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FERULIC ACID – NEITHER "A FREE RADICAL SCAVENGER" NOR "A DIETARY HEALTH MAKER"- A REVIEW

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ABSTRACT

Ferulic acid is a hydroxycinnamic acid, a type of organic compound. It is an abundant phenolic phytochemical found in plant cell wall components such as arabinoxylans as covalent side chains. Ferulic acid, together with dihydro ferulic acid, is a component of ligno cellulose, serving to crosslink the lignin and polysaccharides, thereby conferring rigidity to the cell walls. Ferulic acid, like many natural phenols, is an antioxidant *in vitro* in the sense that it is reactive toward free radicals such as reactive oxygen species. Ferulic acid, being highly abundant, may be useful as a precursor in the manufacturing of vanillin, a synthetic flavoring agent often used in place of natural vanilla extract. In this review we discussed the latest research updates are also elucidating the beneficial effects of this phenolic compound for understanding its potential applications in health and disease and also to help in the development and design of suitable dietary recommendations.

KEWWORDS: Ferulic acid, vanillin, phenolic, dietary, Free radical.

INTRODUCTION

Ferulic Acid is one of the most abundant phenolics arising from the metabolism of phenylalanine and tyrosine by Shikimate pathway and distributed in plants especially cereals, triticale, rye, fruits and vegetables, with a close resemblance to cinnamic acid and

interestingly it is a source of vanillin.[1] Ferulic acid is also used as an antioxidant, and an antimicrobial agent, diabetes, cancer and Parkinson as well as in radioprotection. In 1886, Hlasiwetz Barth, an Austrian, isolated 3-methoxy-4-hydroxycinnamic acid from the genus Ferula foetida for structure determination.[2] The synthesis of Ferulic acid was established by Dutt in 1935 when ferulic acid was used as a precursor in the manufacturing of vanillin and malonic acid.[3] It is also recognized that ferulic acid exhibits a preventive effect on discoloration in various food products and a variety of physiological functions such as suppression of Alzheimer's disease, prevention of muscular fatigue, improvement in hypertension and antitumor activity of breast, liver, and colon.[2, 4] Ferulic acid is a natural polyphenols extracted from rice bran that is approved as a food additive in Japan and antioxidants in the diet has beneficial effects on human health because they protect the biologically important cellular components, such as DNA, proteins, and membrane lipids, from reactive oxygen species (ROS) attacks[5]. Ferulic acid occurs most frequently as ester cross-links with polysaccharides in the cell wall, e.g. as arabinoglycans in grasses, pectin in spinach and sugar beet. Ferulic acid is a phenylpropenoid derived from the cinnamic acid 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid, 4-hydroxy-3-methoxycinnamic acid, or coniferic acid (It shows two isomers: *cis* (a yellow oily liquid) and *trans* (crystalline).[5] It can exist as an extractable form, as free, esterified, and glycosylated phenolic constituents as well as an insoluble-bound occurring in the outer layers of wheat grains and Alkaline hydrolysis is reported to release ferulic acid from the insoluble form.[6]

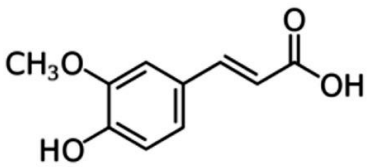
Presence of extended conjugated aromatic structure along with electron donating ability of hydroxyl and methoxy substituted groups, carboxylic group with unsaturated C-C double bond provides strong antioxidant properties to ferulic acid has a wide variety of applications because it has radical and active oxygen erasing effects, absorbs UV causing active oxygen generation, and is a natural substance. It seems to be particularly effective for cosmetic use as a whitening agent and sunscreen, making use of its powerful long wave UV absorbing function. Anti-apoptotic potential of ferulic acid in normal human peripheral blood mono nuclear cells. In murine peripheral blood leukocytes both in pre-irradiation and post radiation administration of ferulic acid lowers gamma irradiation induced dysenteric aberration on bone marrow and lipid peroxidation in cultured lymphocytes. Some studies have shown that phenolic acids can act as germination inhibitors.[7]

CHEMISTRY

Nature, Chemistry and Biochemistry of Ferulic Acid[8]

Ferulic acid ($C_{10}H_{10}O_4$) is the most abundant, ubiquitous hydroxyl cinnamic acid derived from phytochemical phenolic compounds, distributed widely throughout the plant kingdom (spices, vegetables, grains, pulses, legumes, cereals, and fruits), their by-products (tea, cider oil, and beverages) and medicinal plants. It is a renewable resource for the bio-catalytic or chemical conversion to other useful aromatic chemicals from agricultural by-products in nature.

Ferulic acid is a phenyl propenoid derived from the cinnamic Acid,3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid, 4-hydroxy-3-methoxycinnamic acid, or coniferic acid (**Fig. 1**). It shows two isomers: *Cis* (a yellow oily liquid) and *Trans* (crystalline). Its nomenclature comes from Umbelliferae, *Ferula foetida* from which this active compound was isolated for the first time in 1866. It is said that ferulic acid supplies hydrogens to free radicals with phenolic-OH groups to provide the antioxidant effect.



(Fig-1: Ferulic acid)

General methods for the synthesis of ferulic acid and its derivatives are of following

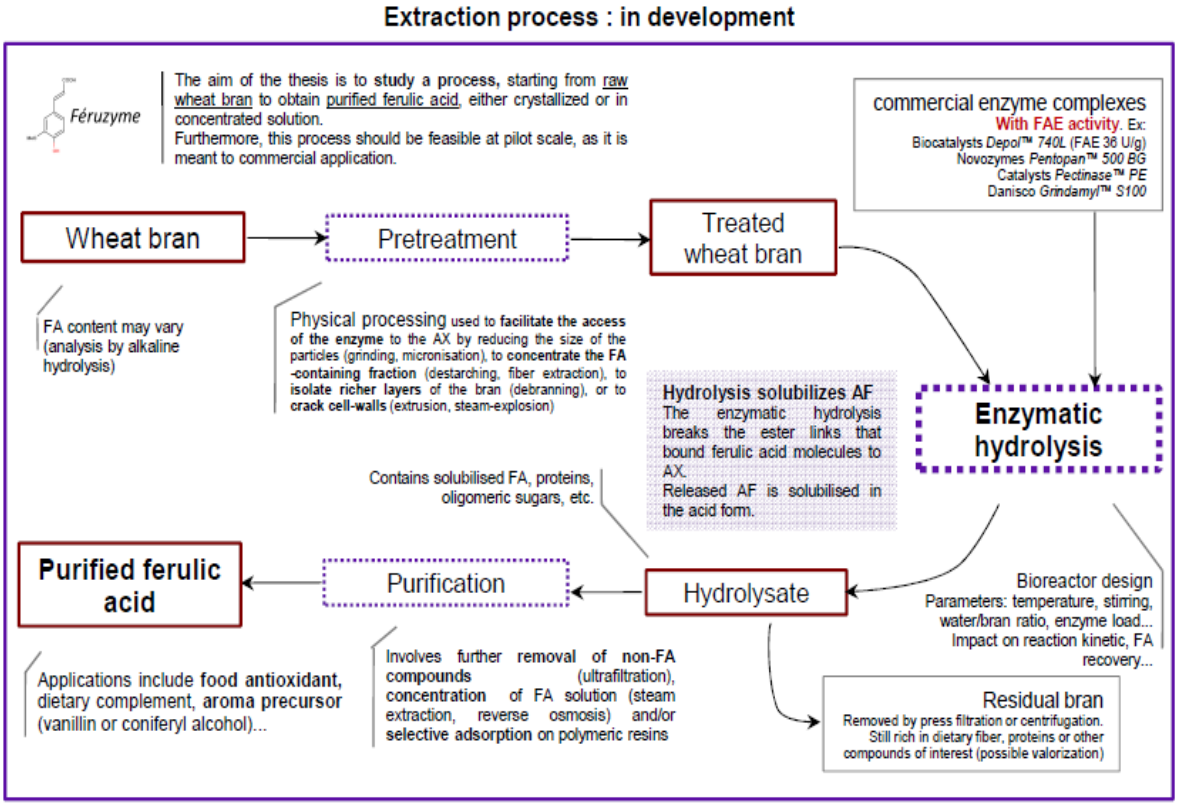
Perkin reaction[9]

Cinnamic acid is easily prepared by Perkin synthesis using benzaldehyde in acetic anhydride and anhydrous sodium acetate. Perkin reaction is the most frequently method for the preparation of the cinnamic acid and its derivatives but the main disadvantage of this reaction is aldehydes in the presence of base lead to formation of unwanted side products formation.

Enzymatic method[10]

Synthesis of two derivatives by using enzymatic method has been carried out by using Novozym 435 as a catalyst. They have reported two derivatives of cinnamic acid i.e. the synthesis of ethyl ferulate (EF) from ferulic acid (4-hydroxy 3-methoxy cinnamic acid) and ethanol, and octyl methoxy cinnamate (OMC) from *p*-methoxy cinnamic acid and 2-ethyl hexanol.

Enzymatic extraction



Biological method

Staphylococcus aureus was isolated from soil and screened for its ability to grow in ferulic acid containing medium in the Department of Botany, Ravenshaw University, and Cuttack. Pure cultures of these strains were maintained on a mixed medium containing both beef extract and peptone and cultures were incubated at 35^0C. In order to obtain high density cultures, the bacterium was grown in a broth medium containing both beef extract and peptone (pH 7.2) for 5 days. The microorganism was grown in minimal medium containing wheat bran as sole carbon source. The initial pH of the minimal medium was adjusted to 7.0, before autoclaving for 15 min at 121^oC. The cultures were incubated at 35^0C and analyses were carried out in duplicates on day basis analyses up to 10 days of incubation.

Dehydrodiferulic Acids from Plant Materials

Compounds dehydrodimers arising from coupling processes, were readily apparent in extracts from several saponified plant materials.

General procedure for the synthesis of amides/anilides of ferulic acid[11]

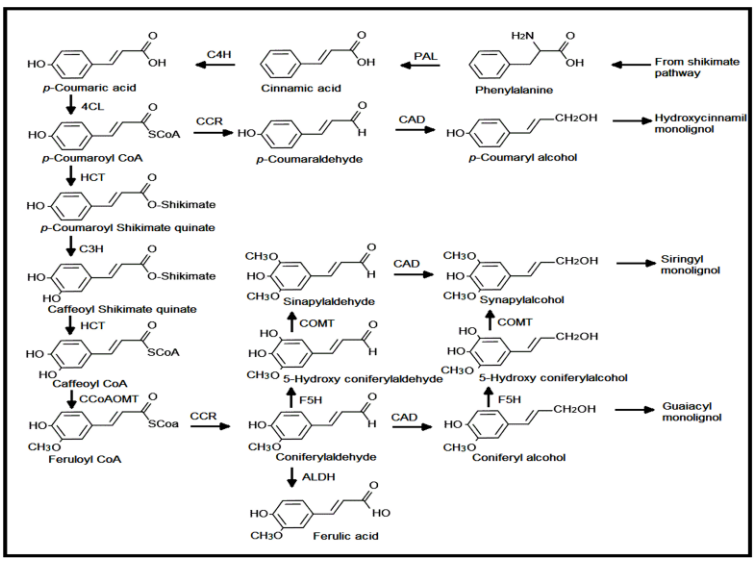
The solution of corresponding amine /aniline (0.1mol) in ether (50 mL) was added drop wise to a solution of ferulic acid chloride (0.1mol) in ether (50 mL) maintained at 0-10^0C

temperature. The solution was stirred for 30 min and the precipitated amide was separated by filtration. The crude amide was recrystallized with alcohol. In case of anilides, the precipitated crude anilide was treated with 5% hydrochloric acid, 4% sodium carbonate and water to remove residual aniline and the resultant anilide was recrystallized with alcohol.

General procedure for the synthesis of esters of ferulic acid[12]

A mixture of ferulic acid (0.08 mol) and appropriate alcohol (0.74 mol) was heated under reflux in presence of sulphuric acid till the completion of reaction which was checked by single spot TLC. Then, the reaction mixture was poured in 200 mL ice cold water, neutralized with sodium bicarbonate solution followed by extraction of ester with ether (50 mL). The ether layer was separated, which on evaporation yielded the ester derivatives of ferulic acid.

For preparation of ferulic acid chloride, thionyl chloride (0.3 mol) was added gradually to ferulic acid (0.25 mol) in a round bottom flask. After addition of thionyl chloride, the mixture was stirred for 4 h and heated to 80^0C for 30 min in water bath and excess of thionyl chloride was removed by distillation. A solution of 8-hydroxy quinoline (0.05 mol) in ether (50 mL) was added to a solution of ferulic acid (0.05 mol) in ether (50 mL). The mixture was heated on water bath until no further evolution of hydrogen chloride was observed and completion of reaction was checked by single spot TLC. The mixture was cooled to room temperature and evaporation of solvent yielded the crude product which was purified by recrystallization with alcohol.



(Fig-2: Preparation of Ferulic Acid)

Natural isolation[13]

MeOH extract of the bark of *Ochrosia oppositifolia* led to the isolation of two ferulic acid esters. The structure of compound **1**, (*E*)-methyl 3-(4'- hydroxy-3',5'-dimethoxyphenyl

acrylate and the compound **2**, (*E*)-methyl 18-((*E*)-3-(4'-hydroxy- 3-methoxyphenyl) acryloyloxy) octadec-3-enoate were deduced from their spectral data and also by comparing their spectral data with those previously reported.

Commercial production[6]

The structure of Ferulic acid is similar to that nor metanephrine, the first metabolite of nor epinephrine, hence mimicking a stimulatory effect on somatotrophin in pituitary gland. Ferulic acid inhibited growth of colon cancer cells *in vitro* and further *in vivo* test confirmed the inhibitory effect on carcinogenesis of colon cancer in rats. It has been documented that ferulic acid may lower blood sugar level of Type I & Type II diabetic mice by enhancing insulin secretion.

In a study group by reported that single administration of Ferulic Acid (9.5mg/kg) may lower blood pressure in rats (SHASP). In a study group by reported that Ferulic acid (100mg/kg) provides neuroprotection against oxidative stress-related apoptosis after cerebral ischemia/reperfusion injury by inhibiting ICAM-1 mRNA expression in rats. It is known that a cranial nerve cell will decrease with age. Reduction of a cranial nerve cell is more significant with brain disease, such as Alzheimer's disease. In 2008, it reported that the preparation ANM176 containing ferulic acid as a principal component showed a suppressive effect on Alzheimer-type Disease (AD). They administered ANM176 containing 100 mg of ferulic acid twice a day for 9 months to 98 AD subjects. Ferulic acid decreased tyrosinase activity was assayed using tyrosine as a substrate. The ratio of tyrosinase inhibition of ferulic acid was higher than that of kojic acid.

Pharmacological activity

Antioxidant and antiradical activities[14] of ferulates (i.e., ferulic acid, Isoferulic acid, coniferyl aldehyde, and methyl ferulate) were investigated using a β-carotene-linoleate model system and a DPPH radical scavenging assay, respectively. Compounds so tested exhibited antioxidant and antiradical properties to varying degrees. Methyl ferulate showed the strongest antioxidant activity, whereas the parent phenolic acid was the most active ferulate to scavenge the DPPH radical (DPPH·). Isoferulic acid at concentrations ranging from 10 to100 nmol/assay did not impart an antiradical efficacy; this may be attributed to the location of the hydroxyl group in the Meta position on the aromatic ring.

Ferulic acid is an important phenolic antioxidant[15] found in or added to diet supplements, beverages, and cosmetic creams. Two designs of paper-based platforms for the fast, simple and inexpensive evaluation of ferulic acid contents in food and pharmaceutical cosmetics were evaluated. The first, a paper-based electrochemical device, was developed for ferulic acid detection in uncomplicated matrix samples and was created by the photolithographic method. The second, a paper-based colorimetric device was preceded by thin layer chromatography (TLC) for the separation and detection of ferulic acid in complex samples using a silica plate stationary phase and an 85:15:1 (v/v/v) chloroform: methanol: formic acid mobile phase.

Ferulic acid is the major cinnamic acid found in the cell wall of woods, grasses and corn hulls.[16] It is widely distributed in higher plants where it is ester-linked to polysaccharide compounds. It plays important roles in plant cell walls including protein protection against pathogen invasion and control of extensibility of cell walls and growth. Ferulic acid endows structural rigidity and strengthens cell wall architecture by cross-linking pentosan chains, arabinoxylans and hemicelluloses, rendering these components less susceptible to hydrolytic enzymes during germination. The efficient pretreatment followed by enzymatic hydrolysis removal of ferulic acid from cell wall materials has been demonstrated and furthermore the acid can be exploited to produce value added aromatic compounds.

Ferulic acid is the main bioactive[5] component of *A. sinensis* root, and our results from ALT/AST assays and histological observations are the first to demonstrate that ferulic acid prevents diosbulbin B-induced liver injury. Furthermore, the results show that ferulic acid enhances the diosbulbin-B induced anti-tumor effect.

The present study demonstrated that, T6FA,[17] a new tacrine-ferulic acid heterodimer, potently inhibit auto- and AChE-induced aggregation. Further, the findings that T6FA blocks or prevents Ab1–40 induced cell death and ROS in vitro and chronically oral administration of T6FA protected mice against Ab1–40-induced cognitive impairment in vivo strongly suggest that T6FA is a novel ‘‘one-compound-multi-targets’’ agent and might be useful as preventive and therapeutic medicines for AD.

Natural antioxidants have been used instead of synthetic antioxidants to retard lipid oxidation[18] in foods to improve their quality and nutritional value. Many herbs, spices, and their extracts have been reported as having high antioxidant capacity, such as some plants of

the Lamiaceae family, e.g., oregano (*Origanum vulgare* L.), rosemary (*Rosmarinus officinalis* L.), and sage (*Salvia officinalis* L.). The antioxidant activity of these plants is attributed to their phenolic compound content, which includes volatile compounds also known as essential oils. Feruloyl esterase represent a diverse group of hydrolyses catalyzing the cleavage and formation of ester bonds between plant cell wall polysaccharide and phenolic acid. They are widely distributed in plants and microorganisms. Besides lipases, a considerable number of microbial feruloyl esterase have also been discovered and over expressed.

Ferulic acid protected the BSA from oxidative modification[5] caused by radiation suggesting that ferulic acid possesses strong antiradical properties. Ferulic acid is known to protect DNA, the prime target of radiation and further its ability to protect protein suggesting its ability to protect different bio-molecules and therefore can be a good candidate for development radio protector. Ferulic acid and ferulic acid derivative/complex were detected in the glutenin fraction of wheat and its enzymatic hydrolysates. The peptide products of glutenin hydrolysis should be recorded at a shorter wavelength, i.e. 220 nm, if HPLC methods are applied, because the peaks of peptides recorded at 280 nm can be overlapped by the peaks of ferulic acid and its derivatives.

Sodium ferulate (SF) or 3-methoxy-4-hydroxy-cinamate[19] sodium is an active principle from Angelica sinensis, Cimicifuga heracleifolia, Lignsticum chuangxiong, and other plants. SF has been widely used in China to treat cardiovascular and cerebrovascular diseases and to prevent thrombosis. Exciting clinical results have been obtained with SF in coronary heart disease, atherosclerosis, pulmonary heart disease and thrombosis. It has been used in traditional Chinese medicine and is approved by State Drugs Administration of China as a drug for treatment of cardiovascular and cerebrovascular diseases. SF has antithrombotic, platelet aggregation inhibitory and antioxidant activities in animals and humans. This article briefly reviews basic pharmacology, pharmacokinetics, toxicology and clinical pharmacology of SF. The *in vitro* and *in vivo* data support the view that SF is a useful drug for the treatment of cardiovascular diseases.

Ferulic acid can be used as an antioxidant or can be transformed by microbial conversion into “natural” vanillin.[20] The latter is a valuable flavouring used in the food, and an antioxidant compound for cosmetic and pharmaceutical industries.

CONCLUSION

The activities of FA can be due to its potent antioxidant capacity, because of conjugation in its nucleus and side chain. Which greatly support the regular intake of FA for providing significant protection associated with a range of oxidative stress related diseases. This review article provides adequate information on natural sources, synthesis, structure, metabolism, and applications of ferulic acid, which can be used for betterment of human healthcare.

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