REVIEW PAPER

FERULIC ACID – A VERSATILE MOLECULE

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Abstract: The review summarizes the main roles of ferulic acid (4-hydroxy-3-methoxy-cinnamic acid), a phenolic compound widespread in the vegetable world, being present in cereals (rice, wheat, oats), coffee, tomatoes, nuts or corn, but also in a range of plants used in Traditional Chinese Medicine. It plays a vital role in ensuring cell wall rigidity and also in the formation of other important organic compounds for plants. Ferulic acid has a wide variety of biological activities such as: antioxidant, anti-inflammatory, antimicrobial, antiallergic, anticancer, antithrombotic, antiviral activities, vasodilator, hepatoprotective and metal chelation actions, enzymatic activity modulation, and wound healing activity. The most important action is the antioxidant one, being studies that demonstrate that ferulic acid acts synergistically with other antioxidants. Also, the antioxidant effect of ferulic acid is enhanced by skin exposure to ultraviolet light, making it a good ingredient for sunscreen cosmetics. It is one of the most powerful natural antioxidant that has the potential to neutralize free radicals, to slow down the aging process of the skin, to accelerate skin regeneration, to heal the skin wounds and also to preserve the health and beauty of the skin.

Keywords: ferulic acid, skin health, antioxidant activity, free radicals, photoprotection.

1. Introduction

Ferulic acid (4-hydroxy-3-methoxy-cinnamic acid) is a phenolic compound found in plant cell walls as a component of lignocelluloses. It plays a key role in the plants self preservation mechanism, ensures cell wall rigidity, protection against microbial invasion as well as sun damage protection. Ferulic acid was isolated first in 1866 from *Ferula foetida* (Order Apiales, Family Apiaceae), its name being based on the botanical name of plant. It is a phenolic derivative of cinnamic acid present in plant cell wall components as covalent side chains (Zhao and Moghadasian, 2008). It has been found in vegetables, fruits, flowers, coffee and cereals both in free and conjugated forms. Mainly, the conjugated forms are esters with the specific polysaccharides, alcohols, sterols, acids etc.

Ferulic acid is present in several plants, including Poaceae, Solanaceae and

Chenopodiaceae, in high concentrations. It is commonly found in cereal seeds (rice, wheat, oats, rye, barley), whole grains, spinach, parsley, grapes, banana, orange, grapefruit, rhubarb, artichoke, beans, berries, pineapple, coffee seeds, peanut and nuts (Drăgan et al., 2018). Cereals and a variety of vegetables and fruits contain 0.5-2% ferulic acid in free and esterified form (Mathew and Abraham, 2004). In **Table 1** the ferulic acid content is presented in different sources (Kumar and Pruthi, 2014; Boz, 2015).

In 1925 it was chemically synthesized (Dutt, 1925), and later the structure was confirmed by spectroscopic techniques (Nethaji et al., 1988), revealing the existence of both *cis* and *trans* isomeric forms (**Fig. 1)**.

Table 1. Ferulic acid content from various known sources

Source	**Ferulic acid content (mg/100 g)**
Bamboo shots	243.6
Soyabean	12
Peanut	8.7
Red beet	25
Spinach	7.4
Eggplant	7.3-35
Red cabbages	6.3-6.5
Radish	4.6
Broccoli	4.1
Tomato	0.29-6
Grapefruit	10.7-11.6
Orange	9.2-9.9
Banana	5.4
Coffee	9.1-14.3
Maize kernels	174
Maize flour	38
Whole-wheat flour	89
Whole-wheat	64-127
Rye bran	280
Rye flour	86
Oat bran	33
Oat flakes	25-52
Whole oats	25-35
Whole brown rice	42

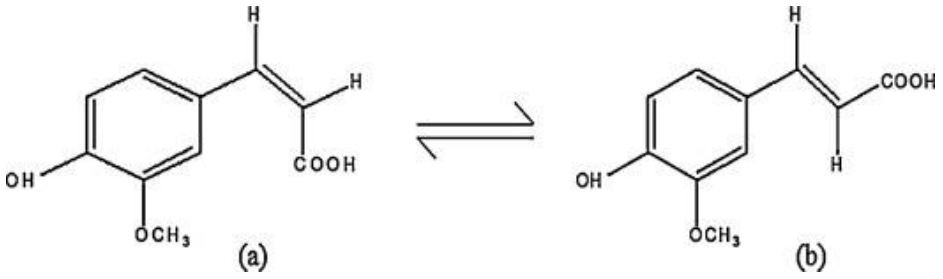

Fig. 1. Ferulic acid *cis-trans* isomers

The aim of this study is to attract attention to ferulic acid, to give summary of obtaining methods, its chemical and pharmacological properties and to better understand its multiple biological effects. Also, the article highlights antioxidant potential, anti-inflammatory, antimutagenic, antiproliferative, antimicrobial, antifungic, antihypertensive, antithrombotic, antihyperglycemic, photoprotective and wound healing activities.

2. Obtaining methods for ferulic acid

Ferulic acid can be obtained by chemically or enzymatically hydrolysis of natural sources. Chemical hydrolysis can be performed as alkaline or acidic methods, in order to extract ferulic acid from different natural sources (Kim et al., 2006; Anvar and Mazza, 2009). Due to the lower yields of such chemical methods, optimization of parameters is required (temperature, pH, time of extraction, concentration of acid or alkali etc.).

A more specific method is enzymatic hydrolysis. Many researchers studied different types of enzymes which can be used to extract ferulic acid with higher yields, using a gentle process. Such enzymes are feruloyl esterases isolated from different organisms or microorganism, such as *Streptomyces viridosporus*, *Streptomyces olivochromogenes*, *Pseudomonas fluorescens* subsp. *cellulosa*, *Penicillium pinophilum*, *Schizophyllum commune*, *Aspergillus niger* and *Clostridium thermocellum* (Deobald and Crawford, 1987; Brézillon et al., 1996; Donaghy and McKay, 1997; Blum et al., 2000b) grown on complex substrates such as xylan, pectin, wheat bran or sugar beet pulp. Nowadays, over 30 microbial feruloyl esterases have already been identified. It had been observed that feruloyl esterases act synergistically with other hemicellulases such as xylanases and pectinases in order to maximize the hydrolyzation of the ester bond between ferulic acid and hemicellulose present in plant cell walls. The yield of ferulic acid was highly dependent on the source of xylanase.

3. Properties of ferulic acid

Ferulic acid is a crystalline powder, insoluble in water at room temperature (0.78 g/L), soluble in water at high temperature, soluble in organic solvents. It has a melting point of 168-172°C and a pK_a value of 4.61.

Multiple chromatographic methods can be used for qualitative and quantitative analysis of ferulic acid: high-performance liquid chromatography (Kováčová and Malinová, 2007; Laokuldilok et al., 2011), thin-layer chromatography (Sharma et al., 1998), high-performance thin layer chromatography (Sharma et al., 2007), capillary tube electrophoresis (Sharma et al., 2007; Aturki et al., 2008) and colorimetry (Garcia et al., 2002; Tee-ngam et al., 2013).

From all these methods high-performance liquid chromatography is the most used technique for ferulic acid analysis. For both qualitative and quantitative analysis several researchers proposed high-performance thin layer chromatography, which is useful for routine assays in pharmaceutical industry (Hingse et al., 2014).

4. Pharmacokinetic profile of ferulic acid

Ferulic acid crosses the intestinal barrier, a major absorption site, by passive transcellular diffusion and facilitated transport mainly as a free form (Konishi et al., 2006; Silberberg et al., 2006). A small percent of ferulic acid is absorbed like conjugates as feruloyl-glucuronide, sulfate and dihydroferulic acid. The free and conjugated forms of ferulic acid are further metabolized by the liver under the action of sulfotransferases and UDP-glucuronosyl transferases. The excretion of ferulic acid in human urine is as free form or

conjugated one as feruloyl-glucuronide (Bourne and Rice-Evans, 1998; Poquet et al., 2008). A small percentage of ferulic acid is excreted in the bile, which explains the presence of free and conjugated ferulic acid in the feces.

5. Pharmacological profile and therapeutic applications of ferulic acid

Free radicals and reactive oxygen species causes serious diseases in human body. Ferulic acid is a powerful antioxidant and has a high radical scavenger effects for free radicals such as hydrogen peroxide, superoxide, hydroxyl radical, and nitrogen dioxide (Zhang et al., 1998; Ou and Kwok, 2004; Réblová, 2012; Abdel-Aal and Rabalski, 2013; Wolszleger et al., 2015; Stan et al., 2016).

The protective effect of ferulic acid against heart disease is due to its antioxidant effects (Price et al., 2008; Boz, 2015). Also, ferulic acid has an antihypertensive effect, reduces left ventricular diastolic rigidity, attenuates the infiltration of inflammatory cells and the collagen deposition in the left ventricle (Alam et al., 2013; Drăgan et al., 2016; Drăgan et al., 2018).

Other recent studies showed that ferulic acid decreases the serum lipids, inhibits platelet aggregation and prevents thrombus formation (Wang et al., 2004; Pagidipati and Gaziano, 2013; Zhang, 2014).

Ferulic acid have an important chemopreventive activity by means of antimutagenic and antiproliferative effects which supports the potential adjuvant role of ferulic acid in cancer therapy (Kroon et al., 1997; Ferguson et al., 2003; Sakthi et al., 2015; Fong et al., 2016).

Researchers revealed that it is possible to use ferulic acid in treating diabetes mellitus, due to decrease blood glucose levels and increase insulin plasma concentration activities (Nomura et al., 2003; Jung et al., 2007; Roy et al., 2013).

Ferulic acid has a photoprotective role for skin structures, beeing a strong UV absorber (Staniforth et al., 2012). It protects the skin against UVB induced erythema. It is used in skin aging and photoaging, hyperpigmentation, seborrheic skin and acne (Bezerra et al., 2017; Zduńska et al., 2018). It has also the ability to inhibit tyrosinase so it can be used in anti-blemish cosmetic formulations.

Ferulic acid accelerates the regeneration of skin, increase epithelialization and healing of wounds (Sangeeta et al., 2015; Zduńska et al., 2018). Recent studies showed that ferulic acid increased synthesis of amino acids involved in wound healing. Also it can inhibit lipid peroxidation and increases catalase, superoxide dismutase and glutathione, these processes significantly accelerates shrinkage of the wound (Ghaisas et al., 2014; Zduńska et al., 2018).

Ferulic acid has an antimicrobial effect against Gram-negative and Gram-positive bacteria, as well as yeasts e.g.: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Citrobacter koseri*, *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Shigella sonnei*, *Bacillus subtilis* and *Streptococcus pneumoniae* (Jeong et al., 2000; Tsou et al., 2000; Ou & Kwok 2004; Mathew and Abraham, 2004; Boz, 2015). It has also antifungal effect against *Sclerotinia sclerotiorum*, *Fusarium oxy-sporum*, *Alternia* sp., *Botrytis cinerea*, and *Penicillium digitatum* (Ou and Kwok, 2004; Boz, 2015).

All these pharmacological roles and medical applications of ferulic acid are represented in **Table 2**.

Table 2. Possible applications of ferulic acid

Crt. no.	Effect of ferulic acid
1.	Antimicrobial
2.	Antiviral
3.	Antidiabetic
4.	Antiageing
5.	Anticarcinogenic
6.	Anti-inflammatory
7.	Antiallergic
8.	Antioxidant
9.	Antiatherogenic
10.	Antiapoptotic
11.	Antihypertensive
12.	Antithrombotic
13.	Antiarrythmic
14.	Photoprotective
15.	Neuroprotective
16.	Hepatoprotective
17.	Cardioprotective
18.	Free radical scavenger activity
19.	Lipid lowering activity
20.	Metal chelation activity
21.	Enzymatic activity modulation
22.	Increase NO synthesis
23.	Regeneration and wound healing activity

Conclusions

Our study has shown that ferulic acid, a widely spread natural bioactive compound, reduces the risk of serious human diseases. Ferulic acid proved to be a strong antioxidant, anti-inflammatory, antimicrobial, cytotoxic, antithrombotic, antihypertensive and antidiabetic molecule. It helps to protect cellular structures, being used in skin disorders like erythema, aging and photoaging processes, acne, hyperpigmentation, wounds and also to reduce fine wrinkles. For such a skin protection role nowadays, ferulic acid is a compound increasingly used in cosmetology and aesthetic dermatology.

In light of current knowledge and literature data, ferulic acid promise to be used in wound healing in diabetic patients, in cancer therapy and in chronic and acute inflammatory diseases. Researchers also suggested that ferulic acid might be of interest as a new compound for development of an antiviral, antimicrobial, or antiparasitic drug.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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