

## Letter to the editor:

### A RECENT OVERVIEW ON THE BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES OF FERULIC ACID

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#### Dear Editor,

Ferulic acid (FA) is an important phenolic acid that is commonly present in the leaves, fruits, and seeds of most plants. Certain types of grasses, including rice, wheat, and oats, are highly concentrated sources of FA. The name, ferulic, originates from the genus, *Ferula*, referring to giant fennel (*Ferula communis*). The International Union of Pure and Applied Chemistry (IUPAC) name for FA is (*E*)-3-(4-hydroxy-3-methoxy-phenyl) prop-2-enoic acid (Srinivasan et al., 2007; Bento-Silva et al., 2018). In plants, FA is biosynthesized from caffeic acid by the enzyme caffeate O-methyltransferase. FA, along with dihydroferulic acid, acts as a component of lignocellulose, which crosslinks lignins and polysaccharides, thereby conferring rigidity to the cell walls (de Oliveira et al., 2015).

FA has been recognized as an important chemical structure serving several biological activities, including antioxidant, anti-inflammatory, antiviral, antiallergic, antimicrobial, antithrombotic, anticarcinogenic, and hepatoprotective actions, directly or indirectly (Kumar and Pruthi, 2014; Mancuso and Santangelo, 2014). The FA enrichment in different food items could reduce oxidative damage and amyloid pathology, especially for Alzheimer disease (Nabavi et al., 2015; Sgarbossa et al., 2015). In this review, we summarize the recent findings on the biological and pharmacological activities of FA (Table 1).

**Table 1:** Recent studies on the biological and pharmacological activities of ferulic acid

| Key findings                                                                                                                                                                                                                                                                                                                                             | Reference                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| In a recent study, it was reported that FA improves hepatic fibrosis through the inhibition of the transforming growth factor (TGF)- $\beta$ 1/ <i>Smad</i> pathway <i>in vitro</i> and <i>in vivo</i> . These findings revealed that FA can potentially be used to protect against liver fibrosis.                                                      | Mu et al., 2018           |
| FA enhances the antibacterial activity of quinolone-based antibiotics against <i>Acinetobacter baumannii</i> by enhancing reactive oxygen species (ROS) generation, energy metabolism, and the activity of the electron transport chain with a concomitant decrease in glutathione                                                                       | Ibitoye and Ajiboye, 2018 |
| Chen et al. reported that FA can potentially treat various disorders, including NG-nitro-L-arginine methyl ester (L-NAME) induced preeclampsia in rats by decreasing placental inflammation and apoptosis.                                                                                                                                               | Chen et al., 2018         |
| Research findings revealed that FA fights against kidney ischemia reperfusion injury by decreasing apoptosis, increasing adenosine generation, reducing inflammation, and upregulating CD39 and CD73 expression.                                                                                                                                         | Zhou et al., 2018         |
| Supplementation of FA in other foods or ingredients enriches the development of the reproductive tract and ovarian activity of pre-pubertal hair breed ewe lambs during the natural anestrus season. An enhancement in the functionality of the glucose-insulin system could be a cause of this beneficial effect of FA.                                 | Macías-Cruz et al., 2018  |
| FA and sugarcane aqueous extract (SCAE) can protect against toxic conditions. All of these effects are not necessarily related to SCAE, because FA requires the <i>skn-1</i> pathway to exert its protective manner in <i>Caenorhabditis elegans</i> .                                                                                                   | Colonnello et al., 2018   |
| FA intervention significantly ameliorates human umbilical vein endothelial cells (HUVEC) radiation injury through the thrombomodulin pathway. Therefore, FA could be effectively used as a potential agent to attenuate radiation-induced damage.                                                                                                        | Shao et al., 2018         |
| FA performs better than caffeic acid as an inhibitor of melanin production; the differences in the inhibitory efficacy of these two substances might be attributed to the difference in their tyrosine-binding activity. This study reveals that both substances effectively inhibited the CK2 (casein kinase 2)-mediated phosphorylation of tyrosinase. | Maruyama et al., 2018     |
| FA and fish oil (FO) demonstrate anti-inflammatory and renoprotective effects through their peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) agonistic activity. Both FA and FO are natural products, and they both can offer a safe intervention strategy after exposure to nephrotoxins.                                             | El-Ashmawy et al., 2018   |
| FA is considered as a remedy for the plaques related to collagen deposition, because it is a potential inhibitor of collagen fibrillation and its propagation.                                                                                                                                                                                           | Jayamani et al., 2018     |
| FA has protective effects against lipopolysaccharide (LPS)-induced acute kidney injury (AKI) in mice, which might suggest a chemopotential role treating AKI in humans.                                                                                                                                                                                  | Mir et al., 2018          |
| FA, along with caspofungin, has synergistic effects against <i>Candida albicans</i> . These two compounds help to combine the existing anticandidal drug with phytochemicals to increase the efficacy of the anticandidal drug.                                                                                                                          | Canturk, 2018             |
| FA and quercetin exhibit excellent bioavailability and bioactivity against some metabolic syndromes, like inflammatory bowel diseases and obesity.                                                                                                                                                                                                       | Zhang et al., 2018        |
| The new poly(ether ester urethane)urea elastomer (PEEUU) adapted with FA could act as a promising candidate for the vascular application of enhancing blood compatibility and vascular cell-compatibility.                                                                                                                                               | Asadpour et al., 2018     |
| FA mixed with nanostructured lipid carriers (NLCs) improves the pharmacological profile of FA and activates the phosphatidylinositol 3-kinase (PI3K) pathway, which has a therapeutic value against cerebral stroke.                                                                                                                                     | Hassanzadeh et al., 2018  |

| Key findings                                                                                                                                                                                                                                                                                                                                       | Reference                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| FA stimulates the synthesis of procollagen and hyaluronic acid, the inhibition of metalloproteinase, and the reduction in matrix metalloproteinase (MMP)-1 and MMP-9 expression in CCD-986sk cells stimulated with ultraviolet B (UV-B). FA can potentially be used as functional food for whitening and anti-wrinkle activities.                  | Park et al., 2018          |
| FA combined with-vinylguaiaicol forms a chemical starting structure for the development of new small molecules that protects against epidermal growth factor receptor (EGFR).                                                                                                                                                                      | Sudhagar et al., 2018      |
| FA has endothelium-independent vascular relaxant responses in different types of arteries. The molecular mechanism of FA-induced vasorelaxation involves the inhibition of a calcium channel and calcium desensitization.                                                                                                                          | Zhou et al., 2017          |
| FA has beneficial effects on diabetes-induced cognition lesions, which was revealed by the regulation of the protein tyrosine phosphatase 1B (PTP1B) and insulin signaling pathways. PTP1B inhibition may be an approach to remedy abnormal signaling linked to diabetes-induced cognitive impairment.                                             | Wang et al., 2017          |
| FA shows potential therapeutic efficacy in enhancing survival and differentiation of neural stem cells (NSCs) to protect against gentamicin-induced neuronal hearing loss.                                                                                                                                                                         | Gu et al., 2017            |
| FA shows antiepileptogenic effects and protects against oxidative stress and cognitive impairment induced by pentylenetetrazol kindling by acting as a promising adjuvant for antiepileptic drugs.                                                                                                                                                 | Hassanzadeh et al., 2017   |
| FA acts as an anti-inflammatory and antioxidant agent on macrophages due to its free radical scavenging activity in a cell free system. Consuming FA in a diet can defend the host from the development and/or progression of inflammation.                                                                                                        | Szulc-Kielbik et al., 2017 |
| In rice bran, FA represents an active component that enhances the expression of mitochondrial biogenesis and dynamics markers. In a vascular damage mouse model, FA decreases oxidative stress in endothelial cells and human mononuclear cells.                                                                                                   | Perez-Tenero et al., 2017  |
| FA could be considered as a novel agent to increase the management of depression, because it repairs stress caused by the hypothalamic-pituitary-adrenal-axis dysfunction.                                                                                                                                                                         | Zeni et al., 2017          |
| FA treatment significantly protects against oxidative stress, shows positive antioxidant activity, and improves histological parameters to normal, exhibiting the nephroprotective and antioxidant effects of this phenolic compound.                                                                                                              | Bami et al., 2017          |
| FA enhances the obesogenic status induced by a high-fat diet (HFD), and the integral effects of FA on a biological system were elucidated.                                                                                                                                                                                                         | Salazar-López et al., 2017 |
| FA reduces preeclampsia symptoms in a rat preeclampsia model, exhibiting its potential value in treating preeclampsia.                                                                                                                                                                                                                             | Gong et al., 2017          |
| FA diminishes the increase in gene expression and assembly of proteins related to the emission of three types of A $\beta$ peptides in H <sub>2</sub> O <sub>2</sub> -stimulated human lens epithelial (HLE) cells. These findings provide evidence of the antioxidative functions of FA in lens epithelial cells.                                 | Nagai et al., 2017         |
| The oxygen-carrying capacity of a hemoglobin site specifically adapted with ferulic acid (FA-Hb) was similar to endogenous Hb, but the rate of autoxidation of FA-Hb was much lower than Hb in various systems.                                                                                                                                    | Qi et al., 2017            |
| Pretreated with 0.1 mM of FA impairs the methylglyoxal (MG)-induced decrease of cell viability and protects against MG-induced cell apoptosis in pancreatic $\beta$ -cells. These findings suggest that FA is capable of protecting $\beta$ -cells from MG-induced cell damage in diabetes.                                                        | Sompong et al., 2017       |
| FA shows protective effects against ultraviolet A (UVA)-induced cell damage through antioxidant and stress-inducible cellular action in human dermal fibroblasts (HDFs).                                                                                                                                                                           | Hahn et al., 2016          |
| FA significantly improved the intracellular concentration of $\delta$ -tocotrienol (T3), enhancing the bioavailability of $\delta$ -T3, and thus increasing the inhibitory power of $\delta$ -T3 on telomerase. For the above mentioned activities, FA could be a promising candidate to target $\delta$ -T3 and augment the anti-cancer activity. | Eitsuka et al., 2016       |

| Key findings                                                                                                                                                                                                                                                                          | Reference              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| FA could effectively act against acetaminophen-induced liver injury by down-regulating the expression of CYP 2E1 and the inhibition of Toll-like receptor (TLR) 4-mediated inflammatory responses.                                                                                    | Yuan et al., 2016      |
| FA could inhibit the interferon- $\gamma$ (IFN- $\gamma$ )-induced inflammatory response by reducing the release of pro-inflammatory cytokines to improve trinitrobenzenesulfonic acid-induced colitis.                                                                               | Sadar et al., 2016     |
| FA protects the initiation of apoptotic signaling in the spleen by obstructing the free radical chain reaction and by scavenging superfluous ROS. FA can prevent the spleen from ionizing radiation.                                                                                  | Das et al., 2016       |
| FA has a potential therapeutic response exhibiting antioxidant and hypoglycemic effects, which might help in circumventing stress-mediated diabetic cardiomyopathy in rats.                                                                                                           | Chowdhury et al., 2016 |
| FA is a promising candidate to treat developmental lead neurotoxicity. These hopeful findings will initiate future investigations evaluating the FA-mediated potentiation of neurite outgrowth following lead exposure <i>in vivo</i> .                                               | Yu et al., 2016        |
| <i>Trans</i> -FA at concentrations between 0.06 to 0.6 mM shows anti-proliferation and anti-migration effects in the human lung cancer cell line, H1299.                                                                                                                              | Fong et al., 2016      |
| FA prevents osteoclast fusion by reducing the expression of dendritic cell-specific transmembrane protein (DC-STAMP) and enhancing apoptosis in mature osteoclasts through the caspase-3 pathway.                                                                                     | Sagar et al., 2016     |
| FA-loaded hydrogel (thermosensitive) could salvage <i>Cisd2</i> -deficient ( <i>Cisd2</i> <sup>-/-</sup> ) cardiomyocytes (CM) from oxidative stress-induced damage and could act as a potential therapeutic in the future treatment of cardiovascular diseases (CVD).                | Cheng et al., 2016     |
| The anti-hyperalgesia response of FA, which might be related to its antioxidant and anti-inflammatory activity, in rats with chronic constriction injury (CCI) could be effective as an adjuvant to conventional medicines. FA is also related to the protection of neuropathic pain. | Aswar and Patil, 2016  |
| A study by Yang et al. shows that FA significantly inhibits important diseases, such as d-galactose(d-gal)-induced AChE (acetylcholinesterase) activity, neuroinflammation and neurodegeneration, and oxidative stress, thus consequently ameliorates memory impairment.              | Yang et al., 2016      |
| FA is a promising hepatoprotective agent against formaldehyde toxicity, because it exhibits positive effects on oxidative stress parameters.                                                                                                                                          | Gerin et al., 2016     |

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### Conflict of interest

The authors declare no conflict of interest.

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