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An Insight Into The Pharmacological Profile Of Hydroxy Cinnamic Acid, An Active Constituent Of Ferulic Acid

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ABSTRACT:

Ferulic acid, a hydroxyl cinnamic acid derivative, belonging to the natural phenolic compound category is known for its anti-inflammatory actions. As inflammatory diseases are one of the major causes of raised chronic diseases in the human body that can be cured with the help of ferulic acid. The functional organs of the body that are more prone to pathogens due to invasive ingestions and changing lifestyles can also be treated with the help of ferulic acid. This biological native substance is active in protective measures of various acquired diseases. The anti-inflammatory effect of ferulic acid is due to the chemical structure similarity with curcumin which inhibits reactive oxygen species (ROS), inflammatory biomarkers including cytokines, inflammasomes, TNF-α, and C-reactive protein (CRP). Also, the presence of the hydroxyl cinnamic acid group within the ring helps in the suppression of free radicals during excessive free radicals' formation. It's anti-inflammatory and activity against oxidative stress make it a helpful and potential compound for the treatment of various neuro-inflammatory diseases such as Parkinson's disease, Alzheimer's disease, etc. In recent studies, it has also been found that the anti-inflammatory properties of ferulic acid can be utilized in cancer studies, immune disorders, and aging.

Keywords: Inflammasomes, Parkinson's diseases, Immune disorders, Hydroxyl cinnamic acid

1. INTRODUCTION:

Ferulic acid (FA), a phenolic acid, is found widely in plants, particularly in the Ranunculaceae and Gramineae umbrella families, which include Angelica, Ligusticum chuanxiong, Cimicifuga, rhizoma spargani, and reed root, among others (1).

Ferulic acid is found in whole grains, spinach, parsley, grapes, rhubarb, and cereal seeds, especially wheat, oats, rye, and barley. Ferulic acid is a hydroxide cinnamic acid made up of trans-cinnamic acid with methoxy and hydroxy side chains at positions 3 and 4 on the phenyl ring (2).

The anti-inflammatory benefits of ferulic acid are linked to the degrees of peroxisome proliferator-activated receptors (PPARs), cellular adhesion molecules (CAM), and nuclear factor kappa B (NF-B), as well as the p38 mitogen-activated protein kinases (P-38 MAPK) signaling pathways. It can eliminate excessive ROS or directly remove reactive oxygen species and enzymes that create free radicals to combat oxidative damage and reduce inflammatory reactions (1, 3). Since they produce inflammatory cytokines including pro-inflammatory and inflammatory cytokines, macrophages are important participants in inflammation. Ferulic acid reduced inflammation by suppressing RAW264's production of monocyte inflammatory protein-2 (MIP-2) (4).

Ferulic acid has low toxicity and a wide range of biological effects, including anti-inflammatory, antibacterial, antitumor (including lung, breast, colon, and skin cancer), anti-arrhythmic, and antithrombotic characteristics, as well as anti-diabetic and immune-stimulant properties. It also helps to heal nerve cells and prevents nerve cell damage. Ferulic acid is a great source of antioxidants as well as a free radical producing enzyme inhibitor (5).

Ferulic acid, which serves a range of physiological functions, has a variety of effects on its count, according to studies (anti-inflammatory, antioxidant, antimicrobial activity, anticancer, and anti-diabetic effect). It's also been employed in topical and oral preparations for skin esthetic and cosmaceutical remedies (6,7).

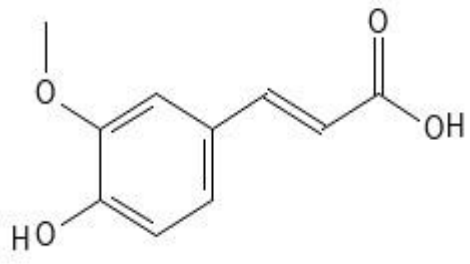

Figure 1: Chemical structure of 4-hydroxycinnamic acid

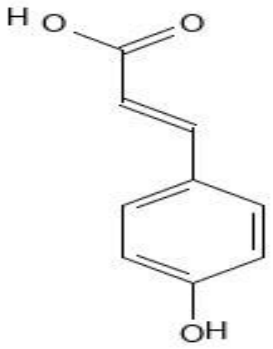

Figure 2: Chemical structure of Ferulic acid

Table 1. Amount of ferulic acid in various food ingredients (8)

Food ingredients	Ferulic acid (mg/kg)
Wheat bran	700
Tomatoes	700
Cucurbit	220
Wheat flour	150
Oatmeal	145
Spinach	110
Blackberry	10

2. METHODOLOGY

Literature search was performed using PubMed and google Scholar data bases using search key of 'Ferulic acid AND Inflammation'. The retrieved relevant articles have been included in this manuscript.

3. MECHANISM OF ACTION TO CONFRONT INFLAMMATION:

Ferulic acid, as a naturally occurring agent, possesses its anti-inflammatory action in several ways. In a study, it was found that lipopolysaccharides which are a part of integral protein-made cell membrane lead to cause inflammation. Lipopolysaccharide (LPS) binds to (LPSBP) lipopolysaccharide-binding proteins, which activates TLR-4 (toll-like receptor-4), and then leads to activation of IKK complex, here IKK is not only activated but also phosphorylate nuclear factor kappa-B (NFKB) with it. Due to the whole of which the activation of PPAR-gamma occurs, which further stimulates AP-1. On the other hand, MAPK gets initiated due to P38, JNK that finally leads to iNOS which generates an impulse to ICAM-1, and VCAM-1 (9, 10). All these factors cause the activation of inflammasomes, proinflammatory cytokines, and other inflammatory mediators to produce inflammation. This whole pathway gets hindered by ferulic acid as an inflammatory protective agent.

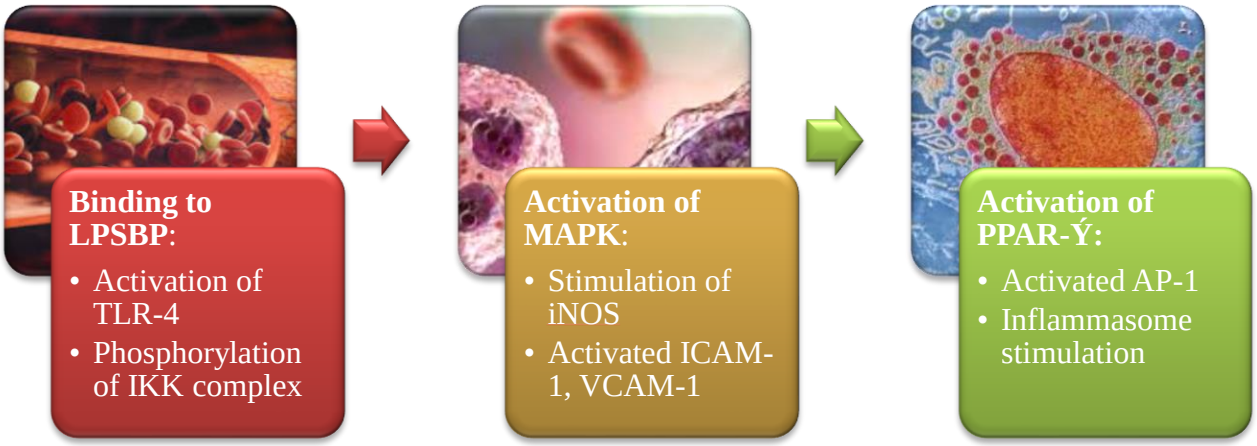

Figure 3: Anti-inflammatory mechanism of ferulic acid (11)

4. ACTIONS OF FERULIC ACID ON VARIOUS ORGANS OF THE BODY

Action on Gastrointestinal tract: In general, gastrointestinal illnesses, such as inflammatory bowel syndrome and peptic ulcers, are investigated and found to be reduced by ferulic acid at a specified dose. It has been established that a polyphenol molecule with one hydroxyl group in the aromatic ring has high antioxidant action (12).

Furthermore, the presence of electron-donating groups connected to the aromatic ring, such as $–OCH_3$ and –OH, may increase free radical scavenging capacity. FA possesses considerably more electron-donating –OH groups attached to the para or 4-position of the aromatic ring due to its higher number of canonical resonances, which contributes to its antioxidant benefits. FA at doses of 20 and 40 mg/kg significantly reduced ulcer area and index when compared to TNBS-induced control rats. The potential of FA to reduce oxidative stress, mortality, the generation of pro-inflammatory cytokines, and the downregulation of COX-2 synthesis in TNBS-induced colitis can all be linked to its anti-inflammatory properties (13, 14).

Action on Respiratory Tract: FA reduced lipopolysaccharide-induced changes in lung wet/dry ratio, protein in bronchoalveolar secretions, and partial oxygen. In addition, LPS significantly increased the release of interleukin (IL-1, IL-6), tumor necrosis factor (TNF), and IL-10 in BALF. To alleviate and resist inflammation, FA largely modulates the generation and expression of related inflammatory factors via numerous molecular mechanisms (15).

FA was found to reduce oxidative stress in the pulmonary by diminishing malondialdehyde levels, myeloperoxidase levels, and total antioxidant capacity in experimental investigations. It inactivated multiple mitogen-activated protein kinase signaling pathways in the lungs and alleviated LPS-induced ARDS through anti-inflammatory and antioxidant activities (16).

LPS is a potent inflammatory inducer that can greatly enhance inflammation, a factor in the development of acute respiratory distress syndrome (ARDS). In a rat model, the effects of ferulic acid (FA) pretreatment on the pro-inflammatory activities of lipopolysaccharide (LPS) was examined. The release of pro-

inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL-1), and interleukin (IL-6) increased significantly in bronchoalveolar lavage fluid (BALF), but FA therapy reduced the discharge of these cytokines and other chemical mediators considerably (17, 18).

Action on the Renal system: Diabetic rats had higher blood glucose, a lower urinary weight ratio, lower serum hormone levels, and considerable renal tissue loss and malfunction, according to a study. Increased intracellular ROS levels, changing mitochondrial membrane potential, and cellular redox balance disturbance revealed the role of oxidative stress in reactive hypoglycemia kidney damage. Ferulic acid administration after diabetes induction could minimize nephrotic damage, renal cell death, and inflammation (19).

Furthermore, in primary hepatocytes under nutrient-rich media, ferulic acid has been shown to improve autophagy by up-regulating the expression of autophagosomes. In Post-diabetes, oral administration of ferulic acid at a dose of 50 mg/kg for 8 weeks was found to be effective in reducing glucose and blood urea nitrogen ranges (20).

When compared to the diabetic control group of mice, ferulic acid treatment helps to reduce total renal volume and glomerular lining damage. These non-clinical data reveal that ferulic acid could protect against diabetic-induced kidney dysfunction and glomerular enlargement. While, it also helps in limiting metabolic impairment followed by inflammatory cytokines, chemokines, and adhesion molecules; which provides proof of its potential as an anti-inflammatory agent (21).

Action on the liver: The flavonoid ferulic acid, which is common in plant-based foods, protects against liver lipotoxicity via the SIRT1/autophagy pathway. Increased ferulic acid ingestion may be a useful measure to avoid and treat metabolic diseases that have lipotoxicity as a hallmark.

With an optimum dose of 100 M, FA inhibited PA-induced caspase-3 breakage, a common sign of apoptosis. Furthermore, FA pretreatment reduced PA-induced DNA constriction and nuclear fragmentation (22).

According to a few studies, ferulic acid reduced (PA) palmitate-induced cell death, restored mitochondrial membrane potential, reduced reactive oxygen species generation, and reduced inflammatory factor activation, including IL-6 and IL-1β. In hepatocytes, ferulic acid promoted autophagy, whereas autophagy inhibition hindered ferulic acid's lipotoxicity-protective action. The anti-lipotoxicity effects of ferulic acid-activated autophagy, which were triggered by SIRT1 overexpression, were mechanistically involved. Silencing SIRT1 blocked the majority of ferulic acid's beneficial effects (21, 23).

Action on the central nervous system: With concurrent administration of a hydroxamine derivative such as ferulic acid to mice, an increase in biogenic amines were detected in the corpus striatum. Ferulic acid and other hydroxycinnamic acid derivatives may represent a viable treatment for degenerative neuronal illness, according to the findings (24).

A dose of 100 mg/kg of ferulic acid was reported to lower the level of biochemical cytokines in brain cells in pre-clinical experiments in mouse models. The use of ferulic acid and other polyphenolic derivatives

was demonstrated to reduce the activation of microglial cells. Ferulic acid has been employed in the creation of neuroprotective drugs for stroke rehabilitation and cerebral ischemia because of its antioxidant capabilities (25).

Ferulic acid treatment improved memory and reduced hippocampal cell loss and oxidative stress in a daily dosage manner, as well as repressing the TLR4-mediated inflammatory pathway, according to another study. Ferulic acid's protective impact on neuronal apoptosis could be linked to the stimulation of the p38 MAPK-mediated signal cascade, which then blocked the cytochrome c-mediated caspase-3-dependent apoptotic pathway (26).

Action on the cardiovascular system: The role of elevated ROS in hypertension is self-explanatory. In a recent study, on spontaneously hypertensive rat models; ferulic acid was administered to reduce the superoxide anion production. As per the results, ferulic acid was known to decrease oxidative stress levels and also to enhance the level of NO in vascular endothelial cells of the arteries which provide hypotensive results (16).

During atherosclerosis, there is a linkage between peroxidation and the production of macrophage foam cells has been studied. In the streptozotocin model of hyperlipidemic rats, it has been evaluated that ferulic acid decreases free fatty acids, triglycerides, and cholesterol. As per further studies it has also been observed to inhibit the rate-limiting step, HMG-CoA reductase enzyme which has a huge role in lipid metabolism. Ferulic acid also suppresses low-density lipoprotein (LDL), which is known to be bad cholesterol as it takes up the cholesterol from the liver to the cells; and increases the level of high-density lipoprotein (HDL) i.e., good cholesterol which takes up the cholesterol to the liver for metabolism (27, 28). Thus, ferulic acid has a much more effective role in atherogenic conditions such as hyperlipidemia, myocardial infarction, and atherosclerosis.

Action on Integumentary system: Ferulic acid, being anti-inflammatory by its nature becomes more helpful in the protection of skin injury prevention. As per pre-clinical studies, a rodent model was studied for diabetes; it was found that ferulic acid accelerates the wound healing properties (29).

The rate of generation of chemokine cells and contraction of the wound was found to be reduced when ferulic acid ointment was applied in the treatment group of rats. A rise in the rate of formation of granulomas was also marked in wounds induced in animal models. A similar study was done by another group of researchers; Ghaisas and partners to study faster shrinkage of the wound and over epithelialization in injured cells (30).

Hence, in the nutshell, we can say that ferulic acid itself acts as a wound healer and serves as the best cell regenerator in case of injury and chronic wounds. While, aesthetic techniques allow a lot more usage of advanced processes and chemicals; there are some herbal chemicals like ferulic acid that build up a powerful profile against free radical and oxidative stress (31).

Miscellaneous: Ferulic acid has a variety of roles like improving immune cells and formation of antibodies that boost the immune system (32).

According to recent studies in dermal in-vivo and in-vitro studies which states that ferulic acid shows the foremost effects in protecting the skin from harmful UV radiations. As far as the activity of ferulic acid against microorganisms is concerned, it acts in various ways. In a research study, it has been found that ferulic acid is active against the P24 antigen which is essential for virus cascade and it inhibits the replication of virus without any toxic effects on cells (33).

Ferulic acid acts negatively on both gram-negative and gram-positive bacteria. An in-vitro study was performed via enzyme-linked immunosorbent assay (ELISA); revealed that ferulic acid suppresses murine interleukin 8 (IL-8) against influenza virus (34).

Ferulic acid is now being used to protect cancer patients from the side effects of anti-cancer medications. As a result, numerous studies have shown that ferulic acid might be administered as a supplement to cancer patients. Ferulic acid aids the generation of systemic inflammation such as TNF-α, ILs, and cytokine storms in a variety of inflammatory disorders. The degree of oxidative stress could also be lowered by regular injection of ferulic acid, as shown in numerous researches (35).

Table 2: Role of ferulic acid on various organ systems

S. No.	System	Roles	References
1.	CNS	• ↑ the creation of astrocytes • Hinders β- secretase enzyme • Triggers Nrf2/ ARE pathway • ↓ level of c-Jun N-terminal kinase • ↑ "extracellular signal-regulated kinase" 1 and 2 • Downregulate JAK/STAT pathway • Constrains MAO activity	(24), (26)
2.	CVS	• ↑ Voltage based K^+ • ↓ Ca^{2+} conc. • ↑ Diastolic tension • Triphasic inotropic retort in papillary muscles (+, - and +) • ↓ Nrf2 and NF-κB expression	(10)
3.	Hepatic	• ↓ Endothelin 1 • ↓Vascular endothelial growth factor • ↓Laminin and type IV collagen • ↓ Epidermal growth factor receptor and STAT3 • ↓ Hypertrophy of lipocytes • ↓ collagen generation • ↓ TNFα and PDGF-BB • Disables NF-κB/TLR-4 pathway	(8), (34)

S. No.	System	Roles	References
		• ↓Cytochrome P-450	
4.	Renal	• Stimulates PKC • Hinders NADPH oxidase 4	(6), (36)
5.	Skin	• Constrains the synthesis of melanin • ↓ MAPK pathway • ↓ DNA binding to AP1, NF-κB, STAT3, PERK	(7), (2)
6.	Bone	• Prevents osteoclast genesis and action	(5)
7.	Immune system	• Impedes IL-6 and TNF-α enlightens its immunosuppressive effects	(37)
8.	Miscellaneous	• Persuades micronuclei • Defeats dendritic cells • ↓ GLUT 1 • ↓ PI3K/Akt pathway • ↓ expression of FOXM1	(38)

Table 3: Pharmacological actions of ferulic acid in different disorders

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
1.	To study the hypoglycemic actions of ferulic acid in diabetes	Male Wistar rats	50 mg/kg by oral route for 8 weeks	• Ferulic Acid Inhibits Hyperglycemia-Mediated MAPK Activation • Prevents programmed cell death • Ferulic Acid Inhibits IκBα degradation • Reduced Renal Cytokines, Chemokine, and	(12)

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
				Adhesion Molecules	
2.	To evaluate the Protective effect of ferulic acid in lipotoxicity induced autophagy in hepatocytes	Swiss albino mice	25, 50 and 100 µM	• Reduced hepatocyte cell death induced by palmitic acid • Improved lipotoxicity-induced mitochondrial dysfunction in hepatocytes • Heals proinflammatory cytokine activation in hepatocytes	(39)
3.	To study the effects of ferulic acid on CNS enzymes	Male Swiss albino mice	50 and 100 mg/kg i.p administration	• Inhibition of monoamine oxidase A/B • Inhibition of acetylcholine • Inhibition of tyrosinase	(1),(26)
4.	To study the inhibitory actions of ferulic acid in Ulcerative colitis	Sprague Dawley rats	10, 20 and 40 mg/kg Oral route for 14days	• Decreased oxide-nitrosative stress • Less alteration in colonic inflammatory expressions • Decreased ulcer area and index	(4)

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
				• Low risk of colonic apoptosis	
5.	To analyze the effect of ferulic acid in lipopolysaccharide-induced acute respiratory distress syndrome (ARDS)	Male Wistar rats	50 mg/kg Intraperitoneal route for 30 days	• It helps in maintaining total protein in BALF, and partial oxygen level in lungs • Less secretion of IL-6, IL-8, and IL-10 in BALF • Low oxidative stress	(40)
6.	To evaluate the potential of ferulic acid against cisplatin-induced nephrotoxicity	Male Wistar Albino rats	50 mg/kg Oral route for 5 days	• Increase in Myeloperoxidase (MPO) levels • Ferulic acid significantly reduces Malondialdehyde (MDA) levels in kidney tissues of rats • Total oxidant status (TAS) level significantly higher • Ferulic acid shows a lower creatinine levels	(36)
7.	The effect of ferulic acid on experimental traumatic brain damage in rats	Wistar rats	50 mg/kg and 100 mg/kg Intraperitoneal route	• Superoxide dismutase (SOD), glutathione peroxidase	(41)

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
				(GSH-Px) enzyme activities, and malondialdehyde (MDA) levels were found to be reduced	
8.	To analyze the effects of hydroxycinnamic acid in the management of depression	Male Swiss albino mice	40 and 80 mg/kg by oral route for 15days	• Ferulic acid supplementation in restores corticosterone level • Minimize IL-1β, TNF-α levels in hippocampus • Decreased immobility time dose-dependently was noticed in the tail suspension test	(38)
9.	To study the effect of Ferulic acid against doxorubicin-induced cardiotoxicity	Wistar rats	100 mg/kg, p.o. 50 µM	Regulation of Nrf2/ARE pathway	(42)
10.	To evaluate the potential of ferulic acid against imiquimod-induced psoriasis	BALB/cByJ mice	100mg/kg, oral route for 14days	• Inhibition of infiltration and cytokine secretion of T helper cell, dendritic cell, and granulocyte subsets in	(43)

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
				psoriatic skin tissues.	
11.	To study ferulic acid activity against placental inflammation with preeclampsia	Female nulliparous Sprague-Dawley rats	100mg/kg, oral gavage for 21 days	• Ferulic acid reduces hypertension and decreased urine volume and urinary protein and preeclampsia • Placental inflammatory factors • Prevent apoptosis and rescued placental anti-inflammatory factors IL-4 and IL-10 expression induced rats preeclampsia	(44)
12.	To study the protective effects of ferulic acid against glucocorticoid-induced osteoporosis	Male albino neonatal rats	10,20 and 30mg/kg via oral route for 6 weeks	• It raises the production of messenger RNA and certain proteins like sirtuin1 (SIRT1), the density of bone, $Ca^{2+,}$ and phosphate in bones, but reduces NF-κB. • Pixel intensity and stiffness of	(12)

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
				bones also get reduced	
13.	To study the potential of ferulic acid against immune response induced via ovalbumin	BALB/c mice	25,50 and 100mg/kg by oral gavage for 14 days	• Ferulic acid suppresses airway remodeling, by reduction of mucus production • Also decreases epithelial-derived chemokines and cytokines	(45)
14.	To study in-vivo Antithrombotic activity of ferulic acid	Swiss albino mice	10 and 20 mg/kg by the intravenous route for 10days	• Doses of 2.5–40 mg/kg produce an anticoagulant effect by delaying blood coagulation • Ferulic acid activates partial thromboplastin time (APTT) and thrombin time (TT) and inhibits erythrocyte agglutination	(46)
15.	To study the activity of ferulic acid against atherosclerotic injury and improper lipid profile	ApoE mice	40 mg/kg/day via oral gavage for 12 weeks	• Ferulic acid alleviates atherosclerosis and regulates lipid levels • Ferulic acid also reduces atherosclerotic	(31)

S. No.	Objectives of study	Animal species used	Dose, Route of administration, and duration of the study	Findings	References
				injury via altering microbial organisms of the intestine and lipid metabolism via the AMPKα/SREBP1 /ACC1 pathway	

5. CONCLUSION:

Currently, ferulic acid is known for its anti-oxidant properties and activity against inflammation. A lot of chronic diseases which get severe due to inflammatory markers release can be diminished with the help of this phenolic hydroxyl-cinnamic acid-derived biologically active compound. This compound is readily available around in plants, seeds, cereals, and other natural products. A daily intake of ferulic acid can not only cure the body of various diseases but also improve the physiological functioning of the body organs. Organs that play a vital role in metabolism including the liver and kidney, are more prone to persistent diseases like cirrhosis and nephritis respectively, such conditions can be suppressed via intake of ferulic acid. The major cause of infectious diseases is ingestion of antigen that stimulates antigen-antibody reaction followed by free radical generation and apoptosis can also be recovered with the help of phenolic acid derivatives. Ferulic acid also helps in the treatment of many lifestyle disorders such as diabetes, hypertension, and hyperlipidemia. As per studies on cancer, it has been found that ferulic acid when administered in parallel to major anti-cancer drugs; decreases the chances of adverse effects that occur due to anti-cancer therapies in cancer patients. Ferulic acid, itself cures the generation of oxidative stress as well as inflammasomes suppression in the body in any chronic condition. In a recent study, it was noted that ferulic acid as an active constituent has shown a maximum of its protective effects in almost every second disease which can't be cured by synthetic drugs. Therefore, this paper summarizes the importance of this bioactive compound, ferulic acid's versatile application in improving physiological functioning and many diseased conditions.

Abbreviations: AMPK: AMP activated protein kinase, SREBP1: Sterol regulatory element binding protein, APTT: Activated partial thromboplastin time, TT: thrombin time, NF-κB: Nuclear factor kappa , TNF-α: Tumor necrosis factor alfa, IL: Interleukin, SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase, MDA: Malondialdehyde, TAS: Total oxidant status, MPO: Myeloperoxidase, BALF: Bronchoalveolar lavage fluid, ARE: Antioxidant responsive element, PI3K: Phosphatidylionositol-3-kinase, FOXM1: Forkhead box protein M1, STAT3: Signal transducer and activator of transcription, NADP: Nicotinamide adenine

dinucleotide phosphate, MAPK: Mitogen-activated protein kinase, ARDS: Acute respiratory distress syndrome, PKC: Protein kinase-C, PDGF: Platelet derived growth factor, MAO: Monoamine oxidase, PA: Palmitic acid, IκBα, ELISA: Enzyme linked immunosorbent assay, HMG-CoA, HDL: High density lipoprotein, LDL: Low density lipoprotein, NO: Nitric oxide, ROS: Reactive oxygen species, TLR: Toll like receptor, LPS: Lipopolysaccharide, FA: Ferulic acid, TNBS, COX: Cyclooxygenase, ICAM-1: Intercellular adhesion molecule-1, VCAM-1: Vascular adhesion molecule-1, AP: Adhesion protein, LPSBP, PPAR-Ý: Peroxisome proliferator-activated gamma**,** MIP: Maximum inspiratory pressure, CRP: C-reactive protein, iNOS: Inducible nitric oxide synthase

Conflict of interest

The authors declare no conflict of interest.

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