International Journal of Advanced Biological and Biomedical Research
Available online at http:www.ijabbr.com
Volume 9, Issue 3 (2021) pp. 228-240 DOI: 10.22034/ijabbr.2021.525197.1350

Review Article

Antioxidant Properties of Ferulic Acid on cardiovascular diseases

Farzaneh Fazeli

Department of Biology, Payam Noor University of Ilam, Ilam, Iran.

*Corresponding Author E-mail: seacorales@yahoo.com

Received: 15 February 2021, Revised: 18 April 2021, Accepted: 19 May 2021

ABSTRACT

Background: As a dietary phytochemical, Ferulic acid (FA) is caused by metabolism between phenylalanine and tyrosine with physiological functions like anti-inflammatory, anti-diabetic, anticancer, antioxidant, antimicrobial and cardioprotective properties. This study aims to investigate FA protective effects on cardiovascular diseases.

Methods: We covered references like these, web-based scientific databases, PubMed publications, ScienceDirect and Springer. Recent patent on FA therapeutic function in treatment of cardiovascular diseases potential was evaluated.

Results: Studies showed that foods rich in FA prevent hypertension. FA, a free radical scavenger, is an enzyme inhibitor which catalyzes free radical generation and enhances scavenger enzyme activity. As a potent scavenger of free radicals, it dilutes oxidative stress, and reduces elevated blood-pressure by improving endothelial function and increasing bioavailability of this oxide in arterial vasculature. FA can enhance angiogenesis and wound healing.

Conclusion: In this review, protective function of FA, an antioxidant compound in some nutrition such as fruits, vegetables, and grains, was discussed in terms of its relationship with cardiovascular diseases. Despite numerous data on FA, its effects on human is not recognized; further clinical studies about therapeutic effects of FA on patients with vascular diseases are required.

Keywords: Phytochemical, Cardioprotective, Oxidative Stress, Free Radicals, Hypertension.

1. Introduction

1.1. Polyphenols and Ferulic acid (FA)

The presence of bioactive compounds along with antioxidant properties, especially polyphenolic compounds and vitamins, in plant- based foods is an effective factor in maintaining human health [1]. Phenolic acids are hydroxylated derivatives of benzoic acid and cinnamic acid. Hydroxy cinnamic acids are found abundantly in most plants, and the most common compounds are chlorogenic acid, vanillic acid, caffeic acid, paracoumaric acid, synaptin, cirrhic and Ferulic acid, but hydroxyacid content is generally very low in edible plants [2-4]. The difference between these two groups relies on the patterns of hydroxylation and methoxylation of their aromatic rings. Most studies have inferred a link between health benefits of phenolic acids and the antioxidant activity of these

compounds. In fact, higher antioxidant activity of Hydroxynamic acids compared with hydroxybenzoic acids in hydroxy cinnamic acid derivatives is due to presence of a propenoic side chain rather than a carboxyl group [5].

According to the main eating habits of Mediterranean people, in the major food which consists of a large amount of plant materials (vegetables, fruits, bread, and cereals) with a small to moderate amount of red meat, fish, and beverages, daily intake of Ferulic acid is about 150-250 (16-24 mmol/kg/body weight). Of course, this rate varies greatly among people based on their eating habits and the rate of vegetable and fruit intake. Ferulic acid in fruits and vegetables often appears in the form of ester compounds with mono, di, and polysaccharides, polyamines, lignin and hydroxy fatty acids sobrin, and cotin [6]. The amount of Ferulic acid available in some grains and fruits is given in Table 1.

Table 1. Ferulic acid content in fruits and grains

Fruits and grains	Ferulic acid content, mg\kg (in liquid mg/dm3)
Black currant	15
Black berry	10
Spinach	110
Tomatoes	700
Cucurbit	220
Wheat flour	150
Wheat bran	700
Oatmeal	145

1.2. Properties of Ferulic acid (FA)

Ferulic acid (FA) (4-hydroxy3-methoxycinnamic acid) with chemical formula $C_{10}H_{10}O_4$ (Fig. 1), which is considered as a derivative of hydroxy-cinnamic acid, is actually a phenolic compound. FA is a dietary phytochemical formed during the metabolism of phenylalanine and tyrosine. The compounds similar to FA are cinnamic acid, p-coumaric acid, caffeic acid, chrlorgenic acid, rosmarinic acid, and curcumin. FA was first introduced by an Australian chemist, Hlasiwetz Barth. Ferula foetida is the source of 3-methoxy-4-hydroxycinnamic acid [7]. FA, found as an ester in rice bran pitch, is one of the most ubiquitous compounds and is usually yielded during rice oil production. Environmentally, using such industrial waste is important, since it is primarily contained in rice, whole grain foods, wheat, barley, oat, roasted coffee, tomatoes, vegetables and citrus fruits, banana, beet root, cabbage, spinach, and broccoli [7-9].

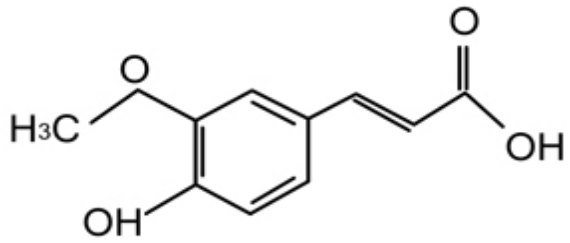
FA is one of the compounds making up the cellular walls in plant tissues. As a covalent, FA can bind with polysaccharide compounds in plants. Moreover, it can be regarded a fundamental compound in some herbal plants like Angelica sinensis, Cimicifuga heracleifolia, and Lignsticum chuangxiong [10].

This compound is also found in nutrition containing hydroxycinnamic acids, that is, the acids which are rich in fresh fruits, vegetables, and all whole grains, and it is proved that it can reduce the rate of incidence to such diseases [10]. Therefore, providing more precise and accurate information on the biological properties of diets with phenolic acids and especially FA may open a new horizon on the beneficial features of such compounds in reducing

the risk of infection to specific diseases [11]. Although the molecular structure of FA was first introduced in 1866, its chemical and industrial production was performed later in 1925 [7]. The antioxidant properties of FA were first reported by a Japanese researcher while he was extracting Ferulic from rice oil. FA has been shown to potentially exert several beneficial effects on health. FA exhibited antioxidant, anticancer, antihypertensive, skinprotective, antihyperlipidemic, antidiabetic, anticarcinogenic, antiinflammatory, hepatoprotective, and radioprotective properties and also demonstrated therapeutic potential as a hormetin for age-related diseases. It has acted as a peroxyl radical scavenger and increased the resistance of low-density lipoprotein (LDL) to oxidation and protected against some chronic diseases such as diabetes, Alzheimer's, colon and breast cancers and atherosclerosis [12].

FA may be to increase intracellular cyclic nucleotides by inhibiting phosphodiesterase. Like most phenol compounds, Ferulic is recognized by its effects (especially its antioxidant ones) on free radicals. In fact, this property is due to H2 isolation from the hydroxyl group in these phenols. Fruits and vegetables rich in such phenol compounds may reduce the risk of Cardiovascular diseases [13].

FA is a phenolic acid of low toxicity; it can be absorbed and easily metabolized in the human body. Because of these properties and its low toxicity, FA is now widely used in the food and cosmetic industries. Although during recent years, a great number of researchers have paid their own attention on FA and its direct antioxidant property, this molecule has some other amazing features as well.



Appearance: Crystalline Powder
Chemical formula: C10H10O4
Chemical name: 3-methoxy-4-hydroxycinnamic acid
Moler mass: 194.18g/mol
Melting point: 168-172°C
Solubilty: Soluble in water 0.78g/mol

Figure 1. The chemical structure of FA and its some Properties

1.3. Ferulic Absorption and Release

After digestion, free Ferulic and its constituent forms which are not affected by the acidic environment of stomach are transported directly to the intestine. In the colon and under the activity of microbial enzymes, Cinnamoyl esterase, xylanase, and Ferulic esterase are separated from their main constituents, and most of them (90%) are absorbed by inactive diffusion. On the other hand, a very small amount is actively absorbed by oxidative transporters [7]. After digestion, FA is rapidly absorbed to reach its highest plasma concentration in 30 minutes. Interestingly, the compound of Ferulic mono- and disaccharide can reduce the final plasma concentration, and meantime, reach the highest plasma concentration and increases the half-life of free Ferulic acid application (Fig. 2).

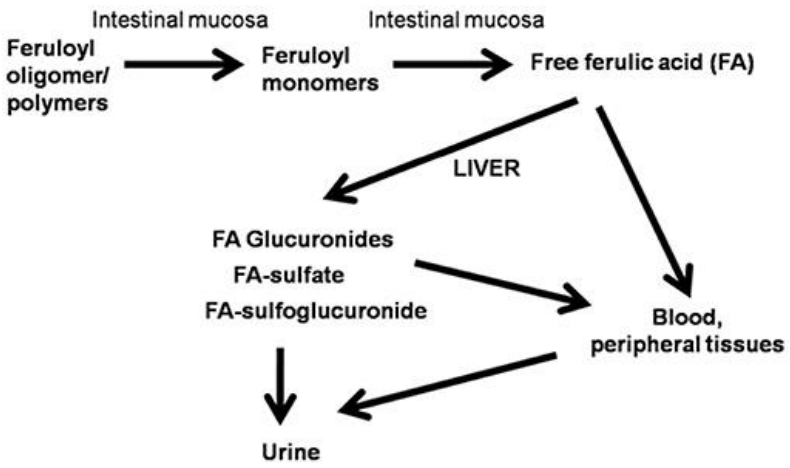


Figure 2. Absorption and metabolism of ferulic acid [25]

1.4. Pharmacodynamics of FA

The 3-methoxy and 4-hydroxyl groups in benzene ring and the carboxylic acid group (adjacent to the carbon-carbon double bond) can either be shared to fix the phenoxyl radical mediator or provide an additional attack site for free radicals. These components are two-way structures that can equip Ferulic with an effective broom to deal with both Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) groups. In other words, evidence shows that the cellular protective property of FA can be related to reducing regulation of pathways which involve cell death, inducible nitric oxide synthase (iNOS), and upregulation of genes-proteins that increases cellular response to stress, co-oxygenase / bilirubin reductase (HO / BVR), superoxide dismutase (SOD), catalase (CAT) and a number of heat shock protein families [6] (Fig. 3).

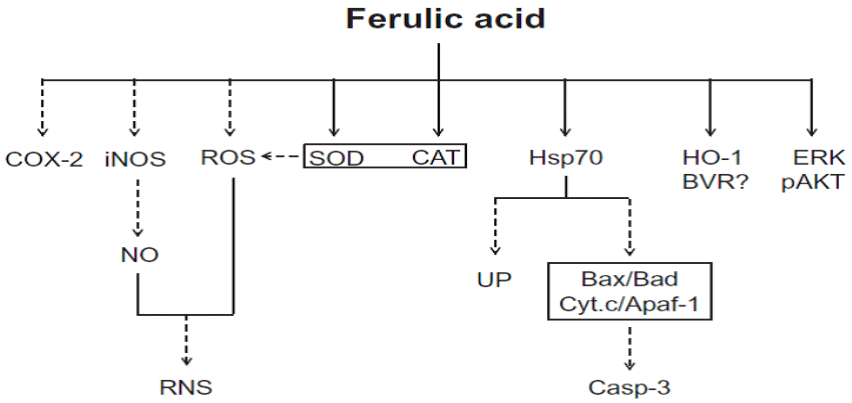


Figure 3. Some intracellular targets with pharmacological applications of ferulic acid [6]

2. Cardiovascular Diseases

Common Cardiovascular diseases are coronary heart disease, cerebrovascular disease, raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease, and heart strokes. Various factors which are involved in incidence of heart diseases are smoking, physical inactivity, malnutrition, obesity, lipid and blood pressure hypertension, and diabetes [15]. The major effective modifiable and non-modifiable risk factors in predicting

the incidence of CVD are displayed in Figure 4.

Cardiovascular diseases (CVDs) are the most pervasive non-contagious diseases which have a considerable mortality in the south east of Asia [16]. One of the most significant factors which results in CVD diseases is the imbalance between the production of free radicals and the activity of antioxidants in the body. Oxidation LDL-C causes inflammatory conditions and especially in hyperlipidemic patients; this unbalanced state between production of the free radicals and the activity of antioxidants is well observed [17].

Decreased bioavailability of nitric oxide (NO), a significant mechanism in pathogenesis, helps maintaining vascular tone and blood pressure [18]. Besides, it is commonly believed that ROS can modulate numerous pathways which monitor systemic vascular resistance and blood pressure. These include decreased bioavailability of nitric oxide (NO), inflammation, imbalance in salt and water homeostasis, hyperactivity of the sympathetic nervous system (SNS), and disturbances of the renin–angiotensin–aldosterone-system (RAAS) [19].

In this review, different possible usages of FA in treating free radical cardiovascular diseases are scrutinized.

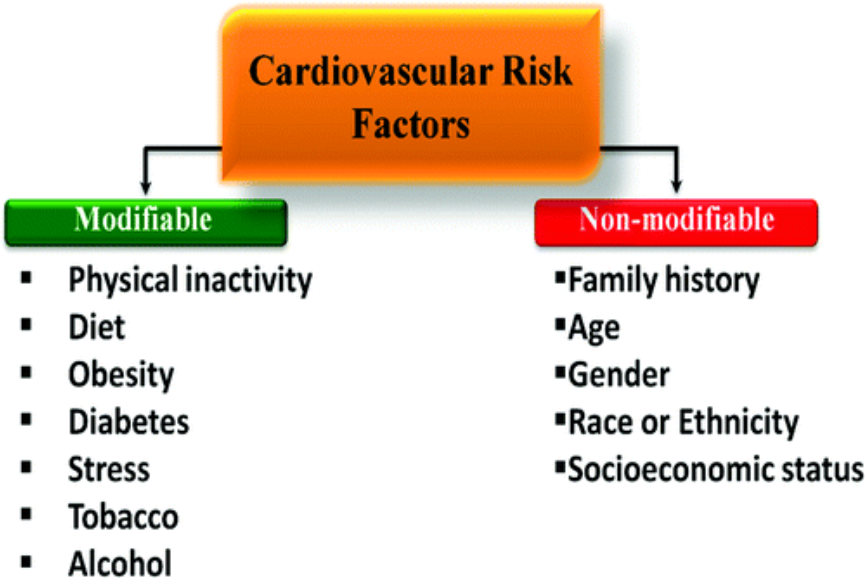


Figure 4. The major modifiable and non-modifiable risk factors in cardiovascular diseases (CVD) [31]

2.1. Oxidative Stress in Cardiovascular Diseases

It is proved that under physiological conditions, human body can make a proportion between the groups of free radicals such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and the content of the antioxidant enzymes or decomposing molecules of the free radicals.

Under physiological conditions, there is an equivalence between the amounts of generated ROS or RNS and the antioxidant enzymes or molecules which modulate these free radicals, but for some certain, yet obscure processes, this balance is at times lost mostly due to an increase in ROS/RNS production which in turn, in the levels of ROS/RNS, it becomes significant for normal cellular function. ROS/RNS accumulation and its resulting damage is at times known as oxidative stress/nitrosative stress.

When this imbalance is absent and the ratio of ROS/RNS increases in the body, this phenomenon affects the normal function of the cells. This destructive condition is known as oxidative stress. Nowadays, various factors such as UV irradiation by light, X-rays, gamma-rays, metal-catalyzed reactions of metals like Fe and hydrogen peroxide which make up hydroxyl radicals can cause inflaming effects on cells. These impacts are resulted by their effect on the mitochondrial electron transport chain in cells and other cellular organs.

In most cardiovascular diseases, an increasing rate of ROS/RNS is reported which is caused by an increase in free radicals. Moreover, the regulators which control the number of ROS/RNS have a key impact on some biological systems like defense system against infectious factors. For example, nitric oxide is a key factor in regulating neurotransmission, defense mechanisms, smooth muscle relaxation, and immune regulation [20].

Redox imbalance is also evaluated in hypertensive cases like elevated level of oxidative stress [21] in which it is an outbalanced production/accumulation of ROS [20]. In other words, similar to other pathways, ROS can decrease NO bioavailability. Due to possible relationship between hypertension and endothelial dysfunction, impairment in hypertension endothelium-dependent vasodilation can be affected by oxidative stress [23].

It is clear that blood pressure in patients with essential hypertension has a positive correlation with biomarkers of oxidative stress and in turn, has a significant negative relationship with the level of antioxidants. Oxidative stress can be measured experimentally in various ways. For example, it is indirectly evaluated noninvasively as an endothelial function in which brachial artery flow-mediated vasodilation is applied [24].

3. Antioxidant Properties of Ferulic acid

As an antioxidant, the activity of FAs in cells occurs in two ways. The first mechanism involves its inhibitory feature on the groups of ROS/RNS free radicals along with its neutralizing effect on the free radicals. The second mechanism is monitoring the production of free radicals in cells. Different studies have shown that FA can improve the performance of heart muscles through increasing the enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These effects are observed by the gene expression from MRNA in presence of two compounds including Ferulic and p-coumaric acid [25].

Using two methods including enzyme inhibiting and scavenging of the free radicals, FA can inhibit any increase in activities of the free radicals in cells. This unique property of Ferulic is due to the chemical structure of Ferulic molecule [26]. This antioxidant property of FA often is caused by scavenging the free radicals and prevention of lipid peroxidation in cells. This antioxidant mechanism of FA is introduced by analysis of the reaction of the free-radical molecules with FA (as an antioxidant). In this method, a series of complex reactions with free radicals are investigated. In presence of the free radicals, these molecules can release hydrogen groups which in turn, have important protective effects on membrane lipids against these radicals. In fact, this process is a kind of self-antioxidant reaction in cells which is commonly seen in presence of phenol compounds. Through connecting with heavy metals such as Fe and Cu, FA and its similar compounds, it can also stop production of radicals. These radicals are actually the causes of peroxidation of the cellular membrane. After joining some

proteins, FA can convert their structures, and in turn, this structural change can cause biological activities in proteins [27].

As reported in a great number of studies, FA and its derivatives cause delay in activities of oxidase and cyclooxygenase. In other words, FA reduces the content of ROS caused by deformation of catalyzing enzymes [28]. FA and its derivatives such as caffeic acid phenethyl ester (CAPE) and curcumin can play the role of a new group of HO^{-1} inducer to defend against the cellular damages caused by oxidative stress [29]. Nutrition containing FA also has some positive effects on BAP. These effects represent the antioxidant activity of FA. These findings are accompanied with a decrease in d-ROMs, MDA, and Low-density lipoprotein cholesterol (LDL-C) oxidase. A unique feature of FA is its function in activating antioxidant acids SOD, CAT, and GPx [30].

The significant ability of FA to modulate the nuclear factor erythroid 2-related factor 2 (Nrf2) can also mediate transcriptional targets such as Phase II enzymes NAD(P)H Quinone Dehydrogenase 1 (NQO1), glutathione S-transferase A2 (GSTA2) and SOD. In addition, in the LPS treated RAW 264.7 cells, depletion of Keap1 repressor and down regulation of NF-κB expression are reported [31]. Also, FA supplementation which increases cardiac Nrf2 protein expression in rats [32] can induce antioxidant enzymes such as HO^{-1}. As discussed in similar studies, FA may increase the antioxidant enzymes in terms of mRNA activity and level [33].

4. Effects of Ferulic Acid on Heart Function and its Vessels

Introduction of FA as an antihypertensive and antihyperlipidemic compound has provided a new perspective in research on the molecular and clinical aspects of FA. In a study, it was found that oral consumption of FA with dose of 1-100 mg/kg can control blood pressure in spontaneously hypertensive rats (SHR) and Spontaneously Hypertensive Stroke Prone rats (SHRSP) immediately two hours after oral administration of FA [34]. Two antihypertensive effects of FA are inhibiting ACE activity and enhancing NO production. Actually, the removal of endothelium or incubation of SHR thoracic aorta with L-NAME has a performance like NOS inhibitor which is related to ignoring the vasorelaxant effect of FA [35]. In addition, it is reported that sources rich in FA which are available in rice oil can improve the risk of factors of cardiovascular diseases (CVD) in hyperlipidemic patients [36]. FA decreases the level of HMG-CoA reductase enzymes. Like a key enzyme, it is involved in synthesis of cholesterol. In another experiment, it was reported that FA can keep and improve the endothelial function in spontaneously hypertensive rat (SHR) aorta through increasing bioavailability [37].

Ang-II, also known as an endogenous vasoconstrictor agent, stimulates VSMC proliferation and migration. Further FA treatment revealed that due to angiotensin II, VSMC proliferation could be inhibited in a dose-dependent manner. Also, it was found that FA may significantly delay Angiotensin converting enzyme (ACE), an enzyme which facilitates the conversion of Ang-I to ANG-II [23].

Some compounds like apocynine which is a natural phenolic compound can act as an inhibitor to delay the performance of NADPH oxidase enzyme. Having an apocynine- like molecular structure, FA can act as a non-selective NADPH oxidase antagonist with sulfhydryl groups [38]. More recently, it was also reported that polyphenolics extract of whole wheat grains containing FA can remove doxorubicin-induced

cardio-toxicity in rat cardiomyocytes. Moreover, FA can hinder the increasing rate in iNOS expression, the activity of NADPH oxidase, as well as Nrf-2/HO-1 impairment in doxorubicin-induced rat cardiomyocytes [39].

Atherosclerosis is another type of cardiovascular diseases which is identified by a chronic inflammatory response of vessel wall which is promoted by oxidized lipid and cholesterol transported by LDL. The transferred cholesterol and lipids are observed with LDL. These processes are observed after accumulation of macrophages and formation of a collection of foam- like cells in atherosclerotic diseases. Finally, the completed plaques which form atherosclerotic reduce the elasticity of vessels. On the other hand, the progression of these diseases leads to luminal stenosis along with thrombus formation which in turn, make the person vulnerable to cardio-cerebral and peripheral vascular diseases [1]. Moreover, experimental studies have shown that FA can reduce the triglyceride levels to -26 mg/dl and -1.77 mmol/l in rats and rabbits, respectively. Also, it lowers blood pressure in rabbits fed with high lipid diets [34, 39].

In a more precise analysis of atherosclerotic plaques, it was observed that in the rabbits treated with FA, the plaques were smaller in size than the control [39]. So far, the mechanism(s) which can monitor any decrease in lipids caused by FA have not been known, yet an increase in removal and uptake of cholesterol and accumulation of lipoproteins in liver may be one of the causes of this lipid level reduction which is mostly led by FA [34].

Likewise, as reported in another experiment, feeding rats with rice extract rich in Ferulic can improve the injuries induced by ischemic in the rats fed with Middle Cerebral Artery Occlusion (MCAO) method [40]. Nitric acid (NO) which acts as a mediator in brain has both neuroprotective and neurotoxic properties in focal cerebral ischemia model. A significant increase is observed in expression of the synthase proteins NO such as iNOS and nNOS in MCA group, whereas the increase in production rate and speed of isoforms in the rats can be limited by FA [41].

In fact, FA can protect the membrane in two ways: First, by defensing the membrane against the attacks of the free radicals, and second, by increasing blood stream in its own membrane which leaves an antioxidant impact on the membrane. However, it decreases blood pressure in stroke-prone hypertensive rats with the highest recorded rate of FA uptake (33-mmHg) [34]. It was also found that FA sodium salt can remove serum lipids, stop platelet aggregation, and prevent thrombus [339].

Based on the latest data, the angiogenesis property is caused by FA's effect on the most important involved factors in angiogenesis. These factors include vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and hypoxia-inducible factor 1 (HIF-1). Lin et al. [42] performed a study on human umbilical vein endothelial cells to represent that FA can improve VEGF and PDGF expression along with the amount of HIF-1in the induced hypoxia, so it can enhance the responses to the induced hypoxia process. According to the data and findings of in vivo and in vitro studies, FA has significant effects on formation and growth of new vessels, [43]. The effect of ferulic acid on vascular system in oxidative stress condition is shown in Figure 5.

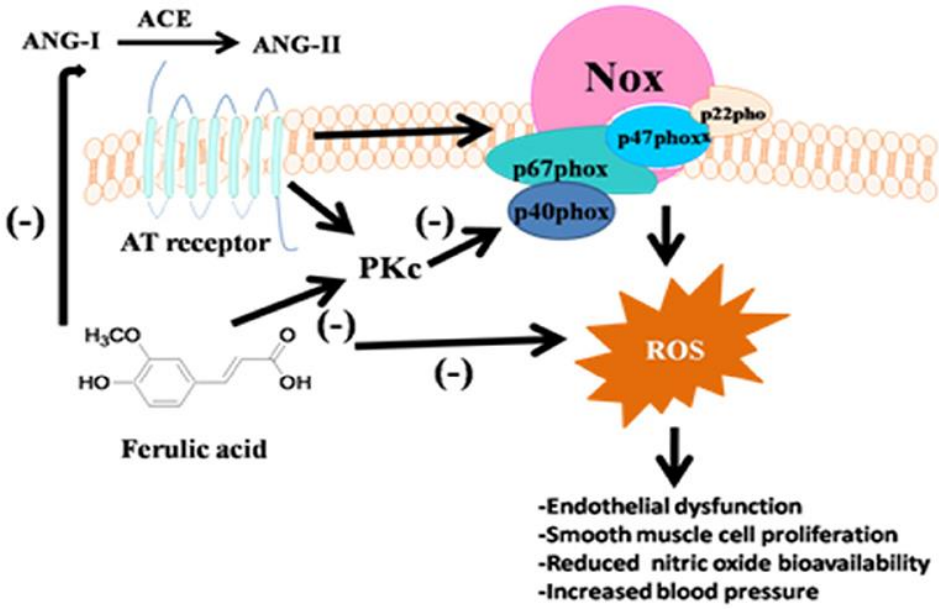


Figure 5. The effect of ferulic acid on vascular response in oxidative stress condition [23]

5. Conclusion

So far there are more than 8000 identified polyphenols identified in fruits and vegetables and FA is one of these polyphenols [4]. FA can be found in herbal antioxidant formula, vitamins, and home- grown wellbeing supplements. Moreover, it can be profitable for the body immune system. Such properties can reveal the possible assurance given by controlled ingestion of FA against various oxidative stress-oriented ailments. In this way, the recently found experimental results support the beneficial effect of FA on redox state and hypertension.

FA plays a significant role in blood pressure regulation and modulation of most commonly known physiological systems and molecular mechanisms. Interestingly yet, the way bioavailability of nitric oxide in vasculature increases by FA has remained unknown. Rare information is at hand to support direct role of FA in increasing nitric oxide from eNOS system or promoting eNOS both in protein and mRNA level. Another crucial research area which requires further research is cardiac structure and function. The results of a few studies have also showed that FA is the improving agent which plays an important role in treatment of left ventricular dysfunction and hypertrophy of heart in human and animal studies.

As discussed earlier in this review, the most beneficial effect of FA is related to its antioxidant and anti- cardiovascular activities against diseases. However, the potential use of supplemental FA in therapy of other diseases has remained to be further researched.

Abbreviation

FA: Ferulic acid
CVD: Cardiovascular diseases
LDL: low-density lipoprotein
ROS: Reactive Oxygen Species
RNS: Reactive Nitrogen Species
iNOS: inducible nitric oxide synthase
CAT: catalase
ACE: Angiotensin converting enzyme
SOD: superoxide dismutase
SNS: Sympathetic Nervous System
RAAS: Renin–Angiotensin–Aldosterone –System
NO: nitric oxide

GPx: Glutathione Peroxidase
CAPE: caffeic acid phenethyl ester
ACE: Angiotensin converting enzyme
SHR: spontaneously hypertensive rats
GSTA2: glutathione S-transferase A2
NQO1: NAD(P)H Quinone Dehydrogenase 1
VEGF: vascular endothelial growth factor
PDGF: platelet derived growth factor
HIF-1: hypoxia-inducible factor 1
MCAO: Middle Cerebral Artery Occlusion

Conflict of interest

The author declare no conflict of interest.

Consent for publications

The author writes, reads and approved the final manuscript for publication.

Availability of data and material

The author declare that embedded all data in the manuscript.

Funding

No company or organization paid for this study.

Ethics approval and consent to participate:

The author did not use any human or animal samples for this study.

References

1. Wang, S., Melnyk, J.P., Tsao, R., Marcone, M.F. 2011. Review how natural dietary antioxidants in fruits, vegetables and legumes promote vascular health. *Food Research International*, 44: 14–22.
2. Sobhanizadeh A, Solouki M, Fazeli-Nasab B. (2017). Optimization of callus induction and effects of biological and non-biological elicitors on content of phenol/flavonoid compounds in *Nigella sativa* under in-vitro conditions. *Journal of Cell & Tissue*, 8(2): 165-184. https://doi.org/10.29252/JCT.8.2.165
3. Fazeli-nasab B, Moshtaghi N, Forouzandeh M. (2019). Effect of Solvent Extraction on Phenol, Flavonoids and Antioxidant Activity of some Iranian Native Herbs. *Scientific Journal of Ilam University of Medical Sciences*, 27(3): 14-26 https:doi.org/10.29252/sjimu.27.3.14
4. Bezerra G, Pereira M, Ostrosky E, Barbosa E, Moura M, Ferrari M, Aragão C, Gomes A. 2017. Compatibility study between ferulic acid and excipients used in cosmetic formulations by TG/DTG, DSC and FTIR. *J Therm Anal Calorim*, 127:1683–1691.
5. Aguilar-Hernández I, Afseth NK, López-Luke T, Contreras-Torres F, Wold JP, Ornelas-Soto N. 2017. Surface enhanced Raman spectroscopy of phenolic antioxidants: a systematic evaluation of ferulic acid, p-coumaric acid, caffeic acid and sinapic acid. *Vib Spectrosc*, 89: 113–122.
6. Barone, E., Calabrese, V., Mancuso, C. 2009. Ferulic acid and its therapeutic potential as a hormetin for age-related diseases. *Biogerontology*, 10: 97–108
7. Poquet, L., Clifford, M.N., Williamson, G. 2008. Transport and metabolism of ferulic acid through the colonic epithelium. *Drug Metab. Dispos*, 36: 190–197
8. Graf E. (2000). Antioxidant potential of ferulic acid. *Free Rad. Biol. Med*, 13:435–448.
9. H. Rasouli, M. H. Farzaei, K. Mansouri, S. Mohammadzadeh and R. Khodarahmi, Plant Cell Cancer: May Natural Phenolic Compounds Prevent Onset and Development of Plant Cell Malignancy? A Literature Review, *Molecules*, 2016, 21, 1104.

10. M. Akbari, H. Rasouli and T. Bahdor, Physiological and pharmaceutical effect of fenugreek: a review, *IOSR J. Pharm*., 2012, 2, 49–53.
11. Jacobs D, Andersen L, Blomhoff R. (2007). Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the Iowa Women' Health Study. *Am. J. of Clin. Nutr*, 85:1606–1614.
12. Jayaprakasam B, Vanisree M, Zhang Y, Dewitt DL, Nair MG. (2006). Impact of alkyl esters of caffeic and FAs on tumor cell proliferation, cyclooxygenase enzyme, and lipid peroxidation. *J. Agric. Food Chem*. 54:5375–5381.
13. Bezerra G, Pereira M, Ostrosky E, Barbosa E, Moura M, Ferrari M, Aragão C, Gomes A 2017). Compatibility study between ferulic acid and excipients used in cosmetic formulations by TG/DTG, DSC and FTIR. *J Therm Anal Calorim,* 127:1683–1691.
14. Stewart, J.; Manmathan, G.; Wilkinson, P. (2017). Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. *JRSM Cardiovasc. Dis*. 6: 2048004016687211.
15. D.A. Wink, H.B. Hines, R.Y. Cheng, C.H. Switzer, W. Flores-Santana, M.P. Vitek, L.A. Ridnour, C.A. Colton. (2011). Nitric oxide and redox mechanisms in the immune response. *J. Leukoc. Biol*, 89:873–891.
16. Chan SH, Chan JY. (2014). Brain stem NOS and ROS in neural mechanisms of hypertension. *Antioxid Redox Signal*, 20:146–63.
17. Choi BH, Kang KS, Kwak MK. (2014). Effect of redox modulating NRF2 activators on chronic kidney disease. *Molecules*, 19:12727–59.
18. Montezano AC, Dulak-Lis M, Tsiropoulou S, Harvey A, Briones AM, Touyz RM. (2015). Oxidative stress human hypertension: vascular mechanisms, biomarkers, and novel therapies. *Can J Cardiol*, 31:631–41.
19. Virdis A, Bacca A, Colucci R, Duranti E, Fornai M, Materazzi G, et al. (2013). Endothelial dysfunction in small arteries of essential hypertensive patients: role of cyclooxygenase-2 in oxidative stress generation. *Hypertension*, 62:337–44.
20. Carrizzo A, Puca A, Damato A, Marino M, Franco E, Pompeo F, et al. (2013). Resveratrol improves vascular function in patients with hypertension and dyslipidemia by modulating NO metabolism. *Hypertension*, 62:359–66.
21. Bezerra G, Pereira M, Ostrosky E, Barbosa E, Moura M, Ferrari M, Aragão C, Gomes A. (2017). Compatibility study between ferulic acid and excipients used in cosmetic formulations by TG/DTG, DSC and FTIR. *J Therm Anal Calorim*, 127:1683–1691.
22. Nile SH, Ko EY, Kim DH, Keum YS. (2016). Screening of ferulic acid related compounds as inhibitors of xanthine oxidase and cyclooxygenase-2 with anti-inflammatory activity. *Rev Bras Farmacogn*, 26:50–55.
23. Alam MA. (2019). Anti-hypertensive Effect of Cereal Antioxidant Ferulic Acid and Its Mechanism of Action. Front. *Nutr*, 6:121. doi: 10.3389/fnut.2019.00121.
24. Bumrungpert A, Lilitchan S, Tuntipopipat S, Tirawanchai N, Komindr S. (2018). Ferulic Acid Supplementation Improves Lipid Profiles, Oxidative Stress, and Inflammatory Status in Hyperlipidemic Subjects: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients*, 2;10(6):713. doi: 10.3390/nu10060713.
25. Kwon, E.Y.; Do, G.M.; Cho, Y.Y.; Park, Y.B.; Jeon, S.M.; Choi, M.S. (2010). Anti-atherogenic property of ferulic acid in apolipoprotein E-deficient mice fed

western diet: Comparison with clofibrate. *Food Chem. Toxicol*, 48:2298–2303.
26. Lampiasi N, Montana G. (2018). An in vitro inflammation model to study the Nrf2 and NF-κB crosstalk in presence of ferulic acid as modulator. *Immunobiology*, 223(4-5): 349-55.19.
27. Yeh C-T, Ching L-C, Yen G-C. (2009). Inducing gene expression of cardiac antioxidant enzymes by dietary phenolic acids in rats. *J Nutr Biochem*, 20:163–71. doi: 10.1016/j.jnutbio.2008.01.005.
28. Riccioni G, Bucciarelli T, Mancini B et al. (2007). The role of the antioxidant vitamin supplementation in the prevention of cardiovascular diseases. *Expert Opin Investig Drugs*, 16:25–32. doi:10.1517/13543784.16.1.25.
29. Wong, N.D. (2014). Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat. Rev. Cardiol*, 11:276–289.
30. Narain, J.P.; Garg, R.; Fric, A. (2011). Non-communicable diseases in the South-East Asia region: Burden, strategies and opportunities. *Natl. Med. J. India*, 24:280–287.
31. Rajesh, Parsanathan., Sushil, K.Jain. 2020. Novel Invasive and Noninvasive Cardiac-Specific Biomarkers in Obesity and Cardiovascular Diseases. *METABOLIC SYNDROME AND RELATED DISORDERS*, 18: 10-30. DOI: 10.1089/met.2019.0073
32. Virdis A, Bacca A, Colucci R, Duranti E, Fornai M, Materazzi G, et al. (2013). Endothelial dysfunction in small arteries of essential hypertensive patients: role of cyclooxygenase-2 in oxidative stress generation. *Hypertension*, 62:337–44.
33. Manrique C, Lastra G, Gardner M, Sowers JR. (2009). The renin angiotensin aldosterone system in hypertension: roles of insulin resistance and oxidative stress. *Med Clin North Am*, 93:569–82.
34. Suzuki A, Yamamoto M, Jokura H et al. (2007). Ferulic acid restores endothelium-dependent vasodilation in aortas of spontaneously hypertensive rats. *Am J Hypertens*, 20:508– 513. doi:10.1016/j.amjhyper.2006.11.008.
35. Zavoshy, R.; Noroozi, M.; Jahanihashemi, H. (2012). Effect of low calorie diet with rice bran oil on cardiovascular risk factors in hyperlipidemic patients. *J. Res. Med. Sci*, 17: 626–631.
36. Ghosh, S.; Basak, P.; Dutta, S.; Chowdhury, S.; Sil, P.C. (2017). New insights into the ameliorative effects of ferulic acid in pathophysiological conditions. *Food Chem. Toxicol*, 103: 41–55.
37. Bhaskaragoud, G.; Rajath, S.; Mahendra, V.; Kumar, G.S.; Krishna, A.G.; Kumar, G.S. (2016). Hypolipidemic mechanism of oryzanol components-ferulic acid and phytosterols. *Biochem. Biophys. Res. Commun*, 476: 82–89.
38. Sahu R, Dua TK, Das S, De Feo V, Dewanjee S. (2019). Wheat phenolics suppress doxorubicin-induced cardiotoxicity via inhibition of oxidative stress, MAP kinase activation, NF-kappaB pathway, PI3K/Akt/mTOR impairment, and cardiac apoptosis. *Food Chem Toxicol*, 125:503–19. doi: 10.1016/j.fct.2019.01.034
39. Hassan HH, Denis M, Krimbou L et al. (2006). Cellular cholesterol homeostasis in vascular endothelial cells. *Can J Cardiol*. 22(Suppl B):35B–40B
40. Baek SE, Kim JY, Song WT, Lee SH, Hong JH, Lee CK, et al. (2014). Neuroprotective effect of rice bran extract supplemented with ferulic acid in the rat model of ischemic brain

injury. *Anim Cells Syst*, 18:93–100. doi: 10.1080/19768354.2014.904249

41. Koh PO. (2012). Ferulic acid modulates nitric oxide synthase expression in focal cerebral ischemia. *Lab Anim Res*, 28:273–8. doi: 10.5625/lar.2012.28.4.273
42. Lin C, Chiu J, Wu I, Wang B, Pan C, Chen Y. (2010). Ferulic acid augments angiogenesis via VEGF, PDGF and HIF-1 alpha. *J Nutr Biochem*, 21:627–633.
43. Yang G, Jiang J, Lu W. (2015). Ferulic acid exerts anti-angiogenic and anti-tumor activity by targeting fibroblast growth factor receptor 1-mediated angiogenesis. *Int J Mol Sci*, 16:24011–24031.

How to cite this article: Farzaneh Fazeli. Antioxidant Properties of Ferulic Acid on cardiovascular diseases. *International Journal of Advanced Biological and Biomedical Research*, 2021, 9(3), 228-240. Link: http://www.ijabbr.com/article_244269.html