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Antioxidant Properties of Ferulic Acid and Its Possible Application

Kamila Zduńska Agnieszka Dana Anna Kolodziejczak Helena Rotsztejn

Chair of Cosmetology, Department of Cosmetology and Aesthetic Dermatology, Faculty of Pharmacy, Medical University of Łódź, Łódź, Poland

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Abstract
Ferulic acid has low toxicity and possesses many physiological functions (anti-inflammatory, antioxidant, antimicrobial activity, anticancer, and antidiabetic effect). It has been widely used in the pharmaceutical, food, and cosmetics industry. Ferulic acid is a free radical scavenger, but also an inhibitor of enzymes that catalyze free radical generation and an enhancer of scavenger enzyme activity. Ferulic acid has a protective role for the main skin structures: keratinocytes, fibroblasts, collagen, elastin. It inhibits melanogenesis, enhances angiogenesis, and accelerates wound healing. It is widely applied in skin care formulations as a photoprotective agent, delayer of skin photoaging processes, and brightening component. Nonetheless, its use is limited by its tendency to be rapidly oxidized.

Introduction

Properties of Ferulic Acid

Ferulic acid ([E]-3-[4-hydroxy-3-methoxy-phenyl] prop-2-enoic acid) (Fig. 1) belongs to the phenolic acid group commonly found in plant tissues [1]. Phenolic acids are secondary metabolites of varying chemical structures and biological properties. The plants are mainly found in bound form as ester or glycosides, lignin components, and hydrolysis tannins [2, 3]. In terms of chemical structure, they can be divided into derivatives of cinnamic and benzoic acid, varying in number and substitution of hydroxyl and methoxy groups, and phenolic acids of unusual character. An additional group is the depside, which is a combination of two or more phenolic acids [2]. Ferulic acid, like caffeic, p-coumaric, synapine, syryte, and vanillin acids, is the most common cinnamic acid derivative [3].

Ferulic acid is most commonly found in whole grains, spinach, parsley, grapes, rhubarb, and cereal seeds, mainly wheat, oats, rye, and barley (Table 1). One of the most important role of phenolic acids, especially cinnamic acid derivatives, is their antioxidant activity, which depends primarily on the number of hydroxyl and methoxy groups attached to the phenyl ring [3, 4]. Ferulic acid is more easily absorbed into the body and stays in the blood longer than any other phenolic acids. Ferulic acid is considered to be a superior antioxidant [5]. Ferulic acid has low toxicity and possesses many physiological functions, including anti-inflammatory, antimicrobial, anticancer (for instance lung, breast, colon and skin cancer), anti-arrhythmic, and antithrombotic activity, and it also demonstrated antidiabetic effects and immunostimulant properties, and it reduces nerve cell damage and may help

Kamila Zduńska
Department of Cosmetology and Aesthetic Dermatology, Faculty of Pharmacy
Medical University of Łódź, Muszyńskiego 1 Street
PL–91-151 Łódź (Poland)
E-Mail kamila.zdunska@stud.umed.lodz.pl

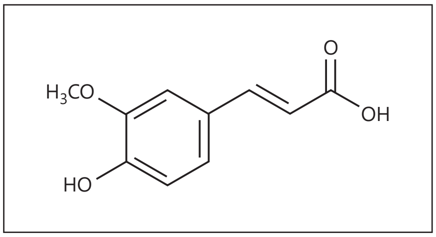

Fig. 1. Chemical structure of ferulic acid.

Table 1. Average ferulic acid content in plant-delivered foods

Foods	Ferulic acid content, mg\kg (in liquid mg/dm^3)
Black currant	15
Black berry	10
Spinach	110
Tomatoes	700
Cucurbit	220
Wheat flour	150
Wheat bran	700
Oatmeal	145

to repair damaged cells. Furthermore, it is a sports supplement because it can neutralize free radicals in muscle tissue (alleviate muscle fatigue). It has been widely used in pharmaceutics and food. Moreover, it is widely applied in skin care formulations as a photoprotective agent (sunscreens), delayer of skin photoaging processes, and brightening component. Nonetheless, its use is limited by its tendency to be rapidly oxidized [3, 5–7].

Antioxidative Activity of Ferulic Acid

The antioxidant action mechanism of ferulic acid is complex, mainly based on the inhibition of the formation of reactive oxygen species (ROS) or nitrogen, but also the neutralization ("sweeping") of free radicals. In addition, this acid is responsible for chelating protonated metal ions, such as Cu(II) or Fe(II) [8, 9]. Ferulic acid is not only a free radical scavenger, but also an inhibitor of enzymes that catalyze free radical generation and an enhancer of scavenger enzyme activity. It is directly related to its chemical structure [3, 10–12]. Its antioxidating properties are primarily related to scavenging of free radicals, binding transition metals such as iron and copper, and lipid peroxidation prevention. The mechanism of antioxidative activity of ferulic acid is the ability to form stable phenoxyl radicals, by the reaction of the radical molecule with the molecule of antioxidant. This makes it difficult to initiate a complex reaction cascade leading to the generation of free radicals. This compound may also act as hydrogen donor, giving atoms directly to the radicals. This is particularly important for the protection of cell membrane lipid acids, from undesired autoxidation processes. As a secondary antioxidant, ferulic acids and their related compounds are able to bind transition metals such as iron and copper [13]. This prevents the formation of toxic hydroxyl radicals, which lead to cell membrane peroxidation [14].

Free radicals may also be formed through natural human physiological processes, such as cell respiration process. These reactions are catalyzed by some enzymes, among others xanthine oxidase and cyclooxygenase-2 [15]. It is suggested that inhibition of this enzyme could prevent the changes caused by oxidative stress, including photophobia [16]. Literature data report high efficacy of ferulic acid and its derivatives in reducing xanthine oxidase and cyclooxygenase activity. It is therefore believed that ferulic acid reduces the amount of ROS produced by the enzyme-catalyzed transformation [17].

Ferulic Acid as an Antioxidant against Negative UV Influence

Highly exposed to UV-induced oxidative stress are keratinocytes and fibroblasts. ROS damage cells by the process of lipid peroxidation, amino acid nitration, and even DNA alterations, leading to cell death. Ferulic acid exhibits its protective antioxidant properties, relative to various skin structures and skin cells. Pluemsamran and partners [18] proved that human endothelial cells and keratinocytes are much less susceptible to UVA-induced free radical damage when exposed to ferulic acid prior to irradiation. It is believed that fibroblasts are exposed to UVA, and the oxidative stress associated with it is greater than that of the more superficially exposed keratinocytes. The human fibroblast test showed that ferulic acid, administered prior to exposure to UVA radiation, significantly reduced its adverse effects. It prevents UV-induced cell cycle alterations and DNA damage and regulates the expression of DNA repair genes. Hahn and partners [19] have shown that intracellular ROS production is nearly 2-fold lower in fibroblasts, which after irradiation with UVA, have ferulic acid applied. Similar effects, in the form of protection against free radical damage, have been observed in UVB-exposed fibroblasts. In their research, Ambothi and Nagarajan [20] demonstrated the protective role of ferulic acid applied to cells 30 min prior to exposure to UVB. Compared to non-antioxidant-exposed cells, cytotoxicity, lipid

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peroxidation, DNA alteration, antioxidant enzyme decline, and reduced ROS production have been observed. As UVB-induced ROS are one of the factors contributing significantly to the development of skin cancer, ferulic acid, which is known to lower their levels, has been found to be a promising anticancer substance [20]. In another study on human fibroblasts, ferulic acid proved to be an effective substance that protects heat shock proteins from degradation caused by hydrogen peroxide. As a result, the cell-treated assay, prior to UV irradiation, showed significantly greater cell survival and less ROS-induced damage. It has been proven to be closely related to significantly increased levels of protective heat shock proteins compared to the ferulic acid trial [21].

The activation of MMP-2 and MMP-9 under the influence of UVB radiation leads to photosaturation and initiation of photocancerogenesis processes [22]. Staniforth et al. [23] have proven that these processes are effectively prevented by the application of ferulic acid, just after exposure to UVB radiation. Studies conducted on mice showed a decrease in MMP-2 and MMP-9 activity by 37 and 83%, respectively, compared to the non-antioxidant-exposed group [23]. Ferulic acid administered before irradiation causes reduced cytotoxicity, less stimulation of MMP-1 matrix metalloproteinases, and the generation of ROS, compared to those exposed without antioxidant. Also, the level of endogenous antioxidants, glutathione and catalase, declined less and restored faster in the probe with ferulic acid. The antioxidant tested proved to be effective not only for its free radical scavenging capacity but also for its protective effect on the intracellular antioxidant system [18]. Bian and partners [24] have demonstrated a high efficacy of ferulic acid in the prevention of H_2O_2-induced damage in human embryonic kidney cells. Ferulic acid application, before exposure to H_2O_2, increased cell survival and antioxidant enzyme levels (catalase, superoxide dismutase). It has been stated that natural antioxidants such as ferulic acid can prevent adverse changes in the body resulting from oxidative stress, including collagen degradation [24].

Kawaguchi et al. [25] in their study on human fibroblasts showed that the main cause of elastosis (accumulation of tropoelastin aggregates in skin reticular layer) are free oxygen radicals. In the cells exposed to ROS, a significant increase in tropoelastin mRNA expression was observed. This process was reduced when the fibroblasts were treated with catalase referred to as free radical scavengers. On this basis, the authors suggest that the use of antioxidants such as ferulic acid could prevent the unfavorable elastosis phenomenon [25, 26].

Angiogenesis Effect

In light of current knowledge, ferulic acid is believed to have an angiogenesis effect by affecting the activity of the main factors involved in it, i.e., vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and hypoxia-inducible factor 1 (HIF-1). Lin and partners [27] in their research conducted using human umbilical vein endothelial cells have shown that ferulic acid enhances VEGF and PDGF expression and increases the amount of hypoxia induced HIF-1, which generates hypoxia-responsive responses. The authors believe that ferulic acid is an effective substance that promotes the formation of new vessels, as evidenced in both in vivo and in vitro studies [27, 28].

Regeneration and Wound Healing Effect

The experiment conducted with the use of diabetic rats demonstrated that ferulic acid accelerates the regeneration and healing of wounds. The wound contraction percentage in rats to whom ferulic acid ointment was given was 27% after 4 days, while in the group which did not receive it, only 14% was administered after 4 days. After 16 days, rats treated with ferulic acid were almost completely healed (96%). In a control group that used an ointment with 1% soframycin, standardized for treatment of difficult-to-heal wounds, the wound was healed in 83% after 16 days. There was also a faster onset of granulomas in the ferulic acid group and faster epithelialization compared to the control group [29]. Ghaisas and partners [30], in a similar study, in addition to faster shrinking of the wound and increased epithelialization, observed an increased hydroxyproline and hydroxylysine synthesis (major amino acids involved in wound healing, which are the precursors of collagen), in the skin of diabetic rats to whom ferulic acid was given. Moreover, it has been shown that the use of ferulic acid ointment during healing inhibits lipid peroxidation and increases catalase, superoxide dismutase, and glutathione. The authors suggest that this phenomenon also significantly accelerates shrinkage of the wound [30].

The Use of Ferulic Acid in Cosmetology and Aesthetic Dermatology

Prevention of skin aging processes is one of the main issues in contemporary cosmetology and aesthetic medicine. Protection against the effects of external factors such as UV radiation, air pollution, and free radical scavenging plays an important role. The compounds with proven antioxidative efficacy include ferulic acid. Initially, it was used in cosmetics as a stabilizer of other commonly known antioxidants such as vitamin C and vitamin E. Research shows, though, that this compound is not only used as an additional compound, but also an active ingredient with antioxidative properties, which supports intracellular antioxidant defense systems. Thanks to this, ferulic acid has a protective role for the main skin structures (keratinocytes, fibroblasts, collagen, elastin), which is used in anti-aging cosmetic formulations. Due to its ability to inhibit the main enzyme of melanogenesis (tyrosinase), it is also used in anti-blemish cosmetic formulations.

Ferulic acid is used in skin-lightening preparations because it inhibits tyrosinase activity (an enzyme involved in melanogenesis) and inhibits melanocytic proliferation [31, 32]. Staniforth et al. [23] noted that ferulic acid absorbs UV (290–320 nm). In order to increase the lightening effect, ferulic acid can be combined with other compounds that also have a brightening effect, but by other processes such as niacinamide (inhibits the movement of melanosomes from melanocytes to keratinocytes). Saint-Leger et al. [33] reported better effects of ferulic acid after adding to it a keratolytic agent such as lipohydroxycarbones.

Ferulic acid is widely applied in skin care formulations as a delayer of skin photoaging processes and photoprotective agent. Its application as a topical antioxidant has become an important administration route due to maintaining a high local concentration and the low cutaneous metabolism [3]. Moreover, local ferulic acid penetrates deeply into the skin, both acidic and neutral pH, in dissociated and non-dissociated form [34]. Saija et al. [35] studied the penetration of ferulic and caffeic acid soluble in saturated aqueous solutions (pH 3 and pH 7.2) by a human skin cut in the Franz cells. It turned out that these acids, regardless of pH, penetrated the stratum corneum. It was noted that ferulic acid has a slightly better penetration capacity, which was explained by the known higher lipophilicity of this acid. Research on phenolic antioxidants has shown that ferulic acid improves the chemical stability of L-ascorbic acid and α-tocopherol preparations, thereby increasing its photoprotection properties.

Ferulic acid is used in the production of face masks, as well as antioxidant, protective, and moisturizing creams/lotions. The recommended acid concentration in cosmetic products of this type is from 0.5 to 1%. Ferulic acid is also used in medical cosmetology and aesthetics salons. It is most often used at a concentration of 12% and in combination with vitamins C and hyaluronic acid. Ferulic acid is used in the following procedures: microneedling and non-needle mesotherapy, chemical peels, and grooming treatments. Indications for the use of ferulic acid include skin aging and photoaging, hyperpigmentation (melasma), seborrheic skin, and acne.

Conclusion

Research conducted so far has shown that ferulic acid has strong antioxidant properties, which is directly involved with its protective role to cellular structures and inhibition of melanogenesis. It is increasingly used in cosmetic preparations, mainly to inhibit photostage. At the same time, it helps to reduce fine wrinkles and existing discoloration. Good penetration into the skin, compatibility with many cosmetic formulas, and stabilizing properties of other ingredients make ferulic acid an increasingly used compound in cosmetology.

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Disclosure Statement

The authors declare no conflict of interest.

References

1 Mattila P, Kumpulainen J: Determination of free and total phenolic acids in plant-derived foods by HPLC with diode-array detection. J Agric Food Chem 2002;50:3660–3667.

2 Parus A: Przeciwutleniające i farmakologiczne właściwości kwasów fenolowych. Post Fitoter 2013;1:48–53.

3 Bezerra G, Pereira M, Ostrosky E, Barbosa E, Moura M, Ferrari M, Aragão C, Gomes A: Compatibility study between ferulic acid and excipients used in cosmetic formulations by TG/DTG, DSC and FTIR. J Therm Anal Calorim 2017;127:1683–1691.

4 Aguilar-Hernández I, Afseth NK, López-Luke T, Contreras-Torres F, Wold JP, Ornelas-Soto N: Surface enhanced Raman spectroscopy of phenolic antioxidants: a systematic evaluation of ferulic acid, p-coumaric acid, caffeic acid and sinapic acid. Vib Spectrosc 2017;89:113–122.

5 Tee-ngam P, Nunant N, Rattanarat P, Siangproh W, Chailapakul O: Simple and rapid determination of ferulic acid levels in food and cosmetic samples using paper-based platforms. Sensors 2013;13:13039–13053.
6 Cota-Arriola O, Plascencia-Jatomea M, Lizardi-Mendoza J, Robles-Sánchez RM, Ezquerra-Brauer JM, Ruíz-García J, Vega-Acosta JR, Cortez-Rocha MO: Preparation of chitosan matrices with ferulic acid: physicochemical characterization and relationship on the growth of *Aspergillus parasiticus*. Journal of Food 2017;15:65–74.
7 Moldovan M, Lahmar A, Bogdan C, Părăuan S, Tomuță I, Crișan M: Formulation and evaluation of a water-in-oil cream containing herbal active ingredients and ferulic acid. Clujul Med 2017;90:212–219.
8 Rice-Evans CA, Miller NJ, Paganga G: Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Rad Biol Med 1996;20:933–956.
9 Rice-Evans CA, Miller NJ, Paganga G: Antioxidant properties of phenolic compounds. Trends Plant Sci 1997;2:152–159.
10 Lodovici M, Guglielmi F, Meoni M, Dolara P: Effect of natural phenolic acids on DNA oxidation in vitro. Food Chem Toxicol 2001;39: 1205–1210.
11 Masella R, Vari R, d'Archivio M, di Benedetto R, Matarrese P, Malorni W, Scazzocchio B, Giovannini C: Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. J Nutr 2004;134: 785–791.
12 Masella R, Cantafora A, Modesti D, Cardilli A, Gennaro L, Bocca A, Coni E: Antioxidant activity of 3,4-DHPEA-EA and protocatechuic acid: a comparative assessment with other olive oil biophenols. Redox Rep 1999;4:113–121.
13 Kiewlicz J, Szymusiak H, Zieliński R: Symthesis. Thermal stability and antioxidant activity of long-chain alkyl esters od ferulic acid. Zywn Nauk Technol Ja 2015;4:188–200.
14 Scharffetter-Kochanek K, Brenneisen P, Wenk J, Herrmann G, Ma W, Kuhr L: Photoaging of the skin from phenotype to mechanisms. Exp Gerontol 2000;35:307–316.
15 Sheu S, Nauduri D, Anders MW: Targeting antioxidants to mitochondria: a new therapeutic direction. Biochim Biophys Acta 2006; 1762:256–265.
16 Higgins P, Dawson J, Walters M: The potential for xanthine oxidase inhibition in the prevention and treatment of cardiovascular and cerebrovascular disease. Cardiovasc Psychiatry Neurol 2009;2009:1–9.
17 Nile SH, Ko EY, Kim DH, Keum YS: Screening of ferulic acid related compounds as inhibitors of xanthine oxidase and cyclooxygenase-2 with anti-inflammatory activity. Rev Bras Farmacogn 2016;26:50–55.
18 Pluemsamran T, Onkoksoong T, Panich U: Caffeic acid and ferulic acid inhibit UVA-induced matrix metalloproteinase-1 through regulation of antioxidant defense system in keratinocyte HaCaT cells. Photochem Photobiol 2012;88:961–968.
19 Hahn HJ, Kim KB, Bae S, Choi BG, An S, Ahn KJ, Kim SJ: Pretreatment of ferulic acid protects human dermal fibroblasts against ultraviolet A irradiation. Ann Dermatol 2016;28: 740–748.
20 Ambothi K, Nagarajan RP: Ferulic acid prevents ultraviolet-B radiation induced oxidative DNA damage in human dermal fibroblasts. Int J Nutr Pharmacol Neurol Dis 2014; 4:203–213.
21 Calabrese V, Calafato S, Puleo E, Cornelius C, Sapienza M, Morganti P, Mancuso C: Redox regulation of cellular stress response by ferulic acid ethyl ester in human dermal fibroblasts: role of vitagenes. Clin Dermatol 2008;26: s.358–s.363.
22 Inomata S, Matsunaga Y, Amano S, Takada K, Kobayashi K, Tsunenaga M: Possible involvement of gelatinases in basement membrane damage and wrinkle formation in chronically ultraviolet B-exposed hairless mouse. J Invest Dermatol 2003;120:128–134.
23 Staniforth V, Huang W, Aravindaram K, Yang N: Ferulic acid, a phenolic phytochemical, inhibits UVB-induced matrix metalloproteinases in mouse skin via posttranslational mechanisms. J Nutr Biochem 2012;23:443–451.
24 Bian Y, Guo J, Majeed H, Zhu K, Guo X, Peng W, Zhou H: Ferulic acid renders protection to HEK293 cells against oxidative damage and apoptosis induced by hydrogen peroxide. In Vitro Cell Dev Biol Anim 2015;51:722–729.
25 Kawaguchi Y, Tanaka H, Okada T, Konishi H, Takahashi M, Ito M, Asai J: Effect of reactive oxygen species on the elastin mRNA expression in cultured human dermal fibroblasts. Free Radic Biol Med 1997;23:162–165.
26 Warren R, Gartstein V, Kligman AM, Montagna W, Allendorf RA, Ridder GM: Age, sunlight, and facial skin: a histologic and quantitative study. J Am Acad Dermatol 1991;25: 751–760.
27 Lin C, Chiu J, Wu I, Wang B, Pan C, Chen Y: Ferulic acid augments angiogenesis via VEGF, PDGF and HIF-1 alpha. J Nutr Biochem 2010;21:627–633.
28 Yang G, Jiang J, Lu W: Ferulic acid exerts anti-angiogenic and anti-tumor activity by targeting fibroblast growth factor receptor 1-mediated angiogenesis. Int J Mol Sci 2015; 16:24011–24031.
29 Sangeeta D, Digvijay S, Pradeep TD, Rupesh S, Rahul T: Healing potential of ferulic acid on dermal wound in diabetic animals. Asian J Molec Model 2015;1:1–16.
30 Ghaisas M, Kshirsagar S, Sahane R: Evaluation of wound healing activity of ferulic acid in diabetic rats. Int Wound J 2014;11:523–532.
31 Oresajo C, Stephens T, Hino PD: Protective effects of a topical antioxidant mixture containing vitamin C, ferulic acid, and phloretin against ultraviolet-induced photodamage in human skin. J Cosmet Dermatol 2008;7:290–297.
32 Murray JC, Burch JA, Streilein RD, Iannacchione MA, Hall RP, Pinnell SR: A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. J Am Acad Dermatol 2008;59:418–425.
33 Saint-Leger D, Leveque JL, Verschoore M: The use of hydroxy acids on the skin: characteristics of C8-lipohydroxy acid. J Cosmet Dermatol 2007;6:59–65.
34 Saija A, Tomaino A, Lo Cascio R, Trombetta D, Proteggente A, De Pasquale A, Uccella N, Bonina F: Ferulic and caffeic acids as potential protective agents against photooxidative skin damage. J Sci Food Agric 1999;79:476–480.
35 Saija A, Tomaino A, Lo Cascio R, Trombetta D, Proteggente A, De Pasquale A, Uccella N, Bonina F: In vitro and in vivo evaluation of caffeic and ferulic acids as topical photoprotective agents. Int J Pharm 2000;1:39–47.