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Review article

Characteristics and biological properties of ferulic acid

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Abstract: *The interest in the properties of hydroxycinnamic acids with health-promoting properties is constantly increasing. That is why more and more research is being conducted to better understand these properties. Ferulic acid, FA (4-hydroxy-3-methoxycinnamic acid) is a derivative of hydroxycinnamic acid found in the plant tissue. It is possible to find him among others in bran cereal, popcorn bamboo shoots, and coffee. According to available literature data ferulic acid has a lot of biological properties, particularly appreciated in medicine. Its bioactive properties effectively contribute to the fight against diseases described as a civilization, including neurodegenerative diseases that increase the incidence. As reported the World Alzheimer Report, the number of people with dementia progression in 2016 exceeded 47.5 million, of which 33.5 million were diagnosed with Alzheimer's disease. According to the WHO estimates, this number will triple by 2050. The manuscript presents health-promoting properties of FA on the example of its antioxidant, antidiabetic, hepatoprotective, anti-atherosclerotic, neuroprotective, antineoplastic and antibacterial properties. In addition, the reaction of its synthesis in plants and in-vivo metabolization have been explained. The collected data suggest that bioactive FA molecules can effectively reduce the risk of civilization diseases and significantly reduce the level of oxidative stress contributing to the formation of neurodegenerative diseases.*

Keywords: *ferulic acid (FA), health-promoting properties of FA, synthesis of FA in plants; metabolism of FA.*

Introduction

Ferulic acid, FA (*4-hydroxy-3-methoxycinnamic acid*), is an organic chemical compound belonging to the phenolic acids with a $C_{10}H_{10}O_4$ total formula. For the first time, it was isolated from the *Ferula foetida* plant, which gave the name, and the research allowed to determine its structural construction [1]. The results of the research indicated the presence of an unsaturated side chain in the FA molecule,

as well as the presence of the *trans* (white crystalline form) and *cis* isomer (yellow oily liquid) (Figure 1) [2].

In 1925, the scientists carried out a successful attempt to obtain a synthetic ferulic acid. In addition to the synthetic form, ferulic acid can be obtained from plant tissues. This compound may be found as a monomer, dimer, free oligomer or making up polymers, covalently linked by ester bonds with polysaccharides, polyamines and glycoproteins, as well as ether linked to lignin [2-5]. Currently, ferulic acid is obtained through the chemical [6] or biotechnology method. The latter is more economical. It uses the enzyme feruloyl esterase (EC 3.1.1.73), produced by microorganisms capable of hydrolyzing ester bonds formed between cell wall polysaccharides and FA [5, 6].

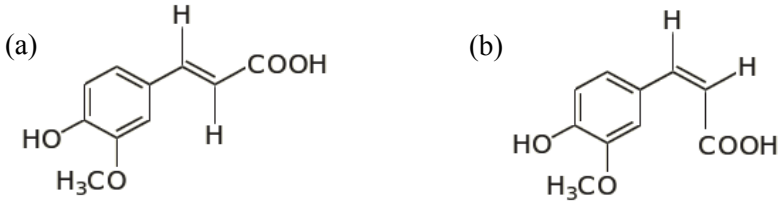

Figure 1. Structural formula of ferulic acid isomers: (a) *trans*, (b) *cis*

Synthesis of ferulic acid in plants

Ferulic acid in the natural environment occurs in the form of a monomer, dimer, a free oligomer or polymers whose structure is enriched by covalently bound via ester bonds polysaccharides, polyamides and glycoproteins [3, 5]. Its synthesis takes place through metabolic changes starting from the shikimate pathway. As a result, the obtained shikimic acid becomes a substrate involved in the biosynthesis of aromatic amino acids – L-phenylalanine and L-tyrosine [7]. The L-phenylalanine obtained in this way is a substrate involved in the phenylpropanoid pathway (Figure 2). Its beginning starts with the deamination reaction involving phenylalanine ammonia-lyase (PAL), which results in the formation of cinnamic acid, a precursor of hydroxycinnamic acids, including ferulic acid. The resulting cinnamic acid is hydroxylated to *p*-coumaric acid due to the reaction catalyzed by cinnamate-4-hydroxylase (C4H). In the case of L-tyrosine, deamination occurs due to the reaction catalyzed by tyrosine ammonia lyase (TAL). As a result, *p*-coumaric acid is directly obtained [8]. Further, *p*-coumaric acid is esterified with 4-coumarate-CoA ligase (4CL) to form *p*-coumaroyl-CoA. The obtained reaction product is transesterified with shikimic acid or quinic acid and hydroxycinnamoyl (HCT) and then hydroxylated on the 3rd carbon with *p*-coumaric acid-3-hydroxylase (C3H) to obtain caffeoyl-shikimate/quinate ester. At a later stage, caffeoyl-shikimate/quinate is transesterified with CoA and methylated on 3rd carbon with cinnamoyl-CoA ortho-methyl transferase to give feruloyl-CoA and the hydroxyl in C3 is methylated by cinnamoyl-coenzyme A orthomethyl transferase to produce feruloyl-CoA. The ester may be exported to feruloylate

polysaccharides in Golgi apparatus by action of a putative feruloyl transferase or released as coniferaldehyde in a reaction mediated by cinnamoyl-coenzyme A reductase (CCR). Finally, free ferulic acid molecules are obtained by the oxidation of coniferyl aldehyde with coniferyl aldehyde dehydrogenase (CALDH) [9].

Esters of cinnamic and quinic acid obtained as a result of the reaction with HCT (Figure 2) are classified as chlorogenic acids. Their main representative is 5-O-caffeoylquinic acid, which occurs mainly in coffee, pears, potato tubers and apples [10].

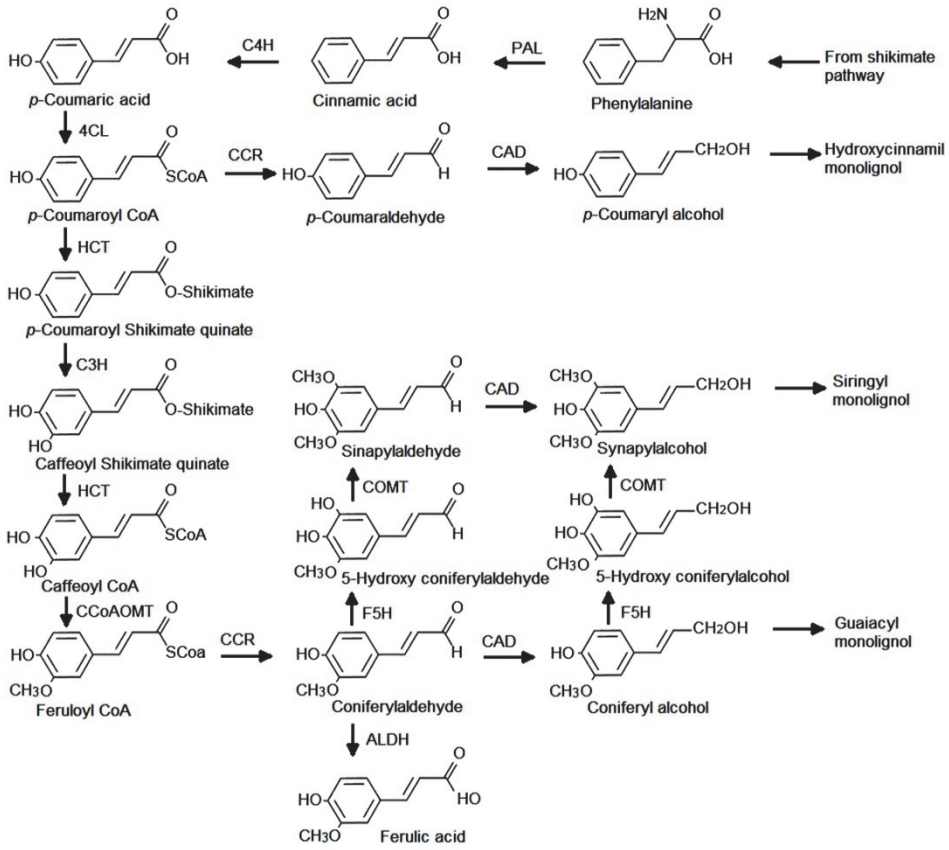

Figure 2. The total phenylpropanoid pathway. PAL, phenylalanine ammonia-lyase; C4H, cinnamate-4-hydroxylase; 4CL, 4-coumarate:CoA ligase; HCT, hydroxycinnamoyl CoA: quinate/shikimate hydroxycinnamoyl transferase; C3H, coumarate-3-hydroxylase; CCoAOMT, caffeoyl coenzyme A 3-*O*-methyltransferase; CCR, cinnamoyl CoA reductase; F5H, ferulate 5-hydroxylase; COMT, caffeic acid 3-*O*-methyltransferase; CAD, cinnamyl alcohol dehydrogenase; ALDH, aldehyde dehydrogenase [9, 11]

In-vivo ferulic acid metabolism

In the course of widespread *in-vivo* studies on ferulic acid metabolism, it has been found that it is converted to various metabolites. These include ferulic acid-sulfate, ferulic acid-glucuronide, ferulic acid-sulfoglucuronide, ferulic acid-diglucuronide, feruloylglycine, *m*-hydroxyphenylpropionic acid, dihydroferulic acid, vanillic acid and vanilloylglycine [12, 13]. The results of the study have clarified that the main FA metabolic pathway is based on the conjugation of glucuronic acid and/or sulfate. The conjugation occurs in the liver in which the activity is mediated by sulfotransferases and uridine diphosphate (UPD) glucuronosyltransferases and to a lesser extent in the intestinal mucosa and kidneys [13-15]. Additionally, the course of the β-oxidation was noted in the liver [16]. Studies carried out by Overhage and co-authors [17] involving *Pseudomonas sp*. strain HR199 bacteria showed that genes involved in the catabolization of FA were located in the area of DNA that was covered by two EcoRI endonuclease fragments, E230 and E94, respectively. Among them, *fcs*, *ech* and *aat* genes encoding feruloyl-CoA synthetase, enoyl-CoA hydratase/aldolase and β-ketothiolase were detected [17]. Other studies on FA transformation into vanillin and other useful organic compounds in the protocatechuate 4,5-cleavage (PCA) pathway occurring in *Sphingomonas paucimobilis* SYK-6 bacteria have confirmed that FA is transformed into feruloyl-CoA by feruloyl-CoA-synthetase (FerA), and then HMPMP-CoA (4-hydroxy-3-methoxyphenyl- β -hydroxypropionyl-coenzyme A) with the participation of feruloyl-CoA hydratases/lyases (FerB and FerB2). Thereafter, $CH_3COSCoA$ (acetyl-CoA) is removed. The vanillin obtained in this way as a result of the PCA pathway is transformed into pyruvate and oxaloacetate. Finally, the products obtained take part in the Krebs cycle (TCA - tricarboxylic acid cycle), according to the diagram in Figure 3 [18].

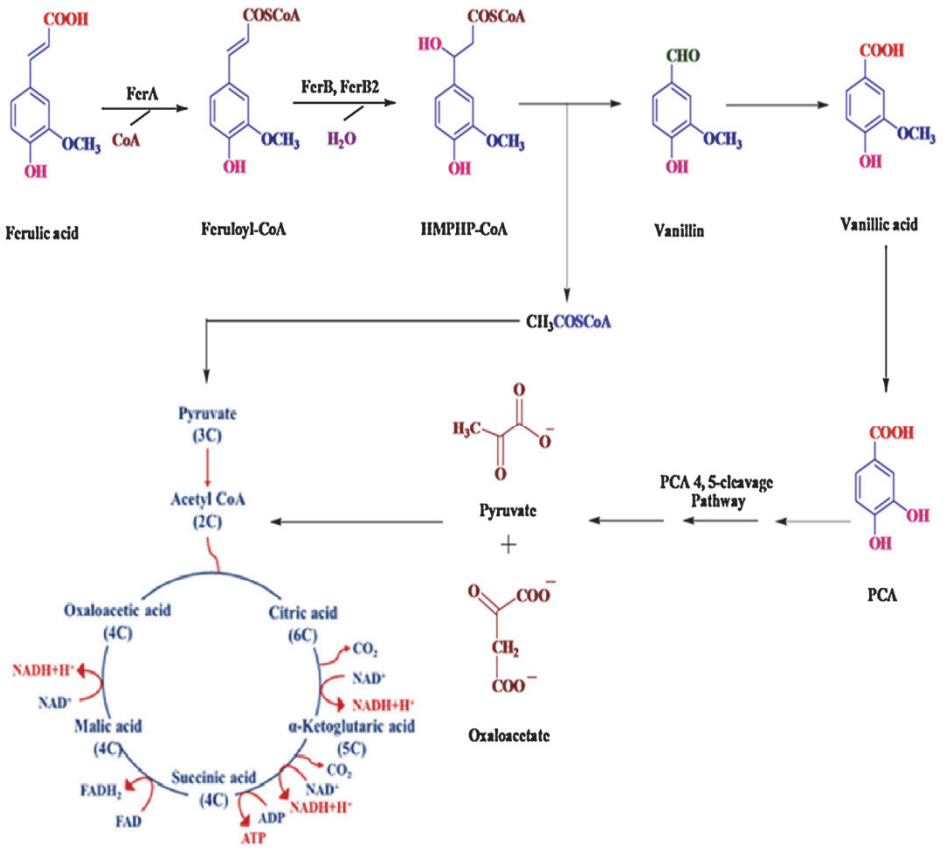

Figure 3. Simplified pathway of ferulic acid metabolism in *S. paucimobilis* SYK-6 (HMPHP-CoA: 4-hydroxy-3-methoxyphenyl-b-hydroxyprpionyl CoA) [19]

Health benefits resulting from the consumption of ferulic acid

Ferulic acid belongs to phenolic compounds – secondary metabolites of the plant world, having diversified structure, molecular weight, and physicochemical properties. It is naturally located in all parts of plants (leaves, roots, bark, flowers, and fruits), in which it occurs in the form of esters and glycosides (Table 1) [20]. Ferulic acid is present in many food raw materials. Its highest concentration was detected in refined corn bran, wheat bran, and sugar beet. Moreover, in a smaller amount, it also occurs in grapefruit, coffee, bananas, and broccoli. A number of animal tests carried out suggest that it has proven antioxidant, antidiabetic, hepatoprotective, anti-atherosclerotic, neuroprotective, anticarcinogenic and antibacterial properties [9]. Its health-promoting properties result from the possibility of donating an electron or a hydrogen atom (reducing properties), balancing unpaired electrons (removing free radicals), enzyme metal ions chelation catalyzing the oxidation reaction, as well as the interruption of numerous oxidative reactions [21, 22]. In addition, the lack of known side effects indicates

its strong application potential in the food, cosmetics and pharmaceutical industries.

Table 1. Ferulic acid content in various food raw materials [12]

Raw material	Ferulic acid content, mg/0.1 kg
Refined corn bran	2610.0-3300.0
Wheat bran	1351.0-1456.0
Sugar beet	800.0
Popcorn	313.0
Rye bran	280.0
Bamboo shoots	243.6
Beetroot	25.0
Soybeans	12.0
Grapefruit	10.7–11.6
Coffee	9.1-14.3
Bananas	5.4
Broccoli	4.1
Plums	1.47
Apples	0.27-0.85

Ferulic acid as a stabilizer of free radicals

Available scientific reports indicate that oxidative stress is responsible for many lifestyle-related diseases. It participates in the pathogenesis of atherosclerosis, hypertension, diabetes, ischemic heart disease and cancer. On the other hand, research has shown that in low concentrations, the use affects the proper functioning of the body. Its positive role is based on the adaptation and regulation of intracellular signalling. That is why the balance between the concentration of free radicals and antioxidants is so important. Oxidative stress is defined as a state in which the excessive activity of reactive oxygen species is recorded (Table 2).

It is caused by the imbalance between their formation and removal from the cell by antioxidative systems [23]. Free radicals are organic and inorganic molecules or atoms that have one or more unpaired independently existing electrons [24]. They show a short half-life and are very reactive. They react with antioxidants that stabilize their concentration in cells [25]. The antioxidant potential of ferulic acid is due to the possibility of forming a phenoxy radical. Due to possible shifts within FA molecules, the resulting radical has low energy, which generates a more stable hybrid resonant structure.

In the case of FA contact with a free radical, the FA hydrogen atom easily passes to the radical forming a stable phenoxy radical. As a result, there is a state of equilibrium. The phenoxy radical thus formed has no degenerative ability. Its presumed path of transformation is conducted towards condensation with another radical, including another phenoxy radical, forming dimers, e.g. curcumin. The carboxyl group present in the FA molecule binds fats protecting against their peroxidation. Thus, the stable resonant structure of the phenoxy radical is responsible for stopping the progress of chain reactions initiated by free radicals, making FA an effective compound to combat scavenging and to stop the chain

reactions of free radicals [7, 26]. Ferulic acid is also presented as an indirect scavenger of free radicals. Its action increases regulation of heme oxygenase by reducing biliverdin [27, 28] which is transformed into bilirubin – an endogenous scavenger of free radicals [29, 30].

Table 2. Non-reactive and reactive oxygen species

Non-reactive molecules (radical precursors)	Radicals
O_2 singlet oxygen	$O_2^{\bullet}$ superoxide radical
O_3 ozone	$HO^{\bullet}$ hydroxyl radical
H_2O_2 hydrogen peroxide	$RS^{\bullet}$ thiol radical
LOOH lipid peroxides	$ROO^{\bullet}$ peroxide radical
HOCl kwas podchlorawy	$RO^{\bullet}$ alkoxy radical
$ONOO^-$ peroxynitrite	

Antidiabetic properties

Diabetes belongs to lifestyle diseases associated with improper carbohydrate metabolism. Currently, it is the most widespread endocrine disorder among people. It is characterized by hyperglycemia and overproduction of free radicals, and thus oxidative stress [31, 32]. Studies conducted by Balasubashini et al. [6] have shown that ferulic acid dosed in rats with diabetes significantly reduced blood glucose and active substances – thiobarbituric acid, hydroperoxides, and free fatty acids while increasing the level of reduced glutathione (GSH) present in the liver of tested animals. In addition, the conducted analysis indicated an increase in superoxide dismutase activity, catalase, glutathione peroxidase, and pancreatic islet expansion. The authors have noticed that better results were obtained when supplementing a lower FA concentration. In this way, greater antioxidant capacity has been achieved. As a result, a stronger neutralization of free radicals was observed, reducing the intensity of diabetes. Studies carried out by other authors on diabetic rats suggest that ferulic acid additionally inhibits lipid peroxidation in brown adipose tissue [33], regenerates pancreatic beta cells [34] and reduces diabetic nephropathy due to the therapeutic reduction of oxidative stress and inflammation [35].

Hepatoprotective properties

The liver is the largest internal organ in the body of a healthy person. It is responsible for metabolizing nutrients, monitoring substances absorbed through the gastrointestinal tract and excreting metabolites [36]. It is very sensitive to hepatotoxic factors. These include alcohol, heavy metals as well as organic and inorganic solvents that promote excessive free radical formation. Free radicals attack liver cells (hepatocytes) causing hepatotoxic changes such as fibrosis, cirrhosis, acute hepatitis, and cancer [37].

The conducted research suggest that ferulic acid is an effective natural hepatoprotective agent. Rukkumani et al. [38] investigated the effect of hepatoprotective properties of FA on alcohol and polyunsaturated fatty acid

(PUFA) toxicity in female Wistar rats. The results of the analysis showed that the applied FA effectively stopped the formation of free radicals and lipid peroxidation after the introduction of ethanol and PUFA into rat organism at the time. The authors showed that the optimal dose of FA given to rats for 45 days was 20 mg/kg body weight. At the indicated FA concentration, the activity of hepatic indicator enzymes (alkaline phosphatase, gamma-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase) and enzymes with antioxidant activity (superoxide dismutase, catalase, and glutathione peroxidase) decreased significantly, suggesting that FA effectively eliminates hepatotoxic toxins introduced to the body with a daily diet.

In turn, Kim et al. [39] attempted to investigate the hepatoprotective effect of FA on carbon tetrachloride (CCl_4), which is the source of acute liver injury. The tests were carried out on mice injected intraperitoneally with carrier or FA (20, 40 and 80 mg/kg body weight) and carbon tetrachloride (20 μL / kg body weight) 1 hour before and 2 hours after. Blood was then collected from animals and serum analyzed. The results of the analysis showed that CCl_4 molecules significantly increased the concentration of *JNK* and *p38* (mitogen-activated protein kinases). In addition, they induced the expression of *TLR4*, *TLR2* and *TLR9* proteins and *m*RNA. In the case of FA administration, the activity of liver aminotransferase was reduced as well as the level of malondialdialdehyde in serum. The results obtained suggest that FA protects the liver from its acute injury due to the toxic activity of CCl_4. Additionally, FA can be used preventively to protect and treat liver diseases caused by drugs and metabolic disorders.

Antiatherosclerotic properties

Atherosclerosis is a disease of the arterial blood vessels caused by improper lipid accumulation, inflammation and proliferation of smooth muscle cells in the walls of medium and large arterial size. The beginning of accumulation is observed during the second decade of life and develops with age. The progress of vascular changes results in a reduction or cessation of blood flow through vessels due to the narrowing of their light by atherosclerotic plaques [40].

Several studies have examined the effect of oxidative stress on the progression of atherogenesis. The first research indicated that oxidative stress only contributes to oxidative modification of the LDL fraction in the walls of the arteries by means of reactive oxygen species (ROS). Current studies indicate that free radicals induce the expression of first vascular endothelial adhesion molecules (VCAM-1) and monocyte 1 chemotactic protein (MCP-1), resulting in changes in the structure and function of endothelial cells and atherosclerosis [41]. In addition, ROS reduce the production of nitric oxide (NO), which leads to vasoconstriction, platelet aggregation and neutrophil adhesion in the endothelium of the arteries [42].

As reported by Rukkumani et al. [43] ferulic acid reduces LDL cholesterol in the blood and prevents its oxidation induced by copper ions. In addition, it reduces the risk of ischemic heart disease. Other authors report that FA has strong hypocholesterolemic and anti-atherosclerotic properties [44]. Its action is based on

the effective prevention of oxidative stress by inhibiting lipid peroxidation, stabilizing the prooxidative-antioxidant balance and activating enzymes that have a positive effect on myocardial function [45]. Moreover, FA is a significant anti-stress protective factor that reduces damage to the gastric mucosa and cardiac tissue [46].

Neuroprotective properties

A number of experimental studies indicate the importance of oxidative stress in pathology and neurotoxicity associated with ageing and many neurodegenerative diseases such as Parkinson's and Alzheimer's [47]. Both diseases are classified as neurodegenerative, associated with chronic inflammation caused by oxidative stress with reactive oxygen species (ROS) and reactive nitrogen species (RNS). These strong oxidants lower the activity of proteins, destroying their RNA and DNA, and are involved in lipid peroxidation. The reaction results in damage to neurons responsible for processing and conduction of information [48, 49].

Kanski et al. [26] found that ferulic acid significantly reduced the toxic effect of peroxide and hydroxyl radicals on the neuronal cellular system. In addition, they proved that FA has greater biological activity than cinnamic acid and its derivatives – vanillic and coumaric acid. Scapagini et al. [50] suggest that FA protective action is based on direct modulation of oxidative stress, thus protecting the hippocampus genes – an element of the limbic system responsible for memory. Moreover, it increases the concentration of protective enzymes – heme oxygenase-1 (HO-1) and heat shock protein 70 (HSP70). In turn, Sultana et al. [51] suggest that a dose of 10-50 μM ferulic acid effectively protects against toxic aggregation of β-amyloid 1-42 (Abeta), intracellular accumulation of ROS, protein oxidation and lipid peroxidation.

Research done by Cheng et al. [52] proved the neuroprotective character of FA on stroke. The authors used a model of complete occlusion of the middle cerebral artery (MCAo) performed on rats. The analysis was based on the application of FA (100 mg/kg body weight, administered intravenously) to animals immediately after the initiation of MCAo. As a result, after 2 hours, inhibition of intracellular adhesion-1 molecules (ICAM-1), as well as suppression of mRNA expression in the macrophage-1 antigen (Mac-1) found in the striatum, were detected. At 10, 24 and 36 hours after reperfusion, a decrease in the number of Mac-1, 4-hydroxynonenal (4-HNE) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in the penumbra (penumbra zone) and areas of ischemia of the core was noted. These data suggest that FA is an effective therapeutic agent that extends the time in transient MCA, indicating that it can be a countermeasure against the development of ischemic stroke**.**

According to Henderson at al. [53], ferulic acid may provide *in-vivo* protection against noise-induced hearing loss (NIHL). It has been shown that the increased production of reactive oxygen and nitrogen species in combination with the lack of balance in antioxidant defence contributes to hearing loss due to noise. This disorder is associated with the death of internal and external ciliary cells due to

apoptosis or necrosis. The study was based on oral administration of 150 mg FA/kg body weight to pigs for 4 days, followed by analysis after 1, 3, 7 and 21 days. The results showed that FA contributed to the reaction of oxidative stress and apoptosis while increasing the viability of ciliary cells in the Corti organ. Moreover, it was found that the FA raises the concentration of the microsomal cytoprotective enzyme and heme oxygenase-1 (HO-1), which increase the cellular stress response by heme catabolism. These results confirmed the antioxidant properties of FA as a potential inhibitor of free radicals and HO-1 activator in the prevention of hearing loss caused by noise.

Antineoplastic properties

Cancer diseases belong to a group of diseases in which invasive cytotoxic cells divide without control and attempt to spread to other healthy tissues through the circulatory and lymphatic systems. These multi-stage diseases are caused by a number of environmental, chemical, physical, metabolic and genetic factors that play a direct or indirect role in the initiation of the expression of a malignant phenotype [54, 55].

There are many studies pointing to the anti-tumour properties of ferulic acid. Mori et al. [56] studied the effect of FA on chemically induced oral carcinogenesis in rats. The carcinogen was 1-oxide-4-nitroquinoline (4-NQO), which was administered to the animals orally (0.02 g NQO / kg body weight) for 5 weeks. After a specified period of time, FA treatment started (0.5 g FA/kg body weight). The conducted research proved that the extent of malignancy on the tongue and premalignant lesions were significantly lower in the group of animals in which FA was administered. This indicates that FA exhibits chemoprotective properties against oral cancer. Other studies conducted by Kawabata et al. [57] have shown that the FA effectively counteracts the formation of colon tumours. The authors initiated colon carcinogenesis in rats with azoxymethane (AOM), and then after 35 weeks, they administered sick animals with 0.25 and 5.00 g FA/kg body weight. The results of the analyzes indicated that FA effectively inhibited colon cancer and contributed to an increase in the activity of enzymes responsible for liver detoxification (glutathione S-transferase and quinone reductase). In turn, Baskaran et al. [58] assessed the FA's chemopreventive potential in preventing breast cancer. Researchers monitored the formation of tumours and analyzed the phase II of enzymatic detoxification during breast carcinogenesis of *Sprague-Dawley* rats, induced by 7,12-dimethylbenz[a]anthracene (DMBA). The results showed that oral administration of a 40 mg FA dose/kg body weight prevented tumour formation in 80% of the tested rat population. This suggests that FA can be used as a therapeutic agent in the prevention of breast cancer.

Antibacterial properties

Ferulic acid has strong antibacterial properties against Gram-negative and Gram-positive bacteria. In addition, it creates a toxic environment for yeast [59] This shows that it is an inhibitor of the growth of many pathogens, including

Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Citrobacter koseri, Pseudomonas aeruginosa, Helicobacter pylori, and *Shigella sonnei*. Moreover, among phenolic acids, it is the most potent antifungal agent against *Sclerotinia sclerotiorum, Fusarium oxysporum, Alternia sp., Botrytis cinerea,* and *Penicillium* [60].

Other *in-vitro* studies with ferulic acid (FA) and ethyl ferulate (FE) for HIV activity have shown that these compounds reduced the release and activity of *p24* antigen after infected cells were treated with 1.5 and 10 μmol L^{-1} FA or FE. Both FA and FE inhibited viral replication at 5 μmol L^{-1} without causing cytotoxicity, suggesting that FA and its derivative can be used in the development of antiviral drugs [61].

Summary

Ferulic acid is a bioactive phenolic compound found in many foods of plant origin. A number of animal tests carried out indicate that it has a wide range of health-promoting properties. Thanks to the analyses it has been proved that it effectively counteracts the emergence of lifestyle diseases, including diabetes, atherosclerosis, and cancer. The known mechanism of combating free radicals suggest that it can be used as a potential therapeutic agent in both the food and pharmaceutical industries.

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