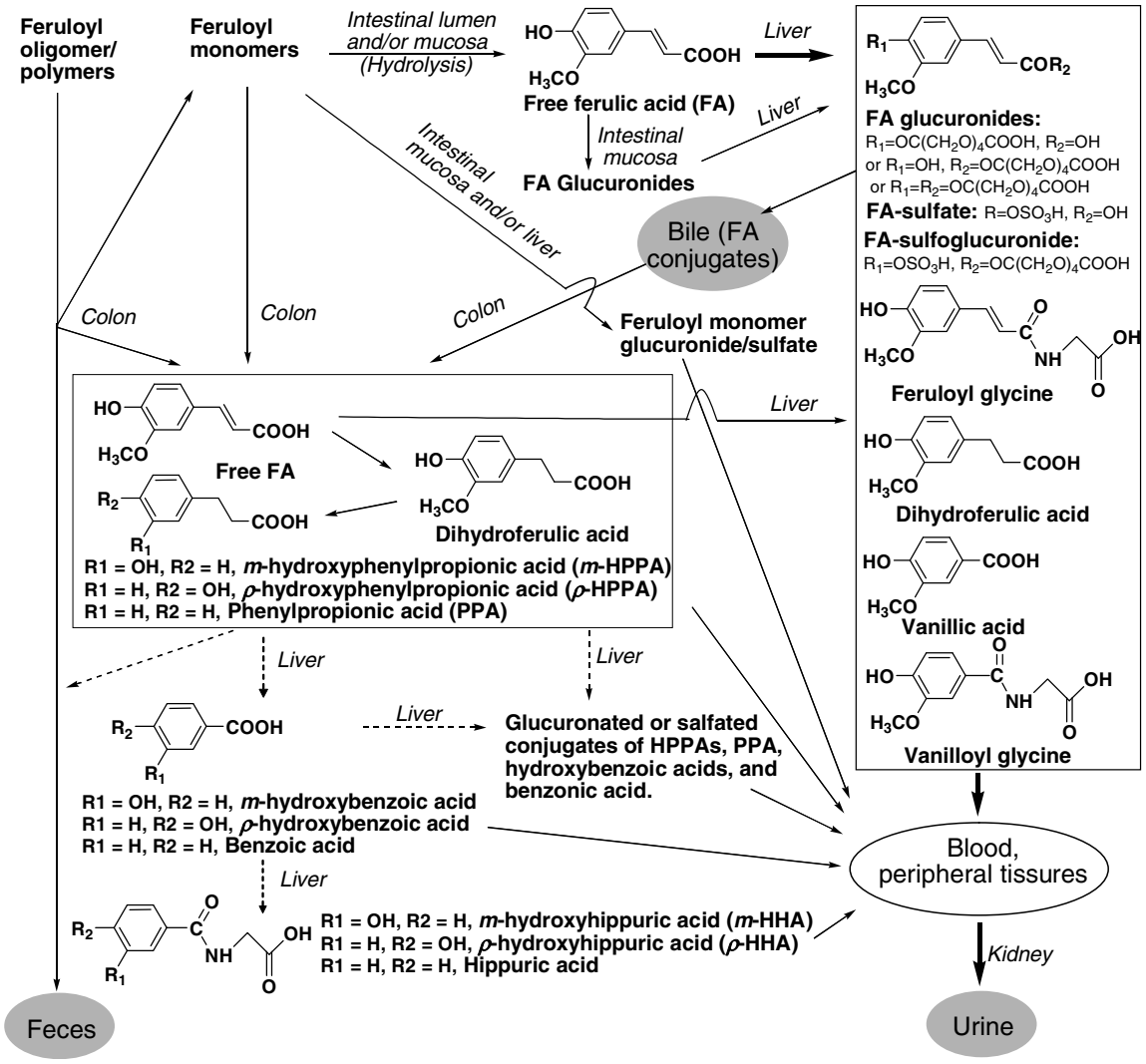

Fig. 2. Proposed possible metabolic pathways of dietary ferulic acid according to Adam et al. (2002), Booth et al. (1957), Bourne and Rice-Evans (1998), Bourne et al. (2000), Chang et al. (1993), Chesson et al. (1999), Choudhury et al. (1999), Kern et al. (2003a), Jacobson et al. (1983), Rechner et al. (2002), Rondini et al. (2002, 2004), Teuchy and Virgili et al. (2000), van der Logt et al. (2003), Van Sumere (1971), Yang et al. (2007), Zhang et al. (2005), Zhao et al.(2003a, 2003b), Zhao et al. (2004, 2005). Free FA and feruloyl monomers like γ-oryzanol can be absorbed in the foregut by different mechanisms. The absorbed FA is mainly metabolized into FA-glucuronides, -sulfates and/or glycine by conjugation in the liver and partly in intestinal mucosa. A small portion of FA may undergo β-oxidation in the liver to produce dihyroferulic acid and vanillic acid. These metabolites as well as unchanged free FA circulate in the circulation system and reach many organs including the liver, intestine, spleen, lung and kidney. Some feruloyl monomers and oligomer of FA are first hydrolyzed in the small intestine, while other forms are hydrolyzed in the large intestine by the action of microflora, generating dihydroferulic acid, hydroxyphenylpropionic acids and phenylpropionic acid. These products are absorbed and then conjugated and/or probably further metabolized into benzonic acids and hippuric acids in the liver before excretion via urine. The arrows with dotted lines indicate presumed fluxes.

can be hydrolyzed by the mucosal esterases in the rat foregut (Andreasen, Kroon, Williamson, & Garcia-Conesa, 2001a; Chanliaud, Roger, Saulnier, & Thibault, 1996), resulting in quick absorption of free FA (Buchanan et al., 1996; Zhao et al., 2003a, 2003b). In contrary, feruloyl polysaccharides and some feruloyl oligosaccharides cannot be hydrolyzed in the foregut by the esterases (Chesson et al., 1999; Kroon, Faulds, Ryden, Robertson, & Williamson, 1997; Zhao et al., 2003a). However, the microflora in the hindgut may hydrolyze these compounds, releasing free FA for absorption or degradation (Adam et al., 2002; Zhao et al., 2003a). FA-sterols like γ-oryzanol may be absorbed by passive diffusion mechanisms due to their high oil/water partition coefficient. Fujiwara (Fujiwara, Sakurai, Sugimoto, & Awata, 1983) found that most of absorbed γ-oryzanol (^{14}C-labeled) can be recovered intact in the mesenteric vein, suggesting a passive diffusion mechanism involved in the transportation of γ-oryzanol through intestinal mucosa.

4.3. Distribution

Serum albumin seems to be the major carrier of FA (Chang et al., 1993; Kang et al., 2004). Zhao et al. (2004) estimated that approximately 4%, 10% and 53% of the orally administered FA can be found in the gastric mucosa,

Table 2
Pharmacokinetic parameters of free ferulic acid (FA) and bound FA in rats and humans

Species	Source[a]	Dose, μmol/kg BW[a]	Bio-markers	Plasma C_{max}, μmol/L[b]	T_{max}min	$t_{1/2}$min	ACU(μmol/L) × min [b]	References
Wistar rats	FA-Na	185 (IV)	F	598	0	10	8515	Chang et al. (1993)
Wistar rats	FA	70	F	25.3 ± 10.1	5	30	500	Zhao et al. (2003b)
Wistar rats	FA	70	T	109.5 ± 30.4	15	30	4815 ± 228	Zhao et al. (2003b)
Wistar rats	FAA	70	T	23.0 ± 1.5	30	100	2678 ± 97	Zhao et al., (2003b)
Wistar rats	FAXn	70	T	1.3 ± 0.7	720	ND	1008 ± 230	Zhao et al. (2003b)
Humans	FA-Na in capsule	4.3	F	2.5 ± 0.5	24	42	114 ± 34	Yang et al. (2007)
Humans	FA in wheat bran	22.5	T	0.2	180	325	ND	Kern et al. (2003a)

F, free FA; T, total FA, including free FA and its all glucuronide/sulfate conjugates; C_{max}, maximum plasma concentrations; T_{max}, time to reach C_{max}; $t_{1/2}$, half life of FA in plasma; AUC, total area under the plasma concentration–time curve; ND, not determined.

[a] FA was administered orally except one study marked with IV. *FAA, 5-O-feruloyl-L-arabinofuranose; FAXn feruloyl-arabinoxyla, FA-Na, sodium ferulate.*

[b] Values are means ± SD.

blood and other tissues including liver and kidney, respectively. Adam et al. (2002) also determined that ~49% of perfused FA in the rat intestine might be distributed in the liver and peripheral tissues. Chang et al. (1993) reported that free FA was recovered in the kidney (~82 μg/g wet tissue), lung (~34 μg/g), liver (~28 μg/g), spleen (~22 μg/g), heart (~14 μg/g), uterus (~15 μg/g) and brain (~ 2.6 μg/g) at approximately 30 min after an oral administration of 521 μ mol/kg BW of FA in rats. The concentrations of free FA in most tissues decreased by 20% in the kidneys, 80% in the lungs and 50% in other tissues 60 min after the administration (Chang et al., 1993). Teuchy and Van Sumere (1971) observed that <1% of the radioactivity of ^{14}C-FA remained in the liver, small intestine, cecum and skin up to 24 h following an i.p. injection of FA in rats.

4.4. Elimination and excretion

FA is excreted mainly through urine in rats in free and conjugated forms (Adam et al., 2002; Booth et al., 1957; Choudhury et al., 1999; Rondini et al., 2002; Zhao et al., 2004). FA is also excreted through bile, which accounts for about 4–6% of the oral dose (Adam et al., 2002; Zhao et al., 2004). FA conjugates were found in the bile only in the beginning period after the i.p. injection (0–5 h) (Scheline, 1968), indicating that high circulating levels of FA are needed for biliary secretion. The bile excretion explains presence of FA and its derivatives in the feces of rats treated with i.p. FA (Teuchy & Van Sumere, 1971). It is estimated that half life of FA could range from 10 to 30 min in rats depending on the dose and the route of administration (Chang et al., 1993; Zhao et al., 2003b) (Table 2).

The short half life of FA may suggest its low toxicity. The acute oral LD_{50} of FA in female and male F344 rats were 2.1 and 2.4 g/kg, respectively (Tada, Tayama, & Aoki, 1999). No significant sub-chronic toxicity was found in female and male F344 rats after long-term (13 weeks) consumption of dietary FA at 0.16 g/kg BW per day (Tada et al., 2001).

4.5. Bioavailability of FA

Generally, the bioavailability of free FA is very low due to its rapid conjugation process in the liver (Chang et al., 1993; Zhao et al., 2004). FA bound with arabinose or arabinoxylan from corn bran showed a lower bioavailability than free FA. In contrast, FA in wheat bran (96% bound with heteroxylans) showed a higher bioavailability than free FA (Rondini et al., 2004). The difference may be due to the existing forms of FA and the oral dose, which affect the fate of dietary FA in the gastrointestinal tract and its systemic concentrations (van der Logt, Roelofs, Nagengast, & Peters, 2003; Zhao et al., 2003a). On the other hand, absorbability is used to describe the fraction of an administered dose of the agent that crosses the intestinal mucosa. The cumulative urinary excretion of total FA may be used to estimate the absorbability of dietary FA, because absorbed FA is excreted mainly through urine (Rondini et al., 2002; Zhao et al., 2003b). The absorbability can partly reflect the bioavailability of FA. The urinary excretion in rats suggests the following order for absorbability of dietary FA: free FA > feruloyl mono-, di-saccharides > feruloyl polysaccharides (Zhao et al., 2003a, 2003b). This is because simple sugar FA esters are easily hydrolyzed by esterases and/or microflora in the intestine. Feruloyl polysaccharides with complex structure may reduce the interactions between the hydrolyzing enzymes (xylanases, ferulate esterases) and the polymers of FA, resulting in reducing the release of FA (Zhao, Egashira, & Sanada, 2005). Therefore, the form of bound FA determines the degree of its absorbability; for example, feruloyl mono- and di-saccharide forms of FA in vegetables is most likely the reason for higher absorbability of FA from spinach as compared to feruloyl polysaccharide forms of FA in bran which has lower degree of absorbability (Adam et al., 2002; Buchanan et al., 1996; Zhao et al., 2005). Also, because FA in corn bran binds with more complex heteroxylans than in wheat bran (Bunzel, Ralph, Marita, Hat-

Table 3
Urinary and fecal excretion of dietary FA in rats and humans

Species	Source of FA[a]	Dose of FA[b] (μmol/kg BW)	Bio-markers	Urinary recovery (% of dose)	Fecal recovery (% of dose)	References
Wistar rat	Free FA	70	F	2.9	0.4	Zhao et al. (2003b)
Wistar rat	Free FA	265	F	5.4	ND	Choudhury et al. (1999)
Wistar rat	Free FA	265IV	F	8.1	ND	Choudhury et al. (1999)
Sprague–Dawley rats	Free FA mixed in diets	328 (daily intake)	F	0.8	0	Jung and Fahey (1983)
Wistar rat	FA-Na	462	F	14.32	0.83	Chang et al. (1993)
Wistar rat	Free FA	70	T	72	0.4	Zhao et al. (2003b)
Wistar rat	FAA	70	T	54	1	Zhao et al. (2003b)
Wistar rat	FAXn	70	T	20	20	Zhao et al. (2003b)
Wistar rat	RCB in diet	23	T	0.5	81	Zhao et al. (2003b)
Wistar rat	Free FA mixed in diets	63 (daily intake)	T	51.8	0.8	Adam et al. (2002)
Wistar rat	Whole wheat diet	81 (daily intake)	T	3.6	21	Adam et al. (2002)
Wistar rat	Wheat bran diet	74 (daily intake)	T	3.9	38	Adam et al. (2002)
Wistar rat	Free FA	195IP	F	25	ND	Teuchy and Van Sumere (1971)
Wistar rat	Free FA	265	Free FA and FA-G	10.5	ND	(Choudhury et al., 1999),
Wistar rat	Free FA	265IV	Free FA and FA-G	11.5	ND	Choudhury et al. (1999)
Sprague–Dawley rats	14^C γ -oryzanol	96	T	10	85	Fujiwara et al. (1983)
Sprague–Dawley rats	14^C γ -oryzanol	96	F	1.3	ND	Fujiwara et al. (1983)
Humans	Tomatoes	2.5	Free FA and FA-G	25–11	ND	Bourne and Rice-Evans (1998)
Humans	Tomatoes	2.5	F	3–5	ND	Bourne and Rice-Evans (1998)
Humans	Beer	0.68	F	37	ND	Rondini et al. (2004)
Humans	Beer	0.68	Free FA and FA-G	74	ND	Rondini et al. (2004)
Humans	PBE	1.9	T	>92	ND	Virgili et al. (2000)
	PBE	0.85	T	>92	ND	Virgili et al. (2000)
Humans	High bran breakfast	22.5	T	3.13	ND	Kern et al. (2003a)

FAA, 5-O-feruloyl-L-arabinofuranose; FAXn feruloyl-arabinoxyla, FA-Na, sodium ferulate, PBE, pine bark extract; F, free FA; T, total FA, including free FA and its all glucuronide/sulfate conjugates; FA-G, FA-glucuronide; ND, not determined.

[a] FA was dissolved in drinking water or ingested through foods as mentioned.

[b] FA was administered orally with one dose or by IV or IP injection.

field, & Steinhart, 2001; Zhao et al., 2005), the absorbability of FA from corn bran is lower than that from the wheat bran (Adam et al., 2002; Zhao et al., 2005). Table 3 summarizes information on the excretion of dietary FA in rats and humans.

4.6. Clinical pharmacokinetics of FA

Clinical pharmacokinetics of FA has not been well documented. Limited studies showed that pharmacokinetics of FA in humans may be similar to those in animals. Free FA was detected in the plasma of humans at 10 min after an oral administration of sodium ferulate (Yang, Tian, Zhang, Xu, & Chen, 2007), indicating that free FA is absorbed quickly in humans. Plasma concentrations of free FA reached the maximum levels at 24 min after the oral administration, with a half-time of 42 min (Table 2). Jacobson, Newmark, Baptista, and Bruce (1983) identified FA, vanillic acid and caffeic acid in the β-glucuronidase- and sulfatase-hydrolyzed human urine after ingestion of 1 g (86 μmol/kg BW) of FA. Kern, Bennett, Mellon, Kroon, and Garcia-Conesa (2003a) also detected free FA and its glucuronic conjugate in the plasma and free FA and its glycine conjugate in the urine after ingestion of FA of wheat bran (23 μmol FA/kg BW). Virgili et al. (2000) showed that 92% of the ingested FA excreted in the urine as free FA and its glucuronic/sulfate conjugates after consumption of 2.4 mg (0.3 μmol FA/kg BW) free FA through French maritime pin bark extract. Another study suggested that FA in humans may be also metabolized into dihydroferulic acid, *m*-hydroxyphenylpropionic acid (*m*-HPPA), vanillic acid, vanilloylglycine, and *m*-hydroxyhippuric acid (Booth et al., 1957). Consumption of FA and other polyphenols-rich foods including tomato, onion, pasta, cooked broccoli, cherry tomatoes, cucumber, continental leaf salad, defrosted raspberries, red grape juice and apple juice was associated with FA plasma concentrations of 22–130 nmol/L (Rechner et al., 2002). Dihydroferulic acid, *m*-HPPA and vanillic acid were also the major phenolic compounds detected in plasma of the 18 subjects consumed the above-mentioned meals. These metabolites were further metabolized into hippuric acid, *m*-hydroxyhippuric acid and *p*-hydroxyhippuric acid before being excreted into urine (Rechner et al., 2002). Further studies are needed to confirm if these metabolites are from FA or from other polyphenols.

Several studies (Bourne, Paganga, Baxter, Hughes, & Rice-Evans, 2000; Bourne & Rice-Evans, 1998; Kern et al., 2003a; Virgili et al., 2000) have suggested that the absorbability of dietary FA in humans may be similar to that in animals. Thereby, free FA and FA bound with simple sugars have higher absorption rates as compared to FA

bound with complex food matrix. For example, the urinary recoveries of the FA in humans drank low alcohol beer or a French maritime pin bark extract were 74% and 92% (Bourne et al., 2000; Virgili et al., 2000), respectively, while that was 11–25% after consumption of tomatoes (Bourne & Rice-Evans, 1998); this significant difference highlights the importance of the form of FA as it is found as free FA in the above-mentioned drinks (Bourne et al., 2000; Virgili et al., 2000) and as FA-*O*-glucoside in tomatoes (Herrmann, 1989). Similarly, the urinary recovery of FA was 3.1% when subjects ingested wheat bran; this was due to high amounts (96%) of bound FA in the form of insoluble polymers in wheat bran (Kern et al., 2003a). Furthermore, no forms of FA were detected in the urine of subjects ingested whole corn (Jacobson et al., 1983); this could be due to the fact that FA in whole corn is completely bound to insoluble matrix of heteroxylans–protein (Bunzel et al., 2001; Saulnier, Marot, Chanliaud, & Thibault, 1995).

5. Comments

The present review article summarizes the evidence for availability and bioavailability of dietary FA in both experimental animals and humans. The current literature seems to provide adequate information on chemistry, synthesis and availability of FA in a number of foods. However, our knowledge on pharmacokinetic and pharmacodynamic properties of FA is limited. Early studies have shown potent antioxidant activities of FA and therefore limited number of animal studies suggested its potential anti-atherogenic, anti-diabetic and anti-Alzheimer's disease effects. Our studies in rats suggest that absorption and metabolism of FA are mainly affected by two parameters: dose and form. FA is found in both free and bound forms in nature, however, it seems that the ratio of free to bound form significantly varies among food groups. Thus, depending on dietary habits, systemic concentrations and half life of FA will significantly vary among subjects. Therefore, this will be a major determinant governing possible biological effects of FA. We have estimated that the daily intake of total FA (both free and bound forms) in individuals who reasonably follow recommended number of servings of grains plus fruit and vegetables could reach 150–250 mg/day. However, currently it is not clear whether this much of dietary intake is adequate to generate biological effects. At the same time, studies reporting a reasonable dose of FA to be used as supplement are missing. As the antioxidant activities of FA are well documented and indeed it has been used as a food preservative for many years, it is reasonable to expect significant effects of this dietary agent in prevention of a number of human disorders. Thus, future studies must aim on characterization of pharmacokinetic and pharmacodynamic properties of this highly promising nutraceutical. Upon documentation of such characterizations, clinical and mechanistic studies are needed to identify therapeutic and preventive profile of FA. Such studies will determine to what extent FA plays a role in an inverse association between cereal consumption and the incidence of cardiovascular disorders and diabetes observed by epidemiological studies (de Munter, Hu, Spiegelman, Franz, & van Dam, 2007; Jacobs & Gallaher, 2004; Mozaffarian et al., 2003; Pereira et al., 2004; Qi & Hu, 2007). It is very likely that FA proves to be an excellent nutraceutical to be used for prevention of a number of disorders, while it possesses a high safety profile and a low financial burden.

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