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Review

Potential applications of ferulic acid from natural sources

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ABSTRACT

Ferulic acid (FA), a ubiquitous natural phenolic phytochemical present in seeds, leaves, bothin its free form and covalently conjugated to the plant cell wall polysaccharides, glycoproteins,polyamines, lignin and hydroxy fatty acids. FA plays a vital role in providing the rigidity to the cell wall and formation of other important organic compounds like coniferyl alcohol, vanillin, sinapic, diferulic acid and curcumin. FA exhibits wide variety of biological activities such as antioxidant, antiinflammatory, antimicrobial, antiallergic, hepatoprotective, anticarcinogenic, antithrombotic, increase sperm viability, antiviral and vasodilatory actions, metal chelation, modulation of enzyme activity, activation of transcriptional factors, gene expression and signal transduction.

Contents

1. Introduction

First time, ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA) was isolated from *Ferula foetida* for its structure determination, and its name was based on the botanical name of plant [27]. In 1925, FA was chemically synthesized and structurally confirmed by spectroscopic techniques, depicted the presence of an unsaturated side chain in FA, and also existence of both *cis* and *trans* isomeric forms [14,56]. The double bond present in the side chain is subjected to *cis–trans* isomerization (Fig. 1), and the resonance stabilized phenoxy radical accounts for its effective antioxidant activity. It catalyzes the stable phenoxy radical formation upon absorption of ultra-violet light, which gives the strength to FA for terminating free radical chain reactions. FA is an enormously copious and almost ubiquitous phytochemical phenolic derivative

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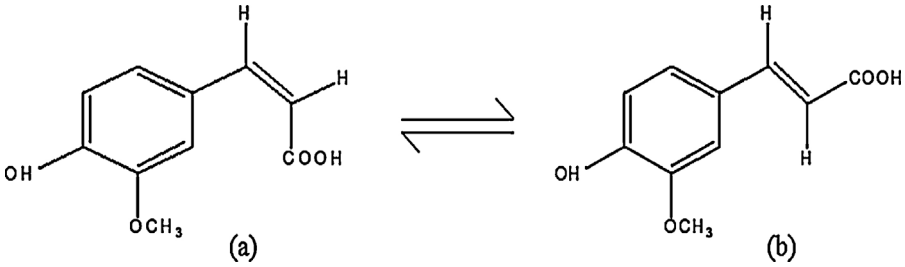

Fig. 1. Schematic representation of two different isomeric forms of ferulic acid found in nature (a) *cis* conformation and (b) *trans* conformation of ferulic acid.

of cinnamic acid, present in plant cell wall components as covalent side chains [66]. Collectively with dihydroferulic acid, it is the component of lignocelluloses, where it confers rigidity to the cell wall by making the crosslink between polysaccharides and lignin. It has been found that FA is linked with a variety of carbohydrates as glycosidic conjugates, different esters and amides with a broad range of natural products [73]. It makes esters by binding with a variety of molecules such as polysaccharides, long chain alcohols, various sterols of plant, tetra-hydroisoquinoline-monoterpene glucoside, a cyanogenetic glycoside and an amino-hydroxy-cyclo-pentenone, flavonoids and different types of hydroxycarboxylic acids including gluconic, tartaric, malic, hydroxycitric, tartronic, quinic, and hydroxy fatty acids [9,17,24,25].

The aim of this review is to provide the organized outline about natural sources, metabolism, and different applications of FA in biomedical, pharmaceutical, food, cosmetic and other industries, which will provide vast information to a wide range of researchers, working on the different applications of natural products.

2. Ferulic acid: natural sources and isolation

FA is commonly found in commelinid plants (rice, wheat, oats, and pineapple), grasses, grains, vegetables, flowers, fruits, leaves, beans, seeds of coffee, artichoke, peanut and nuts [8,47–49,72,85]. Cell walls (1.4% of dry weight) of cereal grains and a variety of food plants (pineapple, bananas, spinach, and beetroot) contains 0.5–2% extractable amount of FA, mostly in the *trans*-isomeric form, and esterified with the specific polysaccharides [21,22,23,57]. Table 1 summarizes the content of FA in different known sources.

Extraction of FA offers accessible business fortuity, and provides supplementary environmental and economic encouragement for industries as it is used in ingredients of many drugs, functional foods and nutraceuticals. Numerous alkaline, acidic and enzymatic methods for the extraction of FA from different sources have been proposed in literature [3,35,45,46,71,86]. However, optimization of critical parameters for isolation of FA such as time of extraction, pH and temperature is essential for its high yield. Study was conducted with the help of response surface methodology which showed 1.3 fold increases in the production of FA as compared to the unoptimized conventional extraction technique [78]. FA is insoluble in water at room temperature but it is soluble in hot water, ethyl acetate, ethanol and ethyl ether, and it has been found that ethanol (60%) is suitable for the successful extraction of FA [18].

Although, FA is found ubiquitously in the cell wall of woods, grasses, and corn hulls, but it is not effortlessly available from these natural sources as it is covalently linked with a variety of carbohydrates as a glycosidic conjugate, or an ester or amide. Therefore, it can only be released from these natural products by alkaline hydrolysis [78]. Generally, FA obtained from the chemical process cannot be considered as natural, so various attempts have been made for enzymatically release of FA from natural sources. Isolation of FA for commercial production by enzymatic means is a difficult challenge because most of the FA contents in plants are covalently linked with lignin and other biopolymers. Recently, Uraji et al. successfully enhanced the enzymatic production of FA from defatted rice bran, and suggested that the enzymes (α-L-arabinofuranosidase, multiple xylanases, and an acetyl xylan esterase) from *Streptomyces* can also be used for the extraction of FA from other sources viz., raw rice bran, wheat bran and corncob [80]. The TLC separation of crude extracts and visualization by a range of spraying reagents and UV-light offers a quick way for the regular high-throughput detection of FA. Approximately >45% (>2.0%/g dry weight) of total FA content was released during enzymatic treatment of sweet potato stem that had been achieved through the incubation period of 12 h with 1.0% Ultraflo L [51]. Biotransformation studies for the production of FA from eugenol

Table 1
Content of ferulic acid in different known sources.
Source: [91]

Source	Ferulic acid (mg/0.1 kg)
Bamboo shoots	243.6
Water dropwort	7.3–34
Eggplant	7.3–35
Redbeet	25
Burdock	7.3–19
Soyabean	12
Peanut	8.7
Spinach/frozen	7.4
Redcabbages	6.3–6.5
Tomato	0.29–6
Radish	4.6
Broccoli	4.1
Carrot	1.2–2.8
Parsnip	2.2
Mizuna	1.4–1.8
Pot grown basil	1.5
Chinese cabbage	1.4
Pot grown lettuces	0.19–1.4
Green bean/fresh	1.2
Avocado	1.1
Grapefruit	10.7–11.6
Orange	9.2–9.9
Banana	5.4
Berries	0.25–2.7
Rhubarb	2
Plum, dark	1.47
Apples	0.27–0.85
Sugar-beet pulp	800
Popcorn	313
Whole grain rye bread	54
Whole grain oat flakes	25–52
Sweet corn	42
Pickled red beet	39
Rice, brown, long grain parboiled	24
Coffee	9.1–14.3
Boiled spaghetti	13.6
Pasta	12
White wheat bread	8.2

have been carried out by using the recombinant strain of *Ralstonia eutropha* H16 [64]. Lambert et al. got almost 90% yields in the production of FA from eugenol and coniferyl alcohol by using a recombinant strain of *Saccharomyces cerevisiae* [37].

3. Metabolism of ferulic acid

The formation of FA in plants occurs through the metabolic route of shikimate pathway starting with aromatic amino acids, L-phenylalanine and L-tyrosine as key entities. Initially, phenylalanine and tyrosine are converted into cinnamic and *p*-coumaric acid with the help of phenylalanine ammonia lyase and tyrosine ammonia lyase, respectively [17]. The *p*-coumaric acid gets converted into FA by hydroxylation and methylation reaction [16]. Oxidation and methylation of FA and other aromatic compounds give di- and tri-hydroxy derivatives of cinnamic acid, which takes part in the lignin formation together with FA. The conversion reactions occur during the formation of FA and other aromatic compounds, which are schematically represented in Fig. 2.

In vivo studies on FA metabolism suggests that it gets converted into a variety of metabolites such as ferulic acid-sulfate, ferulic acid-glucuronide, ferulic acid-sulfoglucuronide (major metabolites in the plasma and urine of rats), ferulic acid-diglucuronide, feruloylglycine, *m*-hydroxyphenylpropionic acid, dihydroferulic acid, vanillic acid and vanilloylglycine [90,91]. The data obtained from these outcomes recommends that the major pathway of FA metabolism is the conjugation reaction with glucuronic acid and/or sulfate. The conjugation of FA takes place mainly in the liver through the activities of sulfotransferases and uridine diphosphate (UDP) glucuronosyl transferases, while small amount of conjugation reaction also takes place in the intestinal mucosa and kidney [10,32,90]. A small portion of free FA possibly metabolized through β-oxidation in the liver [11].

A study was carried out by Overhage et al. with the help of *Pseudomonas sp.* strain HR199 at the end of twentieth century which revealed that the genes involved in the catabolic mechanism of FA were present on a DNA region, which was covered by two EcoRI fragments, E230 and E94, respectively. These genes were *fcs,*

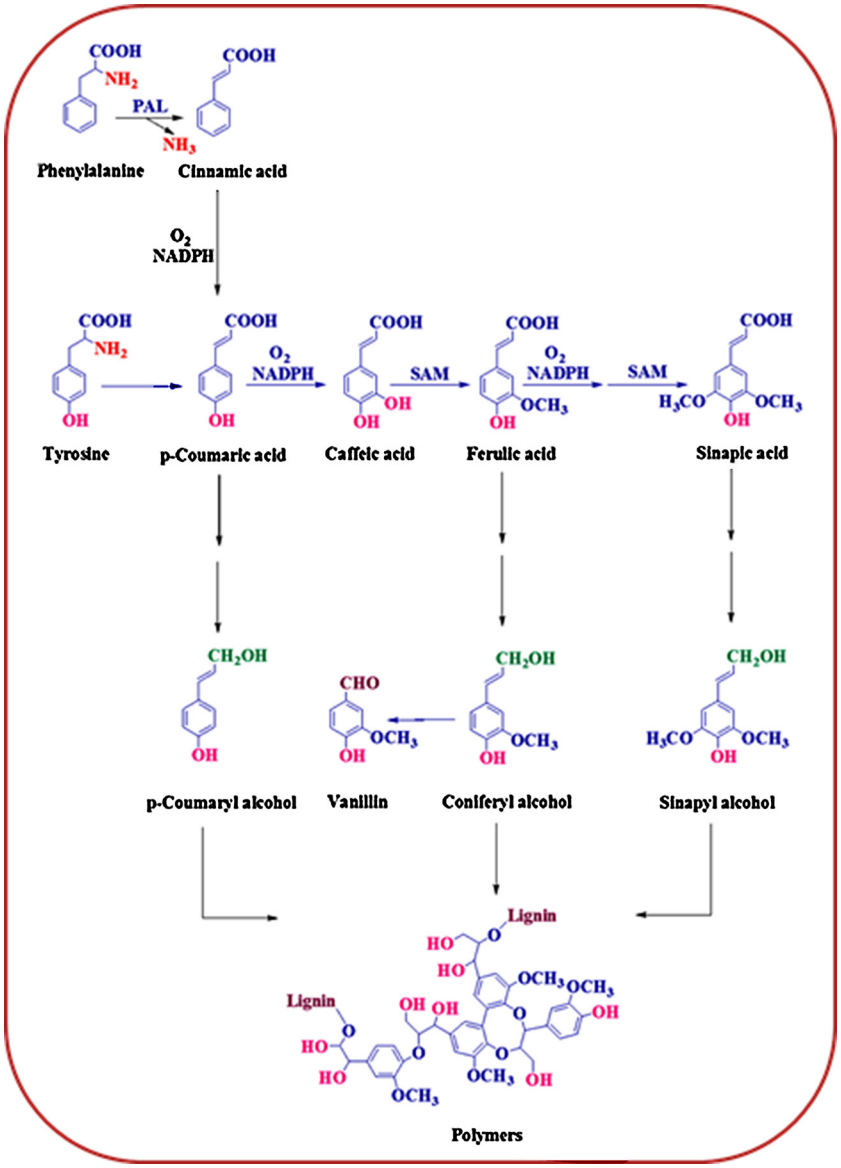

Fig. 2. Schematic depiction of synthesis of ferulic acid and other aromatic compounds *via* shikimate pathway {PAL: phenylalanine ammonia lyase; TAL: tyrosine ammonia lyase; SAM: *S*-adenosyl methionine (acts as a methyl donor)}.

ech, and *aat* encoding for feruloyl coenzyme A synthetase, enoyl-CoA hydratase/aldolase, and β-ketothiolase, respectively [63]. Report on the degradation of FA into vanillin and other useful organic compounds through protocatechuate 4,5-cleavage (PCA) pathway in *Sphingomonas paucimobilis* SYK-6 confirmed that FA got converted into feruloyl-CoA by feruloyl-CoA synthetase (FerA), and further into HMPMP-CoA (4-hydroxy-3-methoxyphenyl-β-hydroxypropionyl-coenzyme A) with the help of feruloyl-CoA hydratases/lyases (FerB and FerB2). It subsequently resulted into vanillin with the removal of $CH_3COSCoA$ (acetyl coenzyme A), and finally vanillin transformed into pyruvate and oxaloacetate through the PCA pathway [43]. The end products of FA catabolism enter into the TCA (tricarboxylic acid cycle), and produce energy in the biological system as shown in Fig. 3.

4. Industrial and biological usages of ferulic acid

The biological usages of FA came into notice when a group of Japanese researchers discovered antioxidant properties of steryl esters of FA, which was extracted from rice oil [87]. FA exhibits a wide range of biomedical effects including antioxidant, antiallergic, hepatoprotective, anticarcinogenic, anti-inflammatory, antimicrobial, antiviral, vasodilatory effect, antithrombotic, and helps to increase the viability of sperms [1,17,62,67]. Also it has applications in food preservation as a cross linking agent [61], photoprotective constituent in sunscreens and skin lotions [68]. An amide derivative of FA, formed by the condensation of FA with tyramine may be used as an indicator of environmental stress in plants. In baking industry, amides of FA with amino acids or dipeptides are commonly used for the purpose of preservation [17]. In many countries, use of FA as food additive has been approved by their government as it affectively scavenges superoxide anion radical, and inhibits the lipid peroxidation [72].

4.1. Ferulic acid as an antioxidant

Like several other phenols, FA also exhibits antioxidant activity in response to free radicals *via* donating one hydrogen atom from its phenolic hydroxyl group, as a result it shows strong anti-inflammatory activity in a carrageenan-induced rat paw edema model and other similar systems [34,55,62]. It has been revealed that the antioxidant capacity of phenolic acid is equivalent to lecithin upon comparison with ghee on inhibition of time dependent peroxide value. The resonance stabilization of FA is the main cause of its antioxidant nature. In addition, the reactive oxygen species of FA show the scavenging effect, which is similar to that of superoxide dismutase [17].

4.2. Ferulic acid as an anti-diabetic and anti-ageing agent

Diabetes, most widespread endocrine disorder in human beings, is characterized by hyperglycemia, over-production of free radicals and oxidative stress [4]. Due to the oxidative stress, an imbalance is started between the levels of pro-oxidants and antioxidants which lead to cellular injury in biological systems [82]. FA helps in neutralizing the free radicals present in the pancreas, which is produced by the use of streptozotocin, thus it decreases the toxicity of streptozotocin. It has been discussed in literature that the blood glucose level in case of streptozotocin induced diabetic animals is controlled by the administration of FA. The reduction in oxidative stress/toxicity might help the β cells to get proliferate and radiate more insulin in the pancreas. Increased

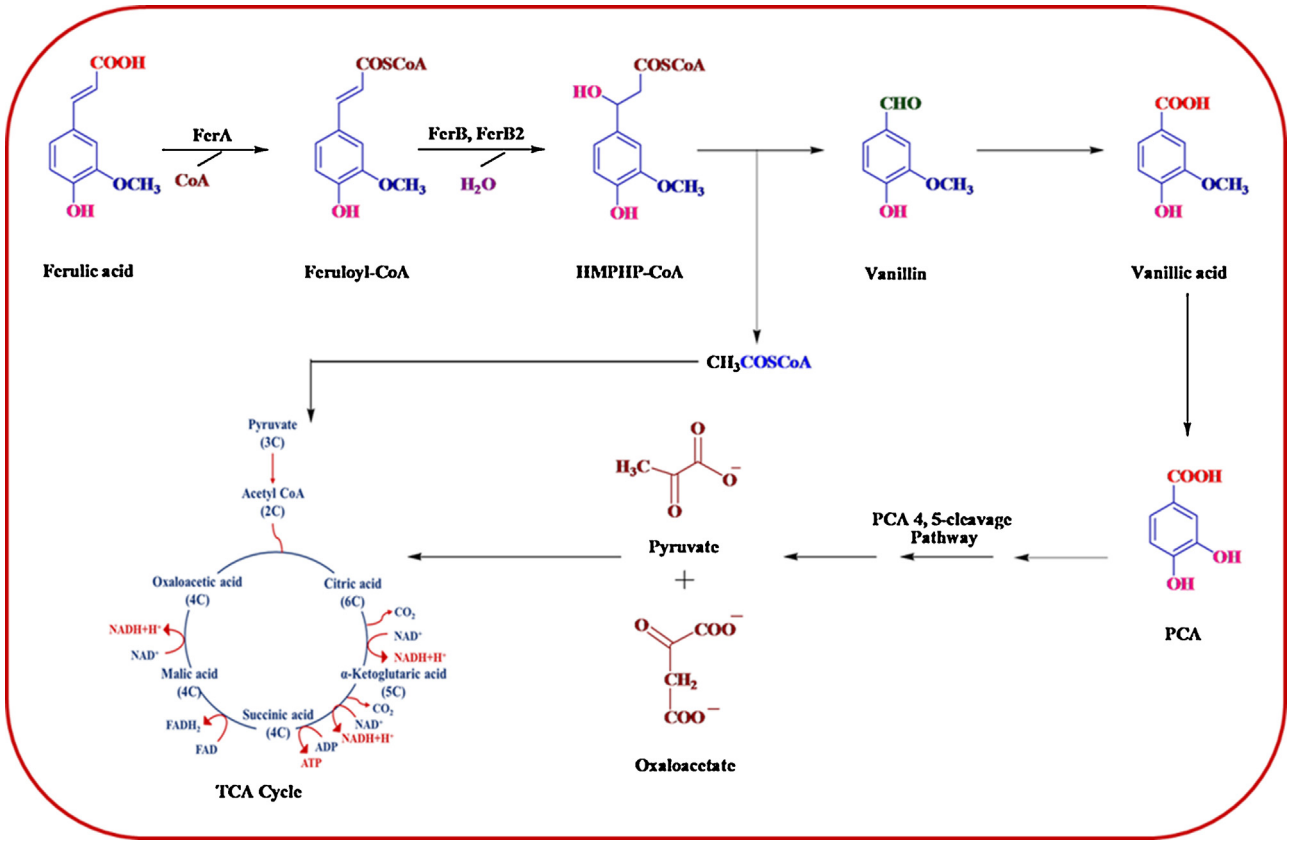

Fig. 3. Pathway for ferulic acid catabolism in *S. paucimobilis* SYK-6 (HMPHP-CoA: 4-hydroxy-3-methoxyphenyl-β-hydroxyprpionyl CoA).

secretion of insulin causes increase in the utilization of glucose from extra hepatic tissues that decreases the blood glucose level [5]. Reports are also available on the stimulatory effects of insulin secretion in rat pancreatic RIN-5F cells by FA amide [58].

4.3. Ferulic acid as preclusion of food discoloration and growth enhancing agent

FA has been used to maintain the color of green peas, prevent discoloration of green tea, and oxidation of banana turning black color i.e., it reduces the bacterial contamination [44]. FA and γ-oryzanol were found to prevent the photo-oxidation of lutein and astaxanthin in Red sea bream [42]. Due to the structural similarity of FA with normetanephrine (first metabolite of norepinephrine), it mimics the stimulatory effect on somatotropin in pituitary gland and hence enhance the growth [15].

4.4. Ferulic acid as precursor of vanillin

In past years, the occurrence of vanillin as an intermediate in the microbial degradation of FA has been reported by many research groups [28,45,54,66]. Natural vanillin has a high demand in the flavor market as it is used as a flavoring agent in foods, beverages, pharmaceuticals and other industries [20]. Industries such as chocolate and ice cream together capture about 75% of the total market of vanillin, while the small amount is used in baking. Vanillin is also used in the fragrance industry for the making of good quality of perfumes, in cleaning products, in livestock fodder and pharmaceuticals to cover the unpleasant odors or tastes of medicines. Biosynthesis of vanillin from FA (Fig. 4) is achieved by the conversion of FA into feruloyl SCoA (reduced feruloyl coenzyme A) using ATP (adenosine triphosphate) and CoASH (reduced coenzyme A). Removal of water and $CH_3COSCoA$ (reduced acetyl coenzyme A) molecule converts feruloyl SCoA finally into vanillin. In addition of above functions, vanillin can also be used in visualization of components in thin layer chromatography staining plates. These stains give a range of colors for the different components. *Pseudomonas putida* is found to convert the FA to into vanillic acid very efficiently.

4.5. Uses of ferulic acid in cosmetics

ROS (reactive oxygen species) formation is the main cause of UV-induced skin damage. During the exposure to radiation, a photon interact with *trans*-urocanic acid in skin and generate singlet oxygen that can activate the entire oxygen free radical cascade with oxidation of proteins, nucleic acid and lipids, resulting in the photoaging changes and skin cancer [6,7]. FA is a strong UV absorber [17], and skin absorbs it at the same rate at acidic and neutral pH [68]. FA structure is similar to tyrosine, and it is believed that FA inhibits the melanin formation through competitive inhibition with tyrosine. It gives a considerable protection to the skin against UVB-induced erythema in a time dependent manner [68]. FA alone or in alliance with vitamin E and vitamin C provides about 4–8 fold protection against solar-simulated radiation damage on most likely interacting pro-oxidative intermediates. Successful photoprotection with solar-simulated ultraviolet induced photodamage was recorded on a pig (*in vivo* experiments) by using a mixture of FA (0.5%), vitamin E (1%) and, vitamin C (15%) [38].

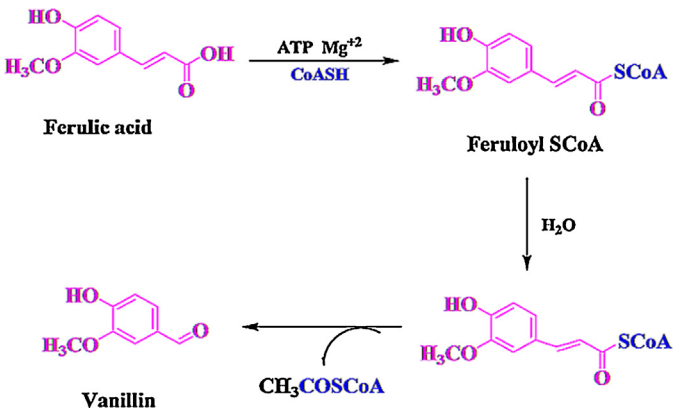

Fig. 4. Pictorial representation of bioconversion of ferulic acid into vanillin.

4.6. Ferulic acid as an anticancer agent

In the etiology of cancer, free radical plays a major role; therefore antioxidants present in diet have fastidious consideration as potential inhibitors of abandoned cell growth. FA's anti-carcinogenic activity is related to its capability of scavenging ROS and stimulation of cytoprotective enzymes [6]. By doing this, FA diminished lipid peroxidation, DNA single-strand rupture, inactivation of certain proteins, and disruption of biological membranes [26]. Due to the construction of free radicals in leucocytes and other cells, nicotine is supposed to have a key role in the pathogenesis of lung cancer. In 2007, Sudheer et al. worked on rat peripheral blood lymphocytes, and concluded that FA (10–150 μM) counteracted nicotine-induced lipid peroxidation and reduction in GSH (reduced glutathione) level [75].

Stimulation of detoxification enzyme seems to be another mechanism for the anticarcinogenic action of FA; it enhances the UGTs enzyme (UDP-glucuronosyltransferases) activity, drastically in liver. Due to this reason better detoxification of carcinogenic compounds occurs, and subsequently leads to the prevention of gastrointestinal cancer [81]. UGTs catalyzes the conjugation of exogenous and endogenous compounds with glucuronic acid, which results in less biologically active molecules with enhanced water solubility that facilitates the excretion through bile or urine [36]. FA also inhibits the growth of colon cancer cells [52]. Further, its inhibitory effect on carcinogenesis of colon cancer in rats was confirmed by *in vivo* test [29]. Polyphenols, including FA, comprise tumor-suppression potential in breast cancer cell lines as well [50]. FA has been claimed to decrease the side effects of chemo and radiotherapy of carcinomas by increasing the natural immune defense [40].

4.7. Pulmonary protection and cardiovascular effect of ferulic acid

Nicotine is one of the major hazardous compounds of cigarette smoke [84]. It causes the oxidative cellular injury by increasing the lipid peroxidation, which is supposed to play a key role in the pathogenesis of several smoking related diseases [89]. Due to the administration of FA, a reverse reaction occurs in the damage, which was induced by nicotine. FA causes a significant increase in the endogenous antioxidant defense, which protect the cells from oxidative damage. FA protects the membrane by successfully quenching of free radicals from attacking the membrane. It also inhibits the leakage of marker enzymes into circulation, and increase the antioxidant status in circulation [74]. It has been shown that the blood pressure was decreased in both SHRSP (stroke-prone spontaneously hypertensive) rats and SHR (spontaneously hypertensive rats) with a maximum effect (−34 mmHg) after 2 h of oral intake of FA (1–100 mg/kg body weight) [59,77]. Studies also showed that sodium salt of FA decreases the serum lipids, inhibits platelet aggregation and prevents thrombus formation [83].

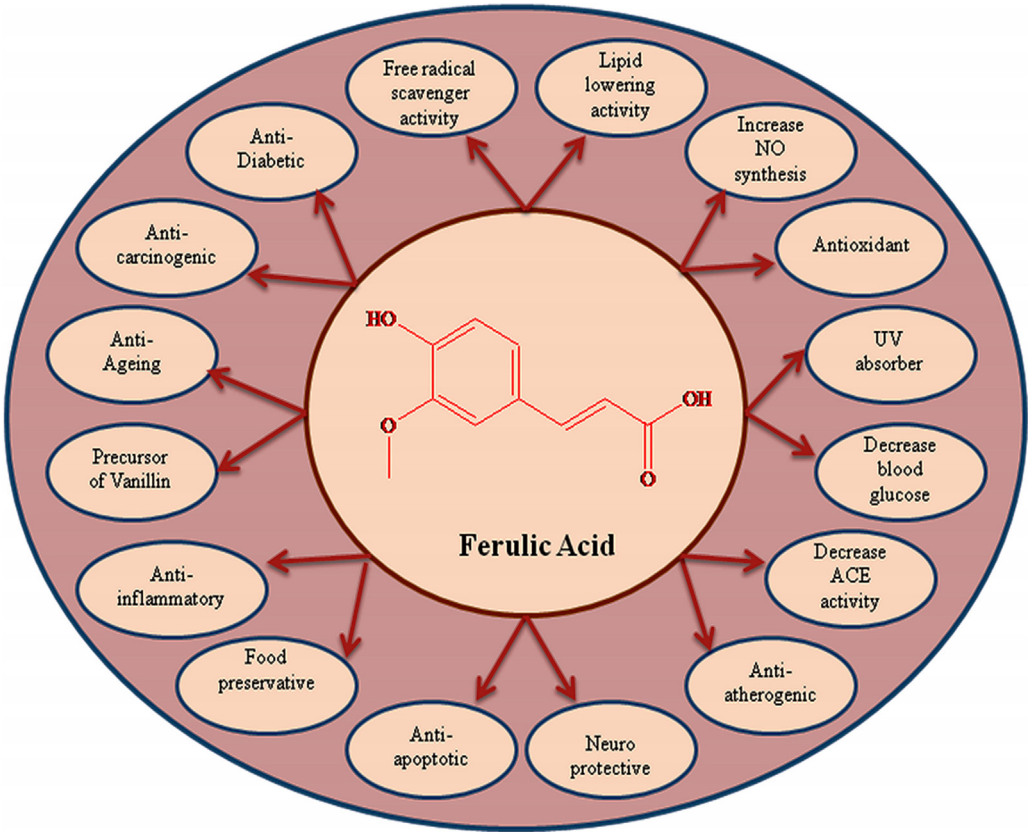

Fig. 5. Different applications of ferulic acid. Ferulic acid known to exhibit a variety of biomedical, pharmaceutical and industrial applications.

4.8. Ferulic acid as food preservative

Report on the first use of FA as food preservative was done in Japan; to preserve oranges and to inhibit the autoxidation of linseed oil [79]. With the addition of copper (Cu) or iron (Fe), phenolic compounds were also found to stabilize the lard and soybean oil. Mixtures of FA and amino acids or dipeptides (such as glycylglycine or alanylalanine) exert a synergistic inhibitory consequence on the peroxidation of linoleic acid. Complete inhibition of oxidation of biscuits (30 °C for 40 days) was done by using the mixture of FA (0.05%) and glycine (0.5%) [60].

5. Additional applications of ferulic acid

Besides the above discussed functions, it also has key role in numerous other applications. It has been proved by *in situ* experiments that mixture of FA and tetramethylpyrazine showed the synergistic inhibitory effect on spontaneous movement in rat [65]. FA utilizes the anthocyanin-type pigments present in tulip flowers having cosmetic properties to stabilize the rouge against oxidative discoloration [31]. FA also increases the stability of cytochrome c, and hence inhibits the apoptosis, which is induced by cytochrome c [88]. Recently, *in vitro* and *in vivo* angiogenic activity of FA *via* stimulation of the VEGF, PDGF and HIF-1α pathways has been done, and concluded that the angiogenic effects of FA occur *via* two pathways which are called as PI3K and MAPK pathway. FA is a new potential therapeutic agent for ischemic diseases [39]; it also enhances IgE binding to pea nut allergens [13]. Different functional role and biomedical applications of FA are schematically represented in Fig. 5.

It has been proved that FA acts as a β-secretase modulator with therapeutic potential against Alzheimer's disease [53], and found to improve the structure and function of the heart, blood vessels, liver, and kidneys in hypertensive rats [2]. Uses of FA grafted chitosan as an antioxidant in food, cosmetics, food packaging, biomedical and pharmaceutical is recently discovered [70]. In plants, environmental stress can be resolute by the use of FA amides with putrescine, tyramine or tryptamine. FA amides with amino acid or dipeptides are used as preservatives in baking [17]. Researchers have also proved that at lower concentration (25–50 μM), FA reduced the cell death in hippocampal neuronal cells induced by peroxyl radical, while at higher concentration (250–500 μM), it diminished the hydroxyl radicals induced by protein oxidation and peroxidation of lipid [30]. FA (200 μM) helped in the reduction of lipid peroxidation in peripheral blood mononuclear cells induced by H_2O_2 [33]. Administration of FA for a very long time inhibits the expression of endothelial and inducible NOS (iNOS) in mouse, hippocampus and rat cortical neurons [12,76].

6. Conclusions

Here, this review article provides adequate information on natural sources, synthesis, structure, metabolism, and uses of FA in biomedical as well as other industries. Industries such as cosmetic, pharmaceutical, baking, ice cream, chocolate, food processing have high demand for FA. Most of the activities as shown by FA can be attributed to its potent antioxidant capacity because of conjugation in its nucleus and side chain. These investigations greatly support the regular ingestion of FA for providing significant protection associated with a range of oxidative stress related diseases. Significant efforts have been made for the development of biotechnological processes as the consumption of natural products in food, cosmetics, pharmaceutical and other industries, and are

increasing day by day that is why the demand and supply of natural products should be maintained. This review deals with the major attainments in the field of extraction, metabolism and applications of ferulic acid, which can be used for betterment of mankind.

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References

[1] T. Akihisa, K. Yasukawa, M. Yamaura, M. Ukiya, Y. Kimura, N. Shimizu, K. Arai, Triterpene alcohol and sterol ferulates from rice bran and their anti-inflammatory effects, J. Agric. Food Chem. 48 (2000) 2313–2322.
[2] M.A. Alam, C. Sernia, L. Brown, Ferulic acid improves cardiovascular and kidney structure and function in hypertensive rats, J. Cardiovasc. Pharmacol. 61 (2013) 240–248.
[3] U.B. Anvar, G. Mazza, Extraction and purification of ferulic acid from flax shives, wheat and corn bran by alkaline hydrolysis and pressurised solvents, Food Chem. 115 (2009) 1542–1548.
[4] M. Aragno, S. Parola, E. Tamagno, E. Brignardello, R. Manti, O. Danni, G. Boccuzzi, Oxidative derangement in rat synaptosomes induced by hyperglycaemia: restorative effect of dehydroepiandrosterone treatment, Biochem. Pharmacol. 60 (2000) 389–395.
[5] M.S. Balasubashini, R. Rukkumani, P. Viswanathan, V.P. Menon, Ferulic acid alleviates lipid peroxidation in diabetic rats, Phytother. Res. 18 (2004) 310–314.
[6] E. Barone, V. Calabrese, C. Mancuso, Ferulic acid and its therapeutic potential as a hormetin for age-related diseases, Biogerontology 10 (2009) 97–108.
[7] Blume G. (2013). Novel Carrier System for the Transport of Active Substances into the Skin. US Patent: 20,130,011,455.
[8] L.C. Bourne, C. Rice-Evans, Bioavailability of ferulic acid, Biochem. Biophys. Res. Commun. 253 (1998) 222–227.
[9] M.V. Boven, S. Toppet, M.M. Cokelaere, P. Daenens, Isolation and structural identification of a new simmondsin ferulate from jojoba meal, J. Agric. Food Chem. 42 (1994) 1118–1123.
[10] M.X. Chang, L.Y. Xu, J.S. Tao, Y. Feng, Metabolism and pharmacokinetics of ferulic acid in rats, Zhongguo Zhong Yao Za Zhi 8 (1993) 300–302.
[11] A. Chesson, G.J. Provan, W.R. Russell, L. Scobbie, A.J. Richardson, C. Stewart, Hydroxycinnamic acids in the digestive tract of livestock and humans, J. Sci. Food Agric. 79 (1999) 373–378.
[12] J.Y. Cho, H.S. Kim, D.H. Kim, J.J. Yan, H.W. Suh, D.K. Song, Inhibitory effects of long-term administration of ferulic acid on astrocyte activation induced by intracerebroventricular injection of β-amyloid peptide (1–42) in mice, Prog. Neuropsychopharmacol. Biol. Psychiatry 29 (2005) 901–907.
[13] S.Y. Chung, E.T. Champagne, Ferulic acid enhances IgE binding to peanut allergens in western blots, Food Chem. 124 (2011) 1639–1642.
[14] S. Dutt, General synthesis of a-unsaturated acids from malonic acid, Q. J. Chem. Soc. 1 (1925) 297–301.
[15] R.C. Gorewit, Pituitary and thyroid hormone responses of heifers after ferulic acid administration, J. Dairy Sci. 66 (1983) 624–633.
[16] G. Gowri, R.C. Bugos, W.H. Campbell, C.A. Maxwell, R.A. Dixon, Stress responses in alfafa (*Medicago sativa* L.). X. Molecular cloning and expression of S-adenosyl-L-methionine: caffeic acid 3-O-methyltransferase, a key enzyme of lignin biosynthesis, Plant Physiol. 97 (1991) 7–14.
[17] E. Graf, Antioxidant potential of ferulic acid, Free Radic. Biol. Med. 3 (1992) 435–513.
[18] T. Guo, Y. Sun, Y. Sui, F. Li, Determination of ferulic acid and adenosine in *Angelicae* radix by micellar electrokinetic chromatography, Anal. Bioanal. Chem. 375 (2003) 840–843.
[20] S. Hagedorn, B. Kaphammer, Microbial biocatalysis in the generation of flavor and fragrance chemicals, Annu. Rev. Microbiol. 48 (1994) 773–780.
[21] P.J. Harris, R.D. Hartley, Phenolic constituents of the cell walls of monocotyledons, Biochem. Syst. Ecol. 8 (1980) 153–160.
[22] R.D. Hartley, C.W. Ford, Phenolic constituents of plant cell walls and wall degradability, in: N.G. Lewis, M.G. Paice (Eds.), Plant Cell Wall Polymers Biogenesis and Biodegradation, American Chemical Society, Washington DC, 1989, pp. 137–145.
[23] R.D. Hartley, P.J. Harris, Phenolic constituents of the cell walls of dicotyledons, Biochem. Syst. Ecol. 9 (1981) 189–203.
[24] K. Herrmann, Occurrence and content of hydroxycinnamic and hydroxybenzoic acid compounds in foods, CRC Crit. Rev. Food Sci. Nutr. 28 (1989) 315–347.
[25] K. Herrmann, Significance of hydroxycinnamic compounds in food. I. Antioxidant activity-effects on the use, digestibility, and microbial spoilage in food, Chem. Mikrobiol. Technol. Lebensm. 12 (1990) 137–144.
[26] M. Hirose, S. Takahashi, K. Ogawa, M. Futakuchi, T. Shirai, Phenolics: blocking agents for heterocyclic amine-induced carcinogenesis, Food Chem. Toxicol. 37 (1999) 985–992.
[27] H. Hlasiwetz, L. Barth, Mittheilungen aus dem chemischen Laboratorium in Innsbruck I, Ueber einige Harze [Zersetzungsproducte derselben durch schmelzendes Kali], Liebig's Annalen der Chem. 138 (1866) 61–76.
[28] D. Hua, C. Ma, L. Song, S. Lin, Z. Zhang, Z. Deng, P. Xu, Enhanced vanillin production from ferulic acid using adsorbent resin, Appl. Microbiol. Biotechnol. 74 (2007) 783–790.
[29] E.A. Hudson, P.A. Dinh, T. Kokubun, M.S. Simmonds, A.C. Gescher, Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells, Cancer Epidemiol. Biomark. Prev. 9 (2000) 1163–1170.
[30] J. Kanski, M. Aksenova, A. Stoyanova, D.A. Butterfield, Ferulic acid antioxidant protection against hydroxyl and peroxyl radical oxidation in synaptosomal and neuronal cell culture systems *in vitro*: structure-activity studies, J. Nutr. Biochem. 13 (2002) 273–281.
[31] Kawai S, Ando Y, Ibata Y. (1990). Cosmetics containing anthocyanin-type pigments and the color stabilizer ferulic acid. Japan Kokai 89:647–692.
[32] S.M. Kern, R.N. Bennett, P.W. Needs, F.A. Mellon, P.A. Kroon, M.T. Garcia-Conesa, Characterization of metabolites of hydroxycinnamates in the *in vitro* model of human small intestinal epithelium caco-2 cells, J. Agric. Food Chem. 51 (2003) 7884–7891.
[33] K.L. Khanduja, P.K. Avti, S. Kumar, N. Mittal, K.K. Sohi, C.M. Pathak, Anti-apoptotic activity of caffeic acid, ellagic acid and ferulic acid in normal human peripheral blood mononuclear cells: a Bcl-2 independent mechanism, Biochim. Biophys. Acta 1760 (2006) 283–289.
[34] H. Kikuzaki, M. Hisamoto, K. Hirose, K. Akiyama, H. Taniguchi, Antioxidant properties of ferulic acid and its related compounds, J. Agric. Food Chem. 50 (2002) 2161–2169.
[35] K.H. Kim, R. Tsao, R. Yang, S.W. Gnu, Phenolic acid profiles and antioxidant activities of wheat bran extracts and the effect of hydrolysis conditions, Food Chem. 95 (2006) 466–473.
[36] C. King, W. Tang, J. Ngui, T. Tephly, M. Braun, Characterization of rat and human UDP-glucuronosyltransferases responsible for the *in vitro* glucuronidation of diclofenac, Toxicol. Sci. 61 (2001) 49–53.
[37] F. Lambert, J. Zucca, F. Ness, M. Aigle, Production of ferulic acid and coniferyl alcohol by conversion of eugenol using a recombinant strain of *Saccharomyces cerevisiae*, Flavour Fragr. J. 29 (2013) 14–21.
[38] F.H. Lin, J.Y. Lin, R.D. Gupta, J.A. Tournas, J.A. Burch, M.A. Selim, N.A. Monteiro-Riviere, J.M. Grichnik, J. Zielinski, S.R. Pinnell, Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin, J. Invest. Dermatol. 125 (2005) 826–832.
[39] C.M. Lina, J.H. Chiuc, I.H. Wu, B.W. Wang, C.M. Pan, Y.H. Cheng, Ferulic acid augments angiogenesis *via* VEGF, PDGF and HIF-1α, J. Nutr. Biochem. 21 (2010) 627–633.
[40] Liu Y. 1987. Pharmaceutical composition for increasing immunity and decreasing side effects of anticancer chemotherapy. US patent: 4,687,761.
[42] Maoka, F. Tanimoto, M. Sano, K. Tsurukawa, T. Tsuno, S. Tsujiwaki, K. Ishimaru, K. Takii, Effects of dietary supplementation of ferulic acid and gamma-oryzanol on integument color and suppression of oxidative stress in cultured red sea bream, *Pagrus major*, J. Oleo Sci. 57 (2008) 133–140.
[43] E. Masai, K. Harada, X. Peng, H. Kitayama, Y. Katayama, M. Fukuda, Cloning and characterization of the ferulic acid catabolic genes of *Sphingomonas paucimobilis* SYK-6, Appl. Environ. Microbiol. 68 (2002) 4416–4424.
[44] Y. Masaji, Preservation measures for food products. Preventive method of coloring agricultural products using ferulic acid, Tech. J. Food Chem. Chem. 8 (1999) 76–79.
[45] S. Mathew, T.E. Abraham, Studies on the production of feruloyl esterase from cereal brans and sugar cane bagasse by microbial fermentation, Enzyme Microb. Technol. 36 (2005) 565–570.
[46] S. Mathew, T.E. Abraham, Bioconversions of ferulic acid, an hydroxycinnamic acid, Crit. Rev. Microbiol. 32 (2006) 115–125.
[47] P. Mattila, J. Hellstrom, Phenolic acids in potatoes, vegetables, and some of their products, J. Food Comp. Anal. 20 (2007) 152–160.
[48] P. Mattila, J. Hellstrom, R. Torronen, Phenolic acids in berries, fruits, and beverages, J. Agric. Food Chem. 54 (2006) 7193–7199.
[49] P. Mattila, J.M. Pihlava, J. Hellstrom, Contents of phenolic acids, alkyl-and alkenylresorcinols, and avenanthramides in commercial grain products, J. Agric. Food Chem. 53 (2005) 8290–8295.
[50] J.A. Menendez, V.M. Alejandro, O.F. Cristina, G.V. Rocio, C.P. Alegria, F.G. Alberto, S.C. Antonio, Analyzing effects of extra-virgin olive oil polyphenols on breast cancer-associated fatty acid synthase protein expression using reverse-phase protein microarrays, Int. J. Mol. Med. 22 (2008) 433–439.
[51] J.Y. Min, S.M. Knag, D.J. Park, Y.D. Kim, H.N. Jung, J.K. Yang, W.T. Seo, S.W. Kim, C. S. Karigar, M.S. Choi, Enzymatic release of ferulic acid from Ipomoea batatas L. (Sweet Potato) stem, Biotechnol. Bioprocess Eng. 11 (2006) 372–376.
[52] H. Mori, K. Kawabata, N. Yoshimi, T. Tanaka, T. Murakami, T. Okada, H. Murai, Chemopreventive effects of ferulic acid on oral and rice germ on large bowel carcinogenesis, Anticancer Res. 19 (1999) 3775–3783.
[53] T. Mori, N. Koyama, M.V. Guillot-Sestier, J. Tan, T. Town, Ferulic acid is a nutraceutical β-secretase modulator that improves behavioral impairment and Alzheimer-like pathology in transgenic mice, PLoS ONE 8 (2013) 1–15.
[54] A. Muheim, K. Lerch, Towards a high-yield bioconversion of ferulic acid to vanillin, Appl. Microbiol. Biotechnol. 51 (1999) 456–461.
[55] N.R. Natalia, D. Claire, P.V. Lullien, M. Valerie, Exposure or release of ferulic acid from wheat aleurone: impact on its antioxidant capacity, Food Chem. 141 (2013) 2355–2362.

[56] M. Nethaji, V. Pattabhi, G.R. Desiraju, Structure of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid (ferulic acid), Acta Cryst. C 44 (1988) 275–277.
[57] C.C. Nicholas, Structure and biogenesis of the cell walls of grasses, Annu. Rev. Plant Physiol. Plant Mol. Biol. 47 (1996) 445–476.
[58] E. Nomura, A. Kashiwada, A. Hosoda, K. Nakamura, H. Morishita, T. Tsuno, H. Taniguchi, Synthesis of amide compounds of ferulic acid and their stimulatory effects on insulin secretion *in vitro*, Bioorg. Med. Chem. 11 (2003) 3807–3813.
[59] A.Y. Ohsaki, H. Shirakawa, T. Koseki, M. Komai, Novel effects of a single administration of ferulic acid on the regulation of blood pressure and the hepatic lipid metabolic profile in stroke-prone spontaneously hypertensive rats, J. Agric. Food Chem. 56 (2008) 2825–2830.
[60] T. Okada, K. Nakagawa, N. Yamaguchi, Antioxidative activities of amino compounds on fats and oils: VIII. Antioxidative activity of ferulate and the synergistic effect of amino compounds, Nippon Shokuhin Kogyo Gakkaishi 29 (1982) 305–309.
[61] A. Oosterveld, I.E. Pol, G. Beldman, A.G.J. Voragen, Isolation of feruloylated arabinans and rhamnogalacturonans from sugar beet pulp and their gel forming ability by oxidative cross-linking, Carbohydr. Polym. 44 (2010) 9–17.
[62] S. Ou, K.C. Kwok, Ferulic acid: pharmaceutical functions, preparation and applications in foods, J. Sci. Food. Agric. 84 (2004) 1261–1269.
[63] J. Overhage, H. Priefert, A. Steinbuchel, Biochemical and genetic analyses of ferulic acid catabolism in *Pseudomonas* sp. Strain HR199, Appl. Environ. Microbiol. 65 (1999) 4837–4847.
[64] J. Overhage, A. Steinbüchel, H. Priefert, Biotransformation of eugenol to ferulic acid by a recombinant strain of *Ralstonia eutropha* H16, Appl. Environ. Microbiol. 68 (2002) 4315–4321.
[65] Y. Ozaki, J.P. Ma, Inhibitory effects of tetramethylpyrazine and ferulic acid on spontaneous movement of rat uterus *in situ*, Chem. Pharm. Bull 38 (1990) 1620–1623.
[66] J.P.N. Rosazza, Z. Huang, L. Dostal, T. Volm, B. Rousseau, Review: Biocatalytic transformations of ferulic acid: an abundant aromatic natural product, J. Ind. Microbiol. 15 (1995) 457–471.
[67] R. Rukkumani, K. Aruna, V.P. Suresh, M.V. Padmanabhan, Hepatoprotective role of ferulic acid: a dose-dependent study, J. Med. Food 7 (2004) 456–461.
[68] A. Saija, A. Tomaino, D. Trombetta, A. De Pasquale, N. Uccella, T. Barbuzzi, D. Paolino, F. Bonina, *In vitro* and *in vivo* evaluation of caffeic and ferulic acids as topical photoprotective agents, Int. J. Pharm. 199 (2000) 39–47.
[70] W. Sarekha, Y. Rangrong, Preparation, characterization and antioxidant property of water-soluble ferulic acid grafted chitosan, Carbohydr. Polym 96 (2013) 495–502.
[71] M.L. Soto, A. Moure, H. Dominguez, J.C. Parajo, Recovery, concentration and purification of phenolic compounds by adsorption: a review, J. Food Eng. 105 (2011) 1–26.
[72] M. Srinivasan, A.R. Sudheer, V.P. Menon, Ferulic acid: therapeutic potential through its antioxidant property, J. Clin. Biochem. Nutr. 40 (2007) 92–100.
[73] D. Strack, Metabolism of hydroxycinnamic acid conjugates, Bull. Liaison Groupe Polyphen. 15 (1990) 55–64.
[74] A.R. Sudheer, C. Kalpana, M. Srinivasan, V.P. Menon, Ferulic acid modulates altered lipid profiles and prooxidant/antioxidant status in circulation during nicotine-induced toxicity: a dose dependent study, Toxicol. Mech. Methods 15 (2005) 375–381.
[75] A.R. Sudheer, S. Muthukumaran, C. Kalpana, M. Srinivasan, V.P. Menon, Protective effect of ferulic acid on nicotine-induced DNA damage and cellular changes in cultured rat peripheral blood lymphocytes: a comparison with *N*-acetylcysteine, Toxicol. In Vitro 21 (2007) 576–585.
[76] R. Sultana, A. Ravagna, A.H. Mohmmad, V. Calabrese, D.A. Butterfield, Ferulic acid ethyl ester protects neurons against amyloid betapeptide(1–42)-induced oxidative stress and neurotoxicity: relationship to antioxidant activity, J. Neurochem. 92 (2005) 749–758.
[77] A. Suzuki, D. Kagawa, A. Fujii, R. Ochiai, I. Tokimitsu, I. Saito, Short- and long-term effects of ferulic acid on blood pressure in spontaneously hypertensive rats, Am. J. Hypertens. 15 (2002) 351–358.
[78] A. Tilay, M. Bule, J. Kishenkumar, U. Annapure, Preparation of ferulic acid from agricultural wastes: Its improved extraction and purification, J. Agric. Food Chem. 56 (2008) 7644–7648.
[79] Tsuchiya T, Takasawa M. (1975). Oryzanol, ferulic acid, and their derivatives as preservatives. Japan. Kokai 07:518–521.
[80] M. Uraji, M. Kimura, Y. Inoue, K. Kawakami, Y. Kumagai, K. Harazono, T. Hatanaka, Enzymatic production of ferulic acid from defatted rice bran by using a combination of bacterial enzymes, Appl. Biochem. Biotechnol. 171 (2013) 1085–1093.
[81] E.M. Van der Logt, H.M. Roelofs, F.M. Nagengast, W.H. Peters, Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogens, Carcinogenesis 24 (2003) 1651–1657.
[82] L. Villa-Caballero, A.A. Nava-Ocampo, A.C. Frati-Munari, H. Ponce-Monter, Oxidative stress. Should it be measured in the diabetic patient? Gac Med Max 136 (2000) 249–256.
[83] B. Wang, J. Ouyang, Y. Liu, J. Yang, L. Wei, K. Li, H. Yang, Sodium ferulate inhibits atherosclerogenesis in hyperlipidemia rabbits, J. Cardiovasc. Pharmacol. 43 (2004) 549–554.
[84] G.W. Warren, A.K. Singh, Nicotine and lung cancer, J. Carcinog. 12 (2013) 1.
[85] D.W. Wong, V.J. Chan, S.B. Batt, G. Sarath, H. Liao, Engineering *Saccharomyces cerevisiae* to produce feruloyl esterase for the release of ferulic acid from switchgrass, J. Ind. Microbiol. Biotechnol. 38 (2011) 1961–1967.
[86] F. Xu, R.C. Sun, J.X. Sun, C.F. Liu, B.H. He, J.S. Fan, Determination of cell wall ferulic and *p*-coumaric acids in sugarcane bagasse, Anal. Chim. Acta 552 (2005) 207–217.
[87] K. Yagi, N. Ohishi, Action of ferulic acid and is derivatives as antioxidants, J. Nutr. Sci. Vitam. 25 (1979) 127–130.
[88] F. Yang, B.R. Zhou, P. Zhang, Y.F. Zhao, J. Chen, Y. Liang, Binding of ferulic acid to cytochrome c enhances stability of the protein at physiological pH and inhibits cytochrome c-induced apoptosis, Chem. Biol. Interact. 170 (2007) 231–243.
[89] D. Yildiz, N. Ercal, D.W. Armstrong, Nicotine enantiomers and oxidative stress, Toxic 130 (1998) 155–165.
[90] Z. Zhao, Y. Egashira, H. Sanada, Ferulic acid sugar esters are recovered in rat plasma and urine mainly as the sulfoglucuronide of ferulic acid, J. Nutr. 133 (2003) 1355–1361.
[91] Z. Zhao, M.H. Moghadasian, Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: a review, Food Chem. 109 (2008) 691–702.