Food and Chemical Toxicology 65 (2014) 185–195

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Invited Review

Ferulic acid: Pharmacological and toxicological aspects

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ARTICLE INFO

Article history:
Received 26 September 2013
Accepted 18 December 2013
Available online 25 December 2013

Keywords:
Aging
Biliverdin reductase
Ferulic acid
Free radicals
Heme oxygenase
Neurodegenerative disorders

ABSTRACT

Ferulic acid (FA) belongs to the family of phenolic acids and is very abundant in fruits and vegetables. Over the past years, several studies have shown that FA acts as a potent antioxidant by scavenging free radicals and enhancing the cell stress response through the up-regulation of cytoprotective systems, e.g. heme oxygenase-1, heat shock protein 70, extracellular signal-regulated kinase 1/2 and the proto-oncogene Akt. Furthermore, FA was shown to inhibit the expression and/or activity of cytotoxic enzymes, including inducible nitric oxide synthase, caspases and cyclooxygenase-2. Based on this evidence, FA has been proposed as a potential treatment for many disorders including Alzheimer's disease, cancer, cardiovascular diseases, diabetes mellitus and skin disease. However, despite the great abundance of preclinical research, only a few studies were carried out in humans, the majority of which used foods containing FA, and therefore the clinical efficacy of this mode of administration needs to be further documented. New efforts and resources are needed in clinical research for the complete evaluation of FA therapeutic potential in chronic diseases.

Contents

Abbreviations: Aβ, amyloid-β-peptide; AD, Alzheimer's disease; BR, bilirubin; BV, biliverdin; BVR, biliverdin reductase; CAT, catalase; CCNA2, gene encoding for cyclin-A2; CCNB1, gene encoding for G2/mitotic-specific cyclin-B1; CEP2, centrosomal protein 2; C_{max}, peak plasma concentration; CYP, cytochrome P-450; eNOS, endothelial nitric oxide synthase; ERK 1/2, extracellular signal-related kinase 1/2; FA, ferulic acid; FAEE, ferulic acid ethyl ester; GFAP, glial fibrillary acidic protein; h, hour(s); HO, heme oxygenase; Hsp, heat shock protein; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LD, lethal dose; ODC1, gene encoding for ornithine decarboxylase; PPB, plasma protein binding; RABGAP1, RAB GTPase activating protein 1; ROS, reactive oxygen species; SF, sodium ferulate; SMC1L1, structural maintenance of chromosomes 1-like 1; SOD, superoxide dismutase; TGF-β, transforming growth factor-β; THD, thiazolidinedione(s); T_{max}, time to reach the C_{max}; UGT, UDP-glucuronosyltransferase.

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http://dx.doi.org/10.1016/j.fct.2013.12.024

1. Introduction

Ferulic acid [(E)-3-(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid)] (Fig. 1) is a caffeic acid derivative widely found in vegetables, fruits and some beverages such as coffee and beer (D'Archivio et al., 2007; Rechner et al., 2001) (Table 1). Moreover, FA is also a component of Chinese medicinal herbs, such as *Angelica sinensis, Cimicifuga racemosa* and *Ligusticum chuangxiong* (Ou and Kwok, 2004) (Table 1).

Although the earlier interest for FA and other caffeic acid-derivatives traces back to the mid-1950s, when Preziosi and collaborators (1957a–c, 1958) unraveled their coleretic, hypolipidemic and diuretic functions, only recently have these phenolic acids gained attention for their potential role as an adjuvant therapy for several free radical-induced diseases. In particular, FA was proposed as a novel antioxidant compound endowed with a strong cytoprotective activity due to both the ability to scavenge free radicals and activate cell stress response (see below). However, the unfavorable pharmacokinetics, which reduces the bioavailability of FA after ingestion (or oral administration) and the restricted number of clinical studies carried out with the purpose of proving FA efficacy and safety, limited the evidence regarding the potential interest of this phenolic acid in humans.

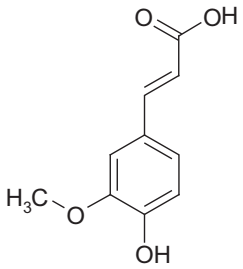

Fig. 1. The chemical structure of ferulic acid.

The aim of this review is to provide the reader with a systematic overview on the pharmacology and toxicology of FA. In addition, the role of FA as a potential therapeutic agent for the prevention and treatment of neurodegenerative disorders, cancer, cardiovascular diseases, diabetes and skin diseases will be critically discussed.

2. Pharmacokinetics of ferulic acid

According to the typical Mediterranean diet, whose characteristics are the abundance of plant foods (3–5 servings/day, including vegetables, fruits, breads and grains) and a low-to-moderate consumption of red meat, fish and wine, the daily amount of FA ingested was calculated around 150–250 mg (16–24 μmol/kg of body weight) (Barone et al., 2009; Zhao and Moghadasian, 2008). However, the amounts of FA ingested and calculated on the basis of the data shown in Table 1 should be considered as theoretical since they can vary according to the eating habits and the number of vegetable/fruit daily servings.

Since in fruits and vegetables FA is covalently conjugated through ester-linkage with mono-, di-, and poly-saccharides [5-O-feruloyl-L-arabinofuranose and 5-O-feruloyl-arabinoxylane are the most common forms of FA in cereals], glycoproteins, polyamines, lignin and the hydroxy fatty acids suberin and cutin (Bourne and Rice-Evans, 1998; Clifford, 1999; Ou and Kwok, 2004; Saulnier et al., 1995), many studies have been carried out to establish if conjugation modifies FA pharmacokinetic parameters.

2.1. Absorption and distribution

After ingestion, both FA and 5-O-feruloyl-L-arabinofuranose are not degraded by the stomach acid environment and undergo

Table 1
Approximate amounts of ferulic acid in some foods and Chinese herbs.

	FA[1] (mg/100 g)	Average daily portion[2] (g/day)	Ingested amount of FA (mg/day)
White wheat bread	8.2	35 (50)	2.87 (4.10)
Pasta	12	100 (80)	12 (9.6)
Cereal brans[3]	1351–3300	5 (20)	68–165 (270–660)
Tomatoes	6	200 (250)	12 (15)
Artichokes	275[4]	250	688
Eggplants	7.3–35	200 (250)	15–70 (18–87)
Broccoli	4.1	200 (250)	8.2 (10.25)
Grapefruit	~11	125 (150)	13.75–16.5
Orange	~9.5	125 (150)	11.88–14.25
Banana	5.4	125 (150)	6.75–8.1
Coffee	9.1–14.3	200	18.2–28.6
Popcorn	313	60	187.8
Angelica sinensis	20–175[5]	3–15[6] (dried root) 3–6[6] (powdered root)	0.6–26.25 0.6–10
Cimicifuga foetida	25[7]	0.04[8]	0.01
Ligusticum chuanxiong	106[7]	Not available	Not available

[1] From Zhao and Moghadsian (2008).
[2] From Zhao and Moghadsian (2008). In brackets the values according to the guidelines of the Italian Society of Human Nutrition.
[3] Include refined corn bran, soft and hard wheat bran and rye bran.
[4] Average content in chlorogenic acid (Mulinacci et al., 2004) which is transformed into ferulic acid (Azzini et al., 2007).
[5] From Yi et al. (2009).
[6] From EFSA Journal (2009).
[7] From Li et al. (2007).
[8] Data not available for *C. foetida*. The average daily portion related to *Cimicifuga racemosa* was reported. WHO Monographs on selected medicinal plants, 1999.