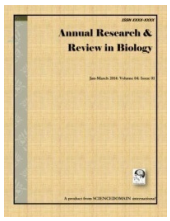


Annual Research & Review in Biology
5(6): 512-528, 2015, Article no.ARRB.2015.054
ISSN: 2347-565X

SCIENCEDOMAIN *international*
www.sciencedomain.org

Derivatives of Ferulic Acid: Structure, Preparation and Biological Activities

Kehan Pei[1], Juanying Ou[2], Caihuan Huang[1] and Shiyi Ou[1*]

[1]Department of Food Science and Engineering, Jinan University, Guangzhou -510632, Guangdong, China.
[2]Food and Nutritional Science Program, School of Biological Sciences, The University of Hong Kong, Hong Kong, China.

Authors' contributions

This work was carried out in collaboration between all authors. Author SO designed the study, wrote the protocol and interpreted the data. Authors KP and JO anchored the field study, gathered the initial data and performed preliminary data analysis. Authors while KP and CH managed the literature searches and produced the initial draft. All authors read and approved the final manuscript

Article Information

DOI: 10.9734/ARRB/2015/14104
Editor(s):
(1) George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Anonymous, Federal University of Rio de Janeiro State, Brazil.
(2) Anonymous, University of Medicine and Pharmacy Cluj-Napoca, Romania.
(3) Norma Almaraz Abarca, Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional, Instituto Politécnico Nacional, México.
(4) Anonymous, University of Maringá, Brazil.
(5) Anonymous, University of Caen Lower Normandy, France.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=795&id=32&aid=7039

Review Article

Received 18th September 2014
Accepted 13th October 2014
Published 21st November 2014

ABSTRACT

Ferulic acid is a natural compound that possesses multiple physiological and pharmaceutical functions. The chemical, physical, and pharmaceutical properties of this phenolic acid can be improved by derivatives with other active compounds. This sentence (Hence, such improvements can widen the applications of ferulic acid in the food, cosmetic, and pharmaceutical industries.) has been deleted. This article reviewed the identification, preparation, and biological activities of feruloyl derivatives of carbohydrates, glycerol and glycerides, amide, fatty alcohol, myo-inositol, and nitric oxide. It also briefly discussed other derivatives. Researchers are encouraged to carry out toxicological, pharmacokinetic, and clinical investigation of potent active feruloyl derivatives and to develop other derivatives.

**Corresponding author: E-mail: tosy@jnu.edu.cn;*

Keywords: Ferulic acid; derivatives; carbohydrates; glycerol; amide; fatty alcohol; myo-inositol.

ABBREVIATIONS

DPPH, 1,1-diphenyl-2-picrylhydrazyl; EDAC, 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide; FAE, ferulic acid esterase; IC_{50}, the half maximal inhibitory concentration; IFNγ, interferon gamma; iNOS, inducible NO synthase; LD_{50}, lethal dose 50%; LPS, lipopolysaccharide; NO, nitric oxide.

1. INTRODUCTION

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phenolic acid commonly found in vegetables, fruits, beverages, and some Chinese medicinal herbs, such as *Angelica sinensis*, *Cimicifuga racemosa*, and *Ligusticum chuangxiong* [1,2]. Ferulic acid shows antioxidant, antimicrobial, anti-inflammatory, anti-thrombosis, and anticancer activities [2], and inhibits the expression of some cytotoxic enzymes, such as nitric oxide synthase, caspase, and cyclooxygenase-2 [1]. Thus, this phenolic acid protects against many disorders, including Alzheimer's disease, cancer, cardiovascular diseases, diabetes mellitus, and skin disease [1,3].

Ferulic acid also has unique toxicological and pharmacokinetic properties. It is absorbed and excreted rapidly in animals and humans, which can be detected in plasma within 5 and 10 min, reaches its peak at 30 min [4,5], and is excreted in the urine within 1.5 h after intake [6]. These properties make ferulic acid a low-toxicity agent, with LD_{50} values of 2445 mg/kg and 2113 mg/kg in male and female rats, respectively [7].

Although ferulic acid shows low toxicity and various biological activities, the clinical use of ferulic acid remains debatable because of its low bioavailability [1]. Moreover, the applications of ferulic acid in the food, pharmaceutical, and cosmetic industries are limited by its low hydrophobicity, hydrophilicity, and stability in various solvent systems [8-10]. However, ferulic acid is a highly reactive compound, which shows potential for preparation of various derivatives. Ferulic acid contains phenyl, hydroxyl and carboxyl groups, an ethylenic bond, and a benzene ring (the methoxy and phenyl hydroxyl groups greatly increase its electrophilic reactivity) [11]. The structural characteristics of this active ingredient make it an optimal substrate to form or synthesize derivatives, such as: ester, ether, amide, anhydride, acyl chloride, ferulic acid polymers, nitrobenzene, benzenesulfonic acid, and benzene halide [11]. The main types of natural feruloyl derivatives are listed in Table 1.

The derivation of ferulic acid significantly changes its physicochemical and biochemical properties and widens its applications (Fig. 1). This review presents the natural occurrence, preparation, and biological activities of ferulic acid derivatives.

Table 1. Feruloyl derivatives in plants

Linking types	Examples of the compounds	Plant sources	References
Esterified with carbohydrates	Feruloylated polysaccharides	In the cell wall of all plants.	[12]
	Feruloylated sucrose	*Bistorta manshuriensis, Bhesa paniculata, Polygala sibirica, Lilium speciosum, et al.*	[13-16]
	Leucosceptoside A	*Eremostachys glabra.*	[17]
Esterified with other phenolics and quinic acid	Quercetin-3-O-(feruloyl) sophoroside-7-O-glucoside	*Brassica oleracea*	[18]
	Feruloyl quinic acid	*Hydrastis canadensis*	[19]
Esterified with sterols	Sitosteryl, campesteryl ferulates	*Oryza sativa*	[20]
Esterified with fatty alcohol	Ethyl ferulate	*Triticum monococcum*	[21]
	Hexacosyl ferulate	*Eremostachys glabra.*	[17]
	C_{22} to C_{26} alkyl ferulates	*Larix kaempferi*	[21]
	Hexadecyl and octadecyl ferulates	*Solanum tuberosum*	[22]
Esterified with glycerol	1-Feruloyl-sn-glycerol, 1,3-diferuloyl-sn-glycerol	*Aegilops ovata, Solanum tuberosum*	[9]

Linking types	Examples of the compounds	Plant sources	References
Etherified linking	Ferulic acid-coniferyl Alcohol dimer	In the lignin of plant cell walls	[23]
	Feruloyl-4-β-glucoside	*Equisetum hyemale*	[24]
	Feruloyl tyramine	*Achyranthes bidentata*	[25]
	Feruloyl octopamine	*Allium sativum*	[26]
Feruloylated amides	Feruloyl methyldopamine	*Beta vulgaris*	[27]
	Feruloyl aminobutyl	*Paris verticillata*	[28]

2. FERULOYLATED CARBOHYDRATES

2.1 Feruloylated Oligosaccharide

Feruloylated oligosaccharides are a group of compounds in which ferulic acid is esterified to oligosaccharide [5]. The most common and widely used feruloylated oligosaccharides are obtained from feruloylated polysaccharides in plant cell walls, in which ferulic acid is esterified to the arabinose, galactopyranose, or galactose residues of arabinoxylans or pectin [12]; feruloylated polysaccharides are often consumed as dietary fibers. Given the poor fermentation of feruloylated polysaccharides in the colon, feruloylated oligosaccharide have been developed from feruloylated polysaccharides by acid [29] or enzymatic hydrolysis, which are easily fermented in the colon and show the physiological functions of both ferulic acid and oligosaccharides. For more detailed information on their preparation and physiological functions, readers may refer to the review article by Ou and Sun [5].

The monosaccharide residues in feruloylated oligosaccharide prepared from feruloylated polysaccharides are usually ester linked to one molecule of ferulic acid or of dehydrodimers or dehydrotrimers [5]. Feruloyl sucrose derivatives are new feruloyl oligosaccharide found in many plant species [13-16,30-32],such as *Bistorta manshuriensis*, *Bhesa paniculata*, *Polygala sibirica*, *Lilium speciosum*, *Heloniopsis orientalis*, *Heterosmilax erythrantha*, and *Polygonum perfoliatum*. Feruloyl sucrose has two molecules of ferulic acid, which are both located in fructose

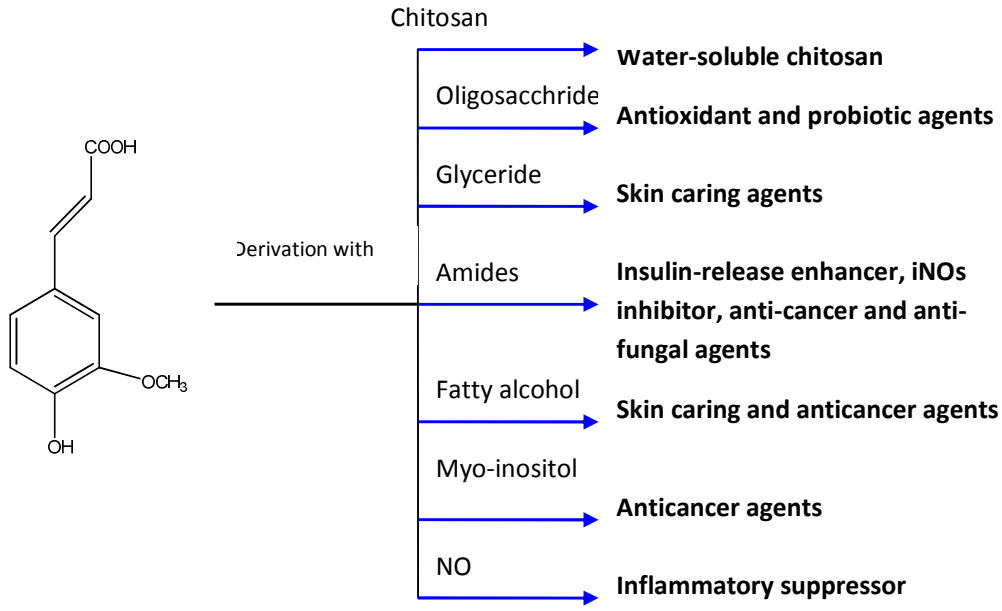


Fig. 1. Main derivatives of ferulic acid and their applications

and esterified to its C_3 and C_6 positions. Interestingly, the taste of sucrose changes from sweet to bitter after esterification with two molecules of ferulic acid [33].

Possibly due to its bitterness, reports on the function of feruloyl sucrose are rare except for a research on their antioxidant activity [30]. Since the aforementioned plants that contain feruloyl sucrose are used in traditional Chinese herbal medicine, the pharmaceutical function and medical treatment effects of feruloyl sucrose need to be investigated.

2.2 Feruloylated Arabinoxylans

Feruloylated arabinoxylans are feruloylated macrobiomolecules commonly found in the plant cell walls of monocots, in which ferulic acid is esterified to arabinoxylans through its carboxylic acid group with the C_5-hydroxyl of a-L-arabinosyl side chains of xylans [34]. Ferulic acid can also be etherified to lignin and form dehydrodiferulic acids or dehydrotrimer and dehydrotetramers between ferulic acid molecules via oxidative and/or photochemical dimerization [5, 34] , making ferulic acid crucial for structuring plant cell walls.

Feruloylated arabinoxylans can be divided into water-extractable (10 kDa to 10,000 kDa) and water-unextractable (more than 10,000 kDa) parts depending on their molecular weights [35]. Feruloylated arabinoxylans can be prepared from the byproducts of the food industry, such as cereal bran, sugar beet pulp, and corn cobs. Feruloylated arabinoxylans are principally used as dietary fibers for chronic diseases, emulsion and foam stabilizers, gel, or colon medicine delivery carriers [35,36]. However, high amounts of arabinoxylans in the dough decrease bread quality, and xylanase is often used to cleave them and improve bread quality [36].

2.3 Feruloylated Chitosan

Chitosan, mainly found in crab and shrimp shells and squid pens, is the second most abundant polysaccharide found in nature after cellulose. It is biodegradable, antimicrobial, non-toxic, non-antigenic, and bicompatible, and it is widely used in the food, pharmaceutical, and cosmetic industries [37,38]. However, the low solubility of chitosan in water limits its application. Grafting of ferulic acid onto the amino groups of chitosan improves water solubility and increases antioxidant activity.

Free radical and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDAC)are often used to catalyze the grafting of ferulic acid onto chitosan. The ascorbic acid/hydrogen peroxide redox pair system designed by Kitagawa et al. [39] has been often used to initiate free radical. In this model, ascorbic acid is oxidized by H_2O_2 at room temperature to generate ascorbate and hydroxyl radicals. The hydroxyl radical abstracts hydrogen atoms from amino groups on chitosan molecules to form chitosan macro radicals. Then, ferulic acid accepts the chitosan macroradicals and grafts onto chitosan [37]. Liu et al. [37] successfully obtained a water-soluble product with a grafting ratio of 66.7 mg ferulic acid/g. Thermogravimetric analysis showed that introducing ferulic acid obstructs chitosan chain packing, which reduces thermal stability. Another research on the grafting of gallic acid onto chitosan found that the addition of gallic acid, ascorbic acid, hydrogen peroxide, and chitosan influence the grafting ratio. The grafting ratio increases with increasing concentrations of gallic acid (2 g/L to 16 g/L), ascorbic acid (1 g/L to 2 g/L), and H_2O_2 (0.025 M to 0.2 M); While it decreases with increasing chitosan concentration (5 g/L to 20 g/L) because the high viscosity of the reaction media restricts the accessibility of ferulic acid onto the active sites of chitosan [40].

Phenolic acids can be grafted onto the chitosan polymer by other catalytic agents, such as 1-ethyl-3-(3′-dimethylaminopropyl) carbodiimide (EDAC), N-hydroxysuccinimide, and laccase [40]. Woranuch and Yoksan [38] grafted ferulic acid onto chitosan through an EDAC -mediated coupling reaction. In the first step, ferulic acid reacts with EDAC to form O-acylisourea, and the latter reacts with chitosan to generate feruloylated chitosan and isourea. In their research, they dropwise added 50 mL of chitosan solution (1.2% dissolved in 1% aqueous acetic acid solution) into 10 mL of ethanol solution that contains ferulic acid and EDAC, and obtained grafted chitosan with a ferulic acid substitution degree of 0.37 when reacted at 60℃ for 3 h at a 1:1 molar ratio of chitosan to ferulic acid.

Recently, Aljawish et al. [41] have successfully used laccase to graft ferulic acid using ferulic acid or ethyl ferulate as the substrate, providing a green pathway to synthesize feruloylated chitosan.

Grafting of ferulic acid onto chitosan confers water solubility and antioxidant activity to chitosan, and improved its properties as

biomedical materials. The solubility of grafted chitosan with a 0.37 ferulic acid substitution degree in water can reach 1.3 mg/mL; in addition, grafted chitosan has 1.25 and 3 times higher scavenging capacity for DPPH free radical and reducing power than its parent chitosan [38]. At 1 mg/mL, grafted chitosan with a grafting ratio of 66.7 mg ferulic acid/g has 6.6, 1.9, and 1.6 times higher scavenging capacity for H_2O_2, hydroxyl free radical, and superoxide radical than ungrafted chitosan. Moreover, grafted chitosan can inhibit lipid oxidation by 50%, whereas ungrafted chitosan can only inhibit 35.9% of this process [37]. Grafted chitosan also increases antioxidant activity *in vivo*. In a D-galactose-induced aging mouse model, ferulic acid-grafted chitosan significantly increases the activity of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and significantly decreasesthe contents of malondialdehyde in serum and livers [37]. Cheng et al. [42] confirmed that grafted chitosan increases antioxidant activity *in vivo*.

It was shown by Aljawish et al. [43] that human umbilical vein endothelial cells grow better on ferulic acid-grafted chitosan than on ungrafted chitosan. They supposed that grafting ferulic acid onto chitosan promotes cell growth by balancing the hydrophobic and hydrophilic properties, reducing positive charges (by free amino groups), and increasing the density of negative charges after introducing phenyl hydroxyl.

Our previous study indicated that ferulic acid in feruloylated starch can be released by colon microbiota [44], further investigation is still necessary to investigate whether or not ferulic acid can be released from grafted chitosan in the colon or human cells after intake.

3. FERULOYLATED GLYCEROL AND GLYCERIDES

Ferulic acid with glycerol has two types of derivatives. The first type (feruloylated glycerol) includes water-soluble compounds in which ferulic acid is esterified to glycerol with no fatty acids. The second type (feruloylated glycerides) includes lipid-soluble compounds in which ferulic acid is esterified to one or two of the hydroxyl groups of glycerol with the left hydroxyl esterified with fatty acids.

3.1 Feruloylated Glycerol

Feruloylated glycerol consists of one or two ferulic acid moieties esterified to glycerol with the remaining glycerol free; this type is naturally found in the plant kingdom, such as wheat and potato [9]. Feruloylated glycerol has higher solubility in water than ferulic acid; thus,considerable efforts have been exerted to directly esterify ferulic acid to glycerol for more than 50 years [10]. Chemical and enzymatic methods are often used to prepare feruloylated glycerol.

3.1.1 Chemical synthesis of feruloylated glycerol

p-Toluenesulfonic acid is a commercially availablecatalyst in the form of solid acid. This acid is an effective, environmentally friendly (can be recovered by simple filtration and reused) catalyst widely used for the alkylation of the aromatic ring with activated aliphatic halides, alkenes, and sulfonic esters [45].

Holser [46] carried out a kinetics study in a 100 mL toluene reaction system, which contains 2 g of glycerol, 2 g of cinnamic acid, and 100 mg of p-toluenesulfonic acid. The reactants were refluxed at 110°C for different times. Their results showed that 30% of the monoester is produced in the first 3 h before the formation of the diester product, and 39.1% of the monoester and 19% of the diester are produced after 8 h.In their previous research, they yielded 20% monoester after 2 h when equimolar amounts of reactants were added to the reaction system [47]. Surprisingly, Sun et al. [48] found that 98% of ferulated glycerol can be produced after 12 h of reaction at 80°C by replacing the solvent toluene with an ion liquid (1-butyl-3-methylimidazolium tetrafluoroborate).

3.1.2 Enzymatic synthesis of feruloylated glycerol

Lipases and ferulic acid esterase are the most common enzymes used to prepare feruloylated glycerol.Lipases (E.C. 3.1.1.3) are enzymes that are primarily responsible for the hydrolysis of acylglycerides, as well as thiol esters, amides, and polyol/polyacid esters. They also catalyze the reverse reaction of synthesis as efficiently as that of hydrolysis, and some lipases are better suited for synthesis than for hydrolysis applications [49].Ferulic acid esterases (EC 3.1.1.73) are a subclass of carboxylic esterases (EC 3.1.1) that cleave ester bonds between hydroxycinnamic acids esterified to arabinoxylans and pectins present in plant cell walls [50]. Four types (A to D) of ferulic acid

esterases exist. Similar to lipases, ferulic acid esterase shows biosynthetic activity, such as enzymatic esterification and transesterification of phenolic acids in ternary water–organic solvent mixtures and oil-in-water microemulsions; however, unlike lipases, ferulic acid esterase can catalyze the esterification of *p*-hydroxylated phenolic acids [51].

Matsuo et al. [52]. used immobilized lipase to synthesize feruloylated glycerol in 92.5% glycerol using ethyl ferulate as the reagent. They reported that 75% of ethyl ferulate is transformed after cycling at 80℃ for 6 d. Zheng et al. [53] found that the solvent used greatly influences the conversion rate of ethyl ferulate to feruloylated monoacylglycerols and feruloylated diacylglycerols when Novozym 435 is used to catalyze this transesterification from triacylglycerols.

Ferulic acid esterase shows higher activity and selectivity for the synthesis of feruloylated glycerol than lipase. Tsuchiyama et al. [54] used a ferulic acid esterase called FAE-PL, which is similar to ferulic acid esterase (FAE-III) from *Aspergillus niger*, to synthesize 1-glyceryl ferulate from ferulic acid. They found that 81% of ferulic acid is converted to 1-glyceryl ferulate when a mixture of 1% ferulic acid, 85% glycerol, and 5% dimethyl sulfoxide is reacted at pH 4.0 and 50℃ for 30 min. A higher conversion rate (95%) was obtained by Kikugawa et al. [55] when they used diglycerin instead of glycerol as the substrate.

3.2 Feruloylated Glycerides

In contrast to feruloylated glycerol, feruloylated acylglycerides increase the hydrophobic capacity of ferulic acid, making it applicable as an antioxidant in oil or oil-containing foods. Two steps are involved in preparing feruloylated glycerides. The first step is to prepare mono- or di-feruloylated glycerol using the chemical or enzymatic methods aforementioned. The second step is to esterify the fatty acid to the remaining hydroxyl on glycerol using lipase [48,53,56-59]. Triacyl glycerides can be directly feruloylated by transesterification using lipase as the catalyst; however, the reaction speed is three- to sixfold slower than that with mono- or di-feruloylated glycerol, and the initial reaction rate is sensitive to water activity [60]. Interesterification between ethyl or methyl ferulate and triacylglycerides may be an alternative choice.

Feruloylated monoacyl glycerides and diacyl glycerides are not suitable antioxidants in oil. In frying soybean oil, these glycerides show less antioxidant activity than TBHQ, but they are more stable [61]. They may function as potential agents for skin care [62] and weight loss [63].

4. FERULOYLATED AMIDES

4.1 Natural Occurrence and Biological Activities

Trace amines, such as tyramine and octopamine, are endogenous biogenic amines that are present in mammalian brain and are speculated to function as sympathomimetic compounds [65]. A large number of feruloyl amides have been isolated from natural resources, particularly medicinal herbs. These amides possess biological activities, including antioxidant and antitumor activity, inhibition of NO production, and increase in insulin secretion from pancreatic β cells. Interestingly, some feruloyldopamine and feruloyltyramine show other biological activities that both ferulic acid and amines cannot offer.

Two feruloyl tyramines, N-trans-feruloyl-3-methoxytyramine-4′-O-β-D-glucopyranoside and N-trans-feruloyl-3-methoxy tyramine-4-O-β-D-glucopyranoside (Figs. 2A, B) were isolated from Niuxi (*Achyranthes bidentata*) [25], a traditional Chinese herbal medicine used to dissipate blood stasis, nourish the liver and kidney, and strengthen the bones and muscles. Zhang et al. [64] identified another feruloyl amide derivative, tribulusamide C (Fig. 2C), from the fruits of *Tribulus terrestris*. These fruits are used in many countries to treat cardiac diseases, eye trouble, edema, urinary troubles, skin disorders, and bladder stones, and as a diuretic and aphrodisiac medicine.

Ichikawa et al. [26] separated N-trans-feruloyloctopamine from garlic skin and found that it shows higher scavenging capacity for DPPH radical than t-ferulic acid.

Kim et al. [27] isolated four feruloylamines from *Beta vulgaris* L. var. cicla L.: N-cis-feruloyl 3-O-methyldopamine, N-cis-feruloyl tyramine, N-transferuloyl 3-O-methyldopamine, and N-trans-feruloyl tyramine (Figs 2D, E). These feruloylamines inhibit lipopolysaccharide (LPS)-induced NO production in RAW 264.7 cells. The IC_{50} values of N-cis-feruloyl 3-O-methyldopamine, N-cis-feruloyl tyramine, N-transferuloyl 3-O-methyldopamine, and N-trans-feruloyl tyramine

for NO synthase are 18.7, 13.3, 17.2, and 16.4 µM, respectively, which are lower than that of the positive control N^G-monomethyl-L-arginine (43.0 µM), a well-known inhibitor of NO synthase. NO, a bioactive free radical catalyzed by NO synthase, is responsible for the pathophysiological processes of atherosclerosis, inflammation, and carcinogenesis [27]. Their results suggest that these compounds can function as preventive ingredients against inflammation and carcinogenesis. Neither ferulic acid nor dopamine and tyramine have been reported to inhibit NO synthase; the mechanism by which these compounds inhibit NO production is interesting.

Lee et al. [66] isolated a compound from *Isodon excisus,* the aerial partsof this plant are used for detoxification. This compound has a similar structure to N-trans-feruloyloctopamine, 3-(4-hydroxy-3-methoxyphenyl)-N-[2-(4-hydroxyphenyl)-2-methoxyethyl]acrylamide (Fig. 2F) and was found to inhibit etoposide-induced apoptosis in U937 cells with an IC_{50} value of 10.2 µg/mL, indicating its potential as an anti-apoptotic agent.

Lee et al. [28] isolated 1-N-feruloyl-aminobutyl-4-ρ-hydroxybenzamide ($C_{21}H_{25}O_5N_2$) from the roots of *Paris verticillata*, a Korean folk medicine used to treat asthma and chronic bronchitis. This compound shows inhibitory activity against four cancer cell lines, namely, A549 (nonsmall cell lung carcinoma), SKOV-3 (ovary malignant ascites), SK-MEL-2 (skin melanoma), and HCT (colon adenocarcinoma).

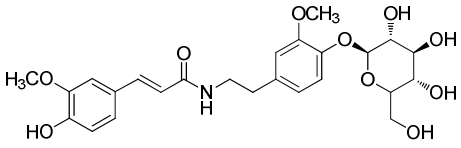
Feruloy amide shows antimicrobial activities both in plants and human. McLusky et al. [67] found that feruloyl-3′-methoxytyramine accumulates in onion epidermis at sites of attempted penetration by *Botrytis allii*. Bake et al. [67, 68] identified this compound along with N-(E)-feruloyl-4′-O-methyloctopamine and N-(E)-feruloyltyramine from potato cell culture suspension (Fig. 2, G, H). They proposed that phenolics elicit protective effects against oxidative stress and resistance by preventing fungal degradation of the cell wall.

Lee et al. [69] isolated trans-N-feruloyloctopamine from an ethyl acetate extract of the root bark of *Lycium chinense* Miller. The minimal inhibitory concentration of this compound is 10 µg/mL for three yeast or fungal strains, namely, *Saccharomyces cerevisiae*, *Candida albicans*, and *Trichosporon beigelii*. Trans-N-feruloyloctopamine is less effective than amphotericin B, a polyene antifungal drug often used intravenously for systemic fungal infections. However, unlike amphotericin B, trans-N-feruloyloctopamine has no side effects, such as hemolytic activity against human erythrocytes. They also isolated dihydro-N-caffeoyltyramine and cis-N-caffeoyltyramine, which show antimicrobial activity against the tree fungal strains.

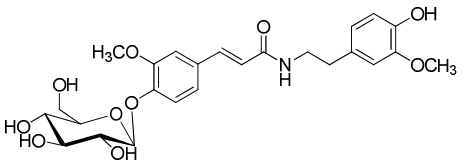
4.2 Synthesized Feruloyl Amides and Their Biological Activities

Since feruloyl amides show various biological activities, and many researchers synthesized feruloyl amides and evaluated their biological activities. Wang et al. [70] synthesized a series of feruloyl amides and tested their inhibitory capacity against histone deacetylases,which remove the acetyl group of lysine residues located on nucleosomal histones andfunction in cell proliferation, cell cycle regulation, and apoptosis. Inhibiting these enzymes is a successful strategy for the development of novel anticancer agents. Results show that three compounds have inhibitory activities for histone deacetylases (Table 2) similar to suberoylanilide hydroxamic acid, the first histone deacetylase inhibitor approved by the FDA in 2006. These compounds also show inhibitory effects on the growth of three cancer cell lines (Table 2).

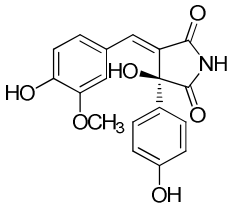
Shi et al. [71] found that some feruloyl amides exhibit anticancer activity by evaluating their inhibitory activities for matrix metalloproteinases. Matrix metalloproteinase-2 (gelatinase A) and -9 (gelatinase B) are stimulated by the tumor. They reported that (E)-3-(4-hydroxy-3-methoxyphenyl)-N-(3-hydroxyphenyl) acrylamide with a hydroxyl group at the meta-position of amino phenyl ring expresses considerable inhibitory activities against matrix metalloproteinase-2 and -9. Its IC_{50} values for matrix metalloproteinase-1 (interstitial collagenase), -2, and -9 are 5927.77, 24.33, and 28.33 nM, respectively; While the IC_{50} values of ferulic acid for the three enzymes are 387.83, 93.47, and 87.22 nM, respectively [71]. These results indicated that this kind of feruloyl amide can selectively inhibit the activity of the two enzymes that are involved in the cancer progress but cannot inhibit metalloproteinase-1.



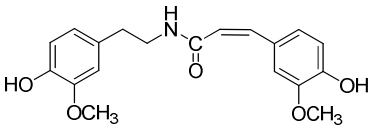
N-trans-feruloyl-3-methoxytyramine-4'-O-β-D-glucopyranoside (A)



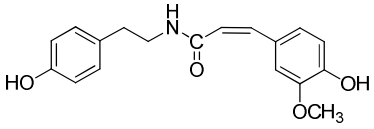
N-trans-feruloyl-3-methoxytyra mine-4-O-β-D-glucopyranoside (B)



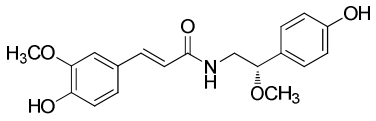
Tribulusamide C (C)



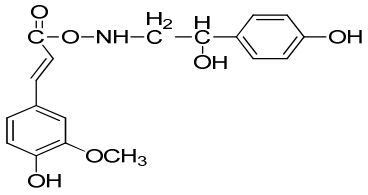
N-cis-feruloyl 3-O-methyldopamine (D)



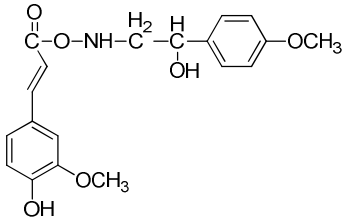
N-cis-feruloyl tyramine (E)



3-(4-hydroxy-3-methoxyphenyl)-N-[2-(4-hydroxyphenyl)-2-methoxyethyl]acrylamide (F)



N-(E)-feruloyloctopamine (G)

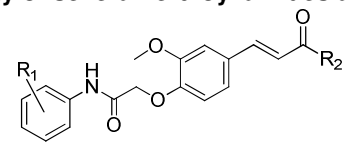


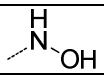
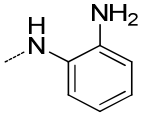
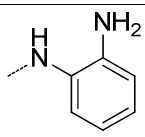
N-(E)-feruloyl-4'-O-methyloctopamine (H)

Fig. 2. Some feruloyl amides isolated from plants

Nomura et al. [72] reported that feruloyl amides can be used to treat diabetes. They prepared a series of feruloyl amides, including feruloylamide, N-feruloyl pyrrolidine, N-feruloyl piperidine, N-feruloyltyramine, N-feruloyl tyrosine, and feruloylamide with the amide group linked to different alkyl groups (N-isopropylferuloylamide, N-butylferuloylamide, N-s-butylferuloylamide, N-pentylferuloylamide, N-hexylferuloylamide, and N-octylferuloylamide). These compounds were used to test the stimulatory effects on insulin secretion using the rat pancreatic RIN-5F cell line; The authors found that the amides having n-butyl, n-pentyl, pyrrolidine, piperidine, tyramine, and tyrosin groups promote insulin release better than ferulic acid at a concentration of 10 μM. All these compounds show no notable cytotoxicity for the RIN-5F cell line. Among them, N-butylferuloylamide, N-pentylferuloylamide,N-feruloyl pyrrolidine, and N-feruloyl piperidine were regarded as the most promising antidiabetic agents, which show sixfold to eightfold and twofold to threefold higher insulin-release activity than the control and ferulic acid, respectively. The authors speculated that the feruloyl amide derivatives follow a similar stimulation of insulin release mechanism to tolbutamide (a common sulfonylurea antidiabetic agent), which binds the sulfonylurea receptors and then closes the ATP-sensitive K^+ channels of β cell plasma membrane, resulting in membrane depolarization, calcium influx, and insulin secretion [73].

Table 2. The inhibitory activity of several feruloyl amides against histone deacetylases[70]



Compounds	R1	R2	IC_{50} (μM) for			
			HDAC	MCF-7	Hela cell	MDA-MB-231
1	2-F		3.94	>100	11.07	8.3
2	3-F		2.82	>100	28.09	>100
3	3,5-CF_3		7.8	43.1	20.82	25.3
Vorinostat			2.59	60.2	9.69	0.16

5. FERULIC ACID ALKYL ESTERS WITH FATTY ALCOHOL

The alkyl ferulates in this article refer to ferulic acid esterified at its carboxyl group or etherified at its phenyl hydroxyl to fatty alcohols. Different from ferulic esters, this kind of etherified ferulic acid does not naturally occur; however, some synthesized ones act as potential pharmaceutical agents.

Ferulic esters are found in plants, such as hexadecyl and octadecyl ferulates in the wound periderm of potato, ferulic acid esters with alkyl groups from C_{22} to C_{26} in*Larix kaempferi* leaves [22], 3-methyl-3-butenyl ferulate in bee propolis [22], and 34-hydroxy tetratriacontanyl ferulate and 34-O-acetyl tetratriacontanyl ferulate in *Plumeria bicolor* [74].

Alkyl ferulates show some properties superior to ferulic acid, such as easier partition into and penetration across the skin through intercellular pathways [75], higher antioxidant activity in membranous systems [76], and prevention against neurodegenerative disorders [77]. Some of these compounds even show chemopreventive effects on cancer [78].

Naturally occurring ferulic acid esters have low contents and limited species; hence, large amounts of ferulic acid esters are available through synthesis. Ferulic acid esters can be obtained by enzymatic catalysis using lipase or ferulic acid esterase, but lipase shows lower efficiency than esterification of ferulic acid to glycerol as previously described; reaching a 30% conversion rate usually took 15 d [22]. Novozym® 435, which contains the activity of ferulic acid esterase, shows higher efficiency than lipases for catalyzing the esterification of fatty alcohols to ferulic acid. Compton et al. [79] converted 83% of 1-octyl alcohol to ferulic acid by vacuum removing the ethanol co-product for 5 min every 24 h after the reaction for 312 h. Lee et al. [80] obtained an 87% conversion rate after reacting ethanol with ferulic acid at 75 ℃ for 2 d using isooctane as the solvent and Novozym® 435 as the catalyst.

p-toluenesulfonic and concentrated sulfuric acids are often used as catalysts to chemically synthesize alkyl ferulates [78]. Li et al. [81] showed that microwave irradiation can highly promote esterification efficiency. A >90% yield of alkyl ferulates can be obtained through microwave irradiation within 5 min. By contrast, obtaining a 46% yield using the conventional heating method takes 28 h.

Many researchers investigated the physiological and pharmaceutical functions of alkyl ferulates. Anselmi et al. [76] synthesized four alkyl ferulates (n-octyl, 2-ethyl-1-hexyl, n-dodecyl, and n-hexadecyl) and tested their antioxidant activities in rat liver microsomes and rat

erythrocytes. The IC_{50} values (after incubation for 90 min) of ferulic acid, n-octyl, 2-ethyl-1-hexyl, n-dodecyl, and n-hexadecyl ferulates for protection against cumene hydroperoxide-induced hemolysis are 31.14, 0.45, 0.70, 0.22, and 0.67 μM, respectively [76]. The compounds show the same trend in a rat liver microsome system. The IC_{50} values of ferulic acid, n-octyl, 2-ethyl-1-hexyl, n-dodecyl, and n-hexadecyl ferulates for antilipoperoxidant activity are 243.79, 12.36, 32.20, 10.70, and 23.47 μM, respectively. The results indicate that fatty alcohol esterification to ferulic acid significantly increases the antioxidant activity; the n-C12 derivative is the most potent among the tested alkyl ferulates. In another research, they carried out in the homogeneous phase (in ethanol solution or phosphate saline buffer), alkyl feruloylation shows no enhancing effect on antioxidant activity compared with ferulic acid [82]. These results indicate that alkyl ferulates have higher affinity for cell membrane than ferulic acid, as confirmed by Anselmi et al. [83] in the erythrocyte membrane. Therefore, alkyl ferulates protect the phospholipid bilayer against oxidation. In addition, 3D studies indicated that the spatial conformation and arrangement of the side chain in the derivatives determine the access and binding to the phospholipid bilayer of cells and the modality of orientation of the scavenging/quenching nucleus (phenol moiety).

Ferulic acid esters are more effective than ferulic acid in cosmetic formulations for protecting against ultraviolet rays from the sun; the ultraviolet promotes skin aging, erythema, inflammation, immunodepression, and photo-carcinogenesis [76]. Zhang et al. [75] carried out *in vitro* (using the dorsal skin of pig) and *in vivo* (using nude rat) studies to compare the absorption capacity of ferulic acid and its derivatives by skin. Their results showed that ethyl ferulate fluxes (nmol/cm^2/h) into the intact porcine skin22- and 51-fold faster than ferulic acid in aqueous solutions at pH 6.0 and 6.9, respectively.Similar trends of skin deposition and flux of ferulic acid and ethyl ferulate were found in an *in vivo* test using nude rat; no significant skin irritation was found 24 h after administration of the compounds [75].

Ferulic esters also show anticancer effect. Murakami et al. [84] synthesized the alkyl ferulate 2-methyl-1-butyl ferulic acid and found that it has better suppressive effect on inflammatory responses and skin tumor promotion than ferulic acid. In another research, they synthesized 23 ferulic acid esters with a number of carbon atoms in each substituent ranging from 1 to 12, including six feruloyl derivativesethered with prenyloxyl, geranyloxyl, and farnesyloxyl at the phenol hydroxyl group, to screen effective chemopreventive agents [78]. They found that almost all derivatives show significant Epstein–Barr virus activation suppression, with 2-methyl-1-butyl ferulate as the most potent chemopreventive agent. Serafim et al. [85] found that hexyl ferulate and feruloylhexylamide show cytotoxicity against three human breast cancer cell lines, namely, MCF-7 (estrogen sensitive), MDA-MB-231 (estrogen insensitive), and HS578T (estrogen insensitive). By contrast, ferulic acid does not demonstrate such a cytotoxic effect.

Ferulic esters also show neuroprotective effects; readers may refer to the review by Sultana [77].

6. FERULOYL MYO-INOSITOL

Myo-inositol (inositol), a six carbon cyclitol containing five equatorial hydroxyl groups and one in axial position, is widely distributed in grains, seeds, and fruits. This compound promotes fertility, pregnancy wellness, and embryo development. It serves important functions in cell morphogenesis and cytogenesis, cell membrane formation, lipid synthesis, and cell growth. It is also the precursor for the synthesis of phosphatidylinositol polyphosphates, the intracellular second messengers for the regulation of several cellular functions [86]. Inositol is a highly safe compound. The only adverse effects of inositol in human are gastrointestinal symptoms (nausea, flatus, loose stools, and diarrhea) when administered at 12 g/d or higher; the inositol dosage of 4 g/d commonly used in clinics is completely free of side effects [87].

The natural existence of feruloyl inositol has not been reported. However, when three hydroxyl groups of inositol at meta positions were feruloylated, the compounds exhibit activities that both of the parent ingredients cannot offer. This result was reported by Hosoda et al [88, 89]. Below is a brief introduction to their work.

They attached ferulic acid to the hydroxyl groups of myo-inositol 1,3,5-orthoformate and found that 2-O-tert-butyldimethylsilyl-4,6-bis-O-[3-(4′-hydroxy-3′-methoxyphenyl)-2-propenyl] -myo-inositol 1,3,5-orthoformate exhibits strong and selective suppressive effects on cyclooxygenase-

2; the overexpression of this enzyme results in the overproduction of prostaglandins for the development of colon cancer [88]. In another work, they introduced three molecules of ferulic acid to inositol and synthesized 14 feruloyl-myo-inositol derivatives. They found that 1,6-O-bis[3-(4′-hydroxy-3′-methoxyphenyl)-2-propenoyl]-myo-inositol can effectively suppress the generation of superoxide free radical at a concentration of 20 μM, and 2,4,6-O-tris[3-(40-hydroxy-30-methoxyphenyl)-2-propenoyl]-myo-inositol 1,3,5-orthoformate can effectively suppress the activation of Epstein–Barr virus [89].

7. NO-RELEASING DERIVATIVE OF FERULIC ACID

Nitric oxide (NO) acts as a signal molecule in many parts of the organism and as a cytotoxic or regulatory effector of the innate immune response. NO is synthesized on demand for short periods of time (seconds to minutes) following enzyme activation of endothelial NO synthase or neuronal NO synthase [90]. By contrast, the inducible NO synthase (iNOS) is expressed after cell activation and produces NO for a long time (hours to days); it acts as an important answer to proinflammatory signals and as a biomarker in inflammatory processes [91]. Thus, developing selective inhibitors of iNOS is a new way to treat pathologies characterized by chronic inflammation. Some derivatives of ferulic acid contain NO-releasing moieties that selectively inhibit iNOS and possess increased anti-inflammatory properties.

Wenk et al. [92] used a NO-releasing derivative of ferulic acid, NCX2057 [3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-nitrooxy)butyl ester], and evaluated its treatment effects on Alzheimer's disease in rat model of chronic neuroinflammation that produces many features of Alzheimer's disease. They found that in the whole rat blood, the derivative produces hemoglobin Fe(II)NO at levels ranging from 0.7 μM to 28.0 μM after 15 min to 4 h incubation, which showed similar effects to isosorbide mononitrate, a drug used principally in the treatment of angina pectoris; the derivative can also significantly reduce microglial activation within the temporal lobe [92]. In another study by Wenk et al. [93], it was shown that this compound inhibits iNOS mRNA and protein expression (IC_{50} = 6.2 μM), and decreases LPS/IFNγ-induced nitrite accumulation in RAW 264.7 cells. However, another ferulic derivative containing no nitrogen oxide, 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-(hydroxyl)butyl ester shows no NO-donating properties and is weakly effective, and ferulic acid is inactive for inhibition of iNOS expression.

Cholinesterase inhibitors, such as tacrine and rivastigmine, have been clinically applied for treatment of Alzheimer's disease. Chen et al. [94] synthesized a NO-releasing derivative of ferulic acid that contains amide and tested its inhibitory effect on cholinesterases, the enzymes responsible for Alzheimer's disease and thus are targets for treating this disease. It was found that, all of the synthesized compounds show higher *in vitro* cholinesterase inhibitory activity than tacrine. They obtained a most potent compound, 3-{2-methoxy-4-[(1E)-3-oxo-3-(3-(1,2,3,4-tetrahydroacridin-9-ylamino)propylamino)prop-1-enyl]phenoxy}propyl nitrate, its IC_{50} value for acetylcholinesterase and butyrylcholinesterase were 10.9, 17.1 nM respectively, much lower than the IC_{50} value of tarcrine for these enzymes (69.8 and 10.6 nM) [94]. In rat and mice model, no-releasing derivative increased antiatherosclerotic activity [95], improved recognition memory [96], suppressed inflammatory and nociceptive responses [97], and could be used as an agent for the treatment of chronic kidney diseases [98].

8. OTHER FERULOYL DERIVATIVES

Other feruloyl derivatives that naturally occur include steryl ferulates; ferulate of other phenolics and quinic acids; and ferulic di-, tri-, andtetramers.Steryl ferulates are bioactive compounds with plant sterols and their saturated form stanols esterified to ferulic acid, such as cycloartenyl, 24-methylenecycloartanyl, campesteryl, Δ^7-campestenyl, sitosteryl, Δ^7-sitostenyl, stigmasteryl, Δ^7-stigmasteryl, sitostanyl, and campestanyl [20]. Steryl ferulates are widely distributed in the germ of cereals; they lower serum total cholesterol, inhibit colon and prostate cancer development, and increase immune function [99,100]. Regarding the ferulate of other phenolics and quinic acids, Fernandes et al. [18] identified three feruloyl quercetins [quercetin-3-O-(feruloyl)sophoroside-7-O-glucoside, quercetin-3-O-(feruloyl)-sophoroside-7-O-diglucoside, and quercetin-3-O-(feruloyl)sophoroside], three feruloyl kaempferols [kaempferol-3-O-(feruloyl)sophoroside-7-O-diglucoside, kaempferol-3-O-(p-coumaroyl)sophoroside-7-O-glucoside, and kaempferol-3-O-(feruloyl)-sophoroside], and two ferulol sinapoyls (sinapoyl, feruloyl-gentiobioside

and disinapoyl, feruloyl-gentiobioside) from *Brassica oleracea* L. These compounds increase glutathione levels in V79 cells, indicating that they play crucial role in providing intracellular protection against oxidative stress. Three feruloylquinic acids, diferuloylquinic acids, three feruloyl-caffeoylquinic acids, and three caffeoyl-feruloylquinic acids were obtained from green coffee beans [19]. Whether or not these compounds contribute to the flavor formation during coffee processing remains unknown. McNamara et al. [101] identified a glycoside of feruloylquinic acid, 5-O-(4′-[β-D-glucopyranosyl]-trans-feruloyl)quinic acid, from *Hydrastis canadensis* L., a valuable medicinal herb used primarily for its antimicrobial properties. This acid possibly acts as one of the active ingredients in this plant. Ferulic di-, tri-, andtetramers are structural components in cereal cell walls. They can be partly released by some colon microorganisms [5] and may possess some functions.

Apart from the derivatives of ferulic acid previously discussed, the association of some medicines with ferulic acid in developing new drugs has been also investigated by many researchers but is not discussed in this article. Readers may refer to a review by Zhang et al. [11].

9. FUTURE PERSPECTIVE

This review presented an introduction on feruloyl derivatives, which are naturally occurring or artificially synthesized. These derivatives exhibit higher activity than their parent compound ferulic acid, such as antioxidant activity in cells, skin protection from UV, and mitigation of diabetes. They also produce new functions that ferulic acid cannot provide; these functions include anticancer and antifungal activities, Alzheimer's disease treatment, and plant infection defense. However, information on the toxicological, pharmaceutical, and pharmacokinetic properties of feruloyl derivatives is insufficient. Future studies should analyze the potent derivatives and develop other functional derivatives, such as feruloyl amino acids, peptides, and vitamins.

10. CONCLUSION

Ferulic acid possesses multiple physiological and pharmaceutical functions. Derivative of ferulic acid with other active compounds can improve the chemical, physical, and pharmaceutical properties of this phenolic acid; some of these derivatives have been found and identified in various plant species, and their physiological functions were extensively investigated in *in vitro*. Future studies could focus ontheir toxicological, pharmaceutical, and pharmacokinetic properties in animals or humans.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mancuso C, Santangelo R. Ferulic acid: pharmacological and toxicological aspects. Food Chem. Toxicol. 2014;65:185-195.
2. Ou S, Kwok KC. Ferulic acid: pharmaceutical functions, preparation and applications in foods.J. Sci. Food Agric. 2004;84:1261-1269.
3. Song Y, Wu TG, Yang XQ, Chen XY, Wang MF, Wang Y, Peng XC, Ou SY. Ferulic acid alleviates the symptoms of diabetes in obese rats. J. Funct. Foods. 2014;9:141-147.
4. Zhao Z, Moghadasian MH. Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: a review. Food Chem. 2008;109:691-702.
5. Ou J, Sun Z. Feruloylated oligosaccharides: structure, metabolism and function. J. Funct. Foods 2013;7:90-100.
6. Rondini L, Peyrat-Maillard MN, Marsset-Baglieri A, Berset C. Sulfated ferulic acid is the main in vivo metabolite found after short-term ingestion of free ferulic acid in rats. J. Agric. Food Chem. 2002;50:3037-3041.
7. Tada Y, Tayama K, Aoki N. Acute oral toxicity of ferulic acid, natural food additive, in rats. Ann. Rep. Tokyo Metr. Lab. P.H. 1999;50:311-313.
8. Stamatis H, Sereti V, Kolisis F. Enzymatic synthesis of hydrophilic and hydrophobic derivatives of natural phenolic acids in organic media. J. Mol. Catal. B: Enzym. 2001;11:323-328.
9. Compton DL, Laszlo JA, Evans KO. Antioxidant properties of feruloyl glycerol derivatives. Ind. Crops Prod. 2012;36:217-221.
10. Qin F, Dou HQ, Bi YL, Lin TT, Sun SD, Yang, GL, Liu W. Progress on synthesis of water soluble glyceryl ferulates. J. Henan Univ. Tech. (Nat. Sci. Edn) 2013;34:101-105.

11. Zhang YL, Wei CM, Wang JT. Study on the synthesis and molecular modification of ferulic acid. J. Huaiyin Teachers College. 2003;2:50-53.
12. Ishii T. Structure and functions of feruloylated polysaccharides. Plant Sci. 1997;127:111-127.
13. Harrison LJ, Sia GL, Sim KY, Tan HTW, Connolly JD, Lavaud C, Massiot GA. Ferulic acid ester of sucrose and other constituents of *Bhesa paniculata*. Phytochem. 1995;38:1497-1500.
14. Kim KH, Chang SW, Lee KR. Feruloyl sucrose derivatives from *Bistorta manshuriensis*. Can. J. Chem. 2010;88:519-523.
15. Miyase T, Noguchi H, Chen XM. Sucrose esters and xanthone C-glycosides from the roots of *Polygala sibirica*. J. Nat.Prod. 1999;62:993-996.
16. Nakano K, Murakami K, Takaishi Y, Tomimatsu T. Feruloyl sucrose derivatives from *Heloniopsis orientalis*.Chem. Pharm. Bull. 1986;34:5005-5010.
17. Delazar A, Shoeb M, Kumarasamy Y, Byres M, Nahar L, Modarresi M, Sarker SD. Two bioactive ferulic acid derivatives from *Eremostachys glabra*. DARU. 2004;12:49-53.
18. Fernandes F, Sousa C, Ferreres F, Valentão P, Remião F, Pereira JA, Andrade PB. Kale extract increases glutathione levels in V79 cells, but does not protect them against acute toxicity induced by hydrogen peroxide. Molecules 2012;17:5269-5288.
19. Clifford MN, Knight S, Surucu B, Kuhnert N. Characterization by LC-MSn of four new classes of chlorogenic acids in green coffee beans: dimethoxycinnamoylquinic acids, diferuloylquinic acids, caffeoyl-dimethoxycinnamoylquinic acids, and feruloyl-dimethoxycinnamoylquinic acids. J. Agric. Food Chem. 2006;54:1957-1969.
20. Hakala P, Lampi AM, Ollilainen V, Werner U, Murkovic M, Wähälä K, Karkola S, Piironen V. Steryl phenolic acid esters in cereals and their milling fractions. J. Agric. Food Chem. 2002;50:5300-5307.
21. Messens E, Dekeyser R, Stachel SE. A nontransformable *Triticum monococcum* monocotyledonous culture produces the potent Agrobacterium vir-inducing compound ethyl ferulate. PNAS. 1990;87:4368-4372.
22. Figueroa-Espinoza MC, Villeneuve P. Phenolic acids enzymatic lipophilization. J. Agric. Food Chem. 2005;53:2779-2787.
23. Jacquet G, Pollet B, Lapierre C, Mhamdi F, Rolando C. New ether-linked ferulic acid-coniferyl alcohol dimers identified in grass straws. J. Agric. Food Chem. 1995;43:2746-2751.
24. Park BJ, Tomohiko M. Feruloyl, caffeoyl, and flavonol glucosides from Equisetum hyemale. Chem. Nat. Compd. 2011;47:363-365.
25. Yang L, Jiang H, Wang QH, Yang BY, Kuang HX. A new feruloyl tyramine glycoside from the roots of *Achyranthes bidentata*. Chin. J. Nat.Med. 2012;10:16-19.
26. Ichikawa M, Ryu K, Yoshida J, Ide N, Kodera Y, Sasaoka T, Rosen RT. Identification of six phenylpropanoids from garlic skin as major antioxidants. J. Agric. Food Chem. 2003;51:7313-7317.
27. Kim Y, Han MS, Lee JS, Kim J, Kim YC. Inhibitory phenolic amides on lipopolysaccharide-induced nitric oxide production in RAW 264.7 cells from Beta vulgaris var. cicla seeds. Phytother. Res. 2003;17:983-985.
28. Lee KH, Yang MC, Kim KH, Kwon HC, Choi SU, Lee KR. A new phenolic amide from the roots of *Paris verticillata*. Molecules 2008;13:41-45.
29. Yao SW, Wen XX, Huang RQ, He RR, Ou SY, Shen WZ, Huang CH, Peng XC. Protection of feruloylated oligosaccharides from corn bran against oxidative stress in PC 12 cell. J. Agric. Food Chem. 2014;62:668–674.
30. Nhiem NX, Van Kiem P, Van Minh C, Ban NK, Cuong NX, Tai BH, Kim YH. Phenylpropanoid glycosides from *Heterosmilax erythrantha* and their antioxidant activity. Arch. Pharm. Res. 2009;32:1373-1377.
31. Sun X, Zimmermann ML, Campagne JM, Sneden AT. New sucrose phenylpropanoid esters from *Polygonum perfoliatum*. J. Nat. Prod. 2000;63:1094-1097.
32. Takasaki M, Kuroki S, Kozuka M, Konoshima T. New phenylpropanoid esters of sucrose from *Polygonum lapathifolium*. J. Nat. Prod. 2001;64:1305-1308.
33. Shimomura H, Sashida Y, Mimaki Y. Bitter phenylpropanoid glycosides from *Lilium speciosum* var. rubrum. Phytochemistry 1986;25:2897-2899.
34. Marcia MDO. Feruloylation in grasses: current and future perspectives. Mol. Plant

2009;2:861-872.

35. Niño-Medina G, Carvajal-Millán E, Rascon-Chu A, Marquez-Escalante JA, Guerrero V, Salas-Muñoz E. Feruloylated arabinoxylans and arabinoxylan gels: Structure, sources and applications. Phytochem. Rev. 2010;9:111-120.
36. Courtin C, Delcour JA. Arabinoxylans and endoxylanases in wheat flour bread-making. J. Cereal Sci. 2002;35:225-243.
37. Liu J, Wen XY, Lu JF, Kan J, Jin CH. Free radical mediated grafting of chitosan with caffeic and ferulic acids: Structures and antioxidant activity. Int. J. Biol. Macromol. 2014;65:97-106.
38. Woranuch S, Yoksan R. Preparation, characterization and antioxidant property of water-soluble ferulic acid grafted chitosan. Carbohydr. Polym. 2013;96:495-502.
39. Kitagawa M, Tokiwa Y. Polymerization of vinyl sugar ester using ascorbic acid and hydrogen peroxide as a redox reagent. Carbohydr. Polym. 2006;64:218-223.
40. Liu J, Lu JF, Kan J, Jin CH. Synthesis of chitosan-gallic acid conjugate: structure characterization and in vitro anti-diabetic potential. Int. J. Biol. Macromol. 2013;62:321-329.
41. Aljawish A, Chevalot I, Jasniewski J, Revol-Junelles AM, Scher J, Muniglia L. Laccase-catalyzed functionalization of chitosan by ferulic acid and ethyl ferulate: evaluation of physicochemical and biofunctional properties. Food Chem. 2014;161:279-287.
42. Cheng YH, Yang SH, Liu CC, Gefen A, Lin FH. Thermosensitive hydrogel made of ferulic acid-gelatin and chitosan glycerophosphate. Carbohydr. Polym. 2013;92:1512-1519.
43. Aljawish A, Muniglia L, Jasniewski J, Klouj A, Scher J, Chevalot I. Adhesion and growth of HUVEC endothelial cells on films of enzymatically functionalized chitosan with phenolic compounds.Process Biochem. 2014;49:863-871.
44. Ou S, Yang AL. A study on synthesis of starch ferulate and its biological properties. Food Chem. 2001; 74:91-95.
45. Mahindaratne MP, Wimalasena K. Detailed characterization of p-toluenesulfonic acid monohydrate as a convenient, recoverable, safe, and selective catalyst for alkylation of the aromatic nucleus. J. Org. Chem. 1998; 63: 2858-2866.
46. Holser RA. Kinetics of cinnamoyl glycerol formation. J. Am. Oil Chem. Soc. 2008; 85: 221-225.
47. Holser R, Mitchell T, Harry-O'kuru R, Vaughn S, Walter E, Himmelsbach D. Preparation and characterization of 4-methoxy cinnamoyl glycerol. J. Am. Oil Chem. Soc. 2008;85:347-351.
48. Sun S, Yang G., Bi Y, Xiao F. Chemoenzymatic synthesis of feruloylated monoacyl-and diacyl-glycerols in ionic liquids. Biotechnol. Lett. 2009;31:1885-1889.
49. Gandhi NN. Applications of lipase. J. Am. Oil Chem. Soc. 1997;74: 621-634.
50. Wong DW. Feruloyl esterase. Appl. Biochem. Biotechnol. 2006;133:87-112.
51. Topakas E, Vafiadi C, Christakopoulos P. Microbial production, characterization and applications of feruloyl esterases. Process Biochem. 2007;42:497-509.
52. Matsuo T, Kobayashi T, Kimura Y, Hosoda A, Taniguchi H, Adachi S. Continuous synthesis of glyceryl ferulate using immobilized *Candida antarctica* lipase.J. Oleo Sci.2007;57:375-380.
53. Zheng Y, Quan J, Zhu LM, Jiang B, Nie HL. Optimization of selective lipase-catalyzed feruloylated monoacylglycerols by response surface methodology. J. Am. Oil Chem.Soc.2008;85:635-639.
54. Tsuchiyama M, Sakamoto T, Fujita T, Murata S, Kawasaki H. Esterification of ferulic acid with polyols using a ferulic acid esterase from *Aspergillus niger*. Biochim. Biophys. Acta Gen. Subjects 2006;1760:1071-1079.
55. Kikugawa M, Tsuchiyama M, Kai K, Sakamoto T. Synthesis of highly water-soluble feruloyl diglycerols by esterification of an *Aspergillus niger* feruloyl esterase. Appl. Microbiol. Biotechnol. 2012;95:615-622.
56. Zheng Y, Quan J, Ning X, Zhu LM. Enhancement in the synthesis of novel feruloyl lipids (feruloyl butyryl glycerides) by enzymatic biotransformation using response surface methodology. J. Agric. Food Chem. 2008;56:11493-11498.
57. Sun S, Shan L, Liu Y, Jin Q, Song Y, Wang X. Solvent-free enzymatic synthesis of feruloylated diacylglycerols and kinetic study. J. Mol. Catal. B: Enzym. 2009;57:104-108.
58. Sun SD, Shan L, Liu YF, Jin QZ, Zhang LX, Wang X. G. Solvent-free enzymatic

preparation of feruloylated monoacylglycerols optimized by response surface methodology. J. Agric. Food Chem. 2007;56:442-447.

59. Sun S, Shan L, Liu Y, Jin Q, Wang X, Wang Z. A novel, two consecutive enzyme synthesis of feruloylated monoacyl-and diacyl-glycerols in a solvent-free system. Biotechnol. Lett. 2007;29:1947-1950.
60. Laszlo JA, Compton DL. Enzymatic glycerolysis and transesterification of vegetable oil for enhanced production of feruloylated glycerols. J. Am. Oil Chem. Soc. 2006;83:765-770.
61. Warner K, Laszlo J. Addition of ferulic acid, ethyl ferulate, and feruloylated monoacyl- and diacylglycerols to salad oils and frying oils. J. Am. Oil Chem. Soc. 2005;82:647-652.
62. Compton DL, DeFilippi LJ, Grall SG, Kinney JF, Laszlo JA. Formulations with feruloyl glycerides and methods of preparation. U.S. Patent 7. 2010;744:856,
63. Totani N, Tateishi S, Takimoto T, Shinohara R, Sasaki H. Ferulic acid esters and weight-loss promoting effects in rats. J. Oleo Sci. 2011;61:331-336.
64. Zhang X, Wei N, Huang J, Tan Y, Jin D. A new feruloyl amide derivative from the fruits of *Tribulus terrestris*.Nat. Prod. Res. 2012;26:1922-1925.
65. Espinoza S, Salahpour A, Masri B, Sotnikova TD, Messa M, Barak LS, Caron MG, Gainetdinov RR. Functional interaction between trace amine-associated receptor 1 and dopamine D2 receptor. Mol. Pharmacol. 2011;80:416-425.
66. Lee C, Kim J, Lee H, Lee S, Kho Y. Two new constituents of Isodon excisus and their evaluation in an apoptosis inhibition assay. J. Nat. Prod. 2001;64:659-660.
67. McLusky SR, Bennett MH, Beale MH, Lewis MJ, Gaskin P, Mansfield JW. Cell wall alterations and localized accumulation of feruloyl-3′-methoxytyramine in onion epidermis at sites of attempted penetration by *Botrytis allii* are associated with actin polarisation, peroxidase activity and suppression of flavonoid biosynthesis. Plant J. 1999;17:523-534.
68. Baker CJ, Whitaker BD, Mock NM, Rice CP, Roberts DP, Deahl KL, Ueng PP,Aver'yanov AA. Differential induction of redox sensitive extracellular phenolic amides in potato.Physiol. Mol. Plant Pathol. 2008;73:109-115.
69. Lee DG, Park Y, Kim MR, Jung HJ, Seu YB, Hahm KS, Woo ER. Anti-fungal effects of phenolic amides isolated from the root bark of *Lycium chinense*. Biotechnol. Lett. 2004;26:1125-1130.
70. Wang F, Lu W, Zhang T, Dong J, Gao H, Li P, Wang S, Zhang J. Development of novel ferulic acid derivatives as potent histone deacetylase inhibitors. Bioorg. Med. Chem. 2013;21:6973-6980.
71. Shi ZH, Li NG, Shi QP, Tang YP, Yang JP, Duan JA. Design, synthesis and biological evaluation of ferulic acid amides as selective matrix metalloproteinase inhibitors. Med. Chem. 2013;9:947-954.
72. Nomura E, Kashiwada A, Hosoda A, Nakamura K, Morishita H, Tsuno T, Taniguchi H. Synthesis of amide compounds of ferulic acid, and their stimulatory effects on insulin secretion in vitro. Bioorg. Med. Chem. 2003;11:3807-3813.
73. Rabuazzo AM, Buscema M, Vinci C, Caltabiano V, Vetri M, Forte F, Vigneri R, Purrello F. Glyburide and tolbutamide induce desensitization of insulin release in rat pancreatic islets by different mechanisms. Endocrinology. 1992;131: 1815-1820.
74. Dobhal M, Hasan AM, Sharma M, Joshi B. Ferulic acid esters from *Plumeria bicolor*. Phytochem. 1999;51:319-321.
75. Zhang LW, Al-Suwayeh SA, Hsieh PW, Fang JYA. Comparison of skin delivery of ferulic acid and its derivatives: evaluation of their efficacy and safety. Int. J. Pharam. 2010;399:44-51.
76. Anselmi C, Centini M, Andreassi M, Buonocore A, Rosa CL, Facino RM, Sega A, Tsuno F. Conformational analysis: A tool for the elucidation of the antioxidant properties of ferulic acid derivatives in membrane models. J. Pharam. Biomed. Anal.2004;35:1241-1249.
77. Sultana R. Ferulic acid ethyl ester as a potential therapy in neurodegenerative disorders. Biochim. Biophys. Acta. Mol. Basis Dis. 2012;1822:748-752.
78. Murakami A, Kadota M, Takahashi D, Taniguchi H, Nomura E, Hosoda A, Tsuno T, Maruta Y, Ohigashi H, Koshimizu K. Suppressive effects of novel ferulic acid derivatives on cellular responses induced by phorbol ester, and by combined lipopolysaccharide and interferon-γ.

Cancer Lett. 2000;157:77-85.

79. Compton DL, Laszlo JA, Berhow MA. Lipase-catalyzed synthesis of ferulate esters. J. Am. Oil Chem. Soc. 2000;77:513-519.
80. Lee GS, Widjaja A, Ju YH. Enzymatic synthesis of cinnamic acid derivatives. Biotechnol. Lett. 2006;28:581-585.
81. Li NG, Shi ZH, Tang YP, Li BQ, Duan JA. Highly efficient esterification of ferulic acid under microwave irradiation. Molecules 2009;14:2118-2126.
82. Anselmi C, Centini M, Granata P, Sega A, Buonocore A, Bernini A, Facino RM. Antioxidant activity of ferulic acid alkyl esters in a heterophasic system: a mechanistic insight. J. Agric. Food Chem. 2004;52:6425-6432.
83. Anselmi C, Bernardi F, Centini M, Gaggelli E, Gaggelli N, Valensin D, Valensin G. Interaction of ferulic acid derivatives with human erythrocytes monitored by pulse field gradient NMR diffusion and NMR relaxation studies. Chem. Phys. Lipids 2005;134:109-117.
84. Murakami A, Nakamura Y, Koshimizu K, Takahashi D, Matsumoto K, Hagihara K, Taniguchi H, Nomura E, Hosoda A, Tsuno T. FA15, a hydrophobic derivative of ferulic acid, suppresses inflammatory responses and skin tumor promotion: Comparison with ferulic acid. Cancer Lett. 2002;180:121-129.
85. Serafim TL, Carvalho FS, Marques MP, Calheiros R, Silva T, Garrido J, Milhazes N, Borges F, Roleira F, Silva ET. Lipophilic caffeic and ferulic acid derivatives presenting cytotoxicity against human breast cancer cells. Chem. Res. Toxicol. 2011; 24: 763-774.
86. Carlomagno G, Nordio M, Chiu T, Unfer V. Contribution of myo-inositol and melatonin to human reproduction. Eur. J. Obstet. Gyn.R. B. 2011;159:267-272.
87. Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur. Rev. Med. Pharmacol. Sci. 2011;15:931-936.
88. Hosoda A, Ozaki Y, Kashiwada A, Mutoh M, Wakabayashi K, Mizuno K, Nomura E, Taniguchi H. Syntheses of ferulic acid derivatives and their suppressive effects on cyclooxygenase-2 promoter activity. Bioorg. Med. Chem. 2002;10:1189-1196.
89. Hosoda A, Nomura E, Murakami A, Koshimizu K, Ohigashi H, Mizuno K, Taniguchi H. Synthesis of feruloyl-myo-insitol derivatives and their inhibitory effects on phorbol ester-induced superoxide generation and esptein–barr virus activation.Bioorg. Med. Chem. 2002;10:1855-1863.
90. Kröncke K, Fehsel K, Kolb-Bachofen V. Inducible nitric oxide synthase in human diseases. Clin. Exp. Immunol. 1998;113:147-156.
91. Nussler A.K, Billiar T. Inflammation, immunoregulation, and inducible nitric oxide synthase. J. Leukocyte Biol. 1993;54:171-178.
92. Wenk GL, McGann-Gramling K, Hauss-Wegrzyniak B, Ronchetti D, Maucci R, Rosi S, Gasparini L, Ongini E. Attenuation of chronic neuroinflammation by a nitric oxide-releasing derivative of the antioxidant ferulic acid. J. Neurochem. 2004;89:484-493.
93. Ronchetti D, Impagnatiello F, Guzzetta M, Gasparini L, Borgatti M, Gambari R, Ongini E. Modulation of iNOS expression by a nitric oxide-releasing derivative of the natural antioxidant ferulic acid in activated RAW 264.7 macrophages.Eur. J. Pharamacol. 2006;532:162-169.
94. Chen Y, Sun J, Fang L, Liu M, Peng, S, Liao H. Lehmann J, Zhang Y. Tacrine-ferulic acid-nitric oxide (NO) donor trihybrids as potent, multifunctional acetyl- and butyrylcholinesterase inhibitors. J. Med. Chem. 2012;55:4309-4321.
95. Li NG, Wang R, Shi ZH, Tang YP,Li BQ, Wang ZJ, Song SL, Qian LH, Li W, Yang JP, Yao LJ, Xi JZ, Xu J, Feng F, Qian DW, Duan JA. Design and synthesis of novel no-donor-ferulic acid hybrids as potential antiatherosclerotic drug candidates. Drug Devel. Res. 2011;72:405–415.
96. Boultadakis A, Liakos P, Pitsikas N. The nitric oxide-releasing derivative of ferulic acid NCX 2057 antagonized delay-dependent and scopolamine-induced performance deficits in a recognition memory task in the rat. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:5–9.
97. Daniela R, Valentina B, Gema G. NCX 2057, a novel NO-releasing derivative of ferulic acid, suppresses inflammatory and nociceptive responses in *in vitro* and *in vivo* models. British J. Pharmacol. 2009;158:569-579.
98. Liu HR, Liu Y, Li YL, Qi MY, Liu WK. Synthesis and biological activity of nitric

oxide-releasing derivatives of ferulic acid as potential agents for the treatment of chronic kidney diseases. Med. Chem. 2013;9:875-880.

99. De Jong A, Plat J, Mensink RP. Metabolic effects of plant sterols and stanols (Review). J. Nutr, Biochem. 2003;14:362-369.

100. Moghadasian MH. Pharmacological properties of plant sterols: *in vivo* and *in vitro* observations. Life Sci. 2000;67:605-615.

101. McNamara CE, Perry NB, Follett JM, Parmenter GA., Douglas JA. A new glucosyl feruloyl quinic acid as a potential marker for roots and rhizomes of goldenseal, *Hydrastis canadensis*.J. Nat. Prod. 2004;67:1818-1822.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=795&id=32&aid=7039