



Scan to know paper details and author's profile

An Insight into Pharmacological Profile of Hydroxy Cinnamic Acid, an Active Constituent of Ferulic Acid

Dr. Tejesvi Mishra

ABSTRACT

Ferulic acid, a hydroxyl cinnamic acid derivative, belonging to 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 human body that can be cured by the help of ferulic acid. The functional organs of body that are more prone to the pathogens due to the invasive ingestions and changing lifestyle can also be treated by 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) etc. Also, the presence hydroxyl cinnamic acid group within the ring helps in suppression of free radicals during excessive free radicals formation. Its anti-inflammatory and activity against oxidative stress makes it helpful and potential compound for the treatment in various neuro-inflammatory diseases such as Parkinson's diseases, Alzheimer's diseases, etc.

Keywords: inflammasomes, parkinson's diseases, immune disorders and hydroxyl cinnamic acid.

Classification: DDC Code: 615.1 LCC Code: RM300

Language: English



LJP Copyright ID: 392845

London Journal of Medical and Health Research

Volume 22 | Issue 6 | Compilation 1.0



© 2022. Dr. Tejesvi Mishra. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 4.0 Unported License <http://creativecommons.org/licenses/by-nc/4.0/>, permitting all noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

An Insight into Pharmacological Profile of Hydroxy Cinnamic Acid, an Active Constituent of Ferulic Acid

Dr. Tejesvi Mishra

ABSTRACT

Ferulic acid, a hydroxyl cinnamic acid derivative, belonging to 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 human body that can be cured by the help of ferulic acid. The functional organs of body that are more prone to the pathogens due to the invasive ingestions and changing lifestyle can also be treated by 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) etc. Also, the presence hydroxyl cinnamic acid group within the ring helps in suppression of free radicals during excessive free radicals formation. Its anti-inflammatory and activity against oxidative stress makes it helpful and potential compound for the treatment in various neuro-inflammatory diseases such as Parkinson's diseases, Alzheimer's diseases, etc. in recent studies, it has also found the anti-inflammatory properties of ferulic acid can be utilized in Cancer studies, Immune disorders and aging.

Keywords: inflammasomes, parkinson's diseases, immune disorders and hydroxyl cinnamic acid.

I. 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 (Choudhary et al, 2019).

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 chain at positions 3 and 4 on the phenyl ring (Zdunska et al, 2018).

The anti-inflammatory benefits of ferulic acid are linked to the degrees of PPAR, CAM, and NF-B, as well as the P-38 MAPK signalling 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. (Xu and colleagues, 2021) in addition (Rea et al, 2021) 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) (Sadar et al, 2016).

Ferulic acid has a 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 (Zhang et al, 2018).

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 (Shivraj et al, 2016) and (Li et al, 2021).

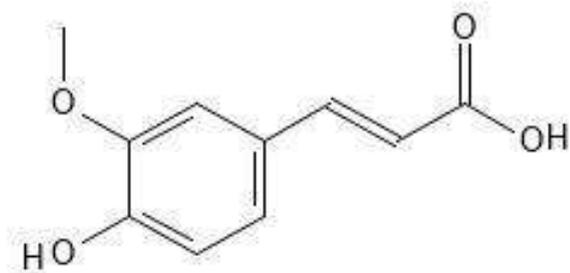


Figure 1: Chemical structure of 4-hydroxycinnamic acid

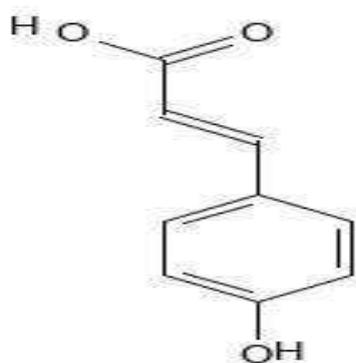


Figure 2: Chemical Structure of Ferulic Acid

Table 1: Amount of ferulic acid in various food ingredients (Aziz et al, 2012)

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

II. 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 leads 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 not only activated but also phosphorylate nuclear factor kappa-B (NFkB) with it. Due to whole of which the activation of PPAR-gamma occurs, which further stimulate AP-1. On the other hand, MAPK, get initiated due to P38, JNK that finally leads to iNOS which generate impulse to ICAM-1, and VCAM-1 (Bian et al, 2013) and (Bourne et al, 2000). All these factors cause 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.

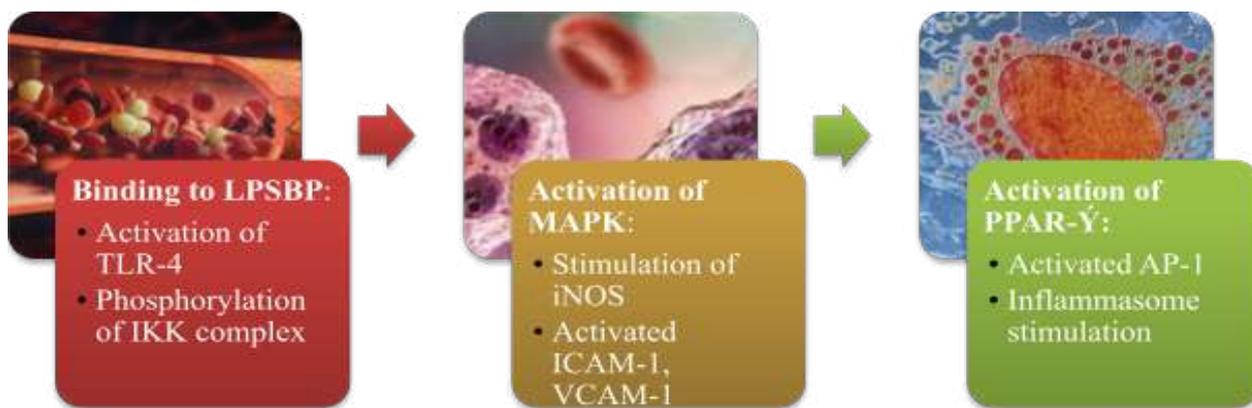


Figure 3: Anti-inflammatory mechanism of ferulic acid (Buranov and Mazza, 2009)

III. ACTIONS OF FERULIC ACID ON VARIOUS ORGANS OF BODY

Action on Gastrointestinal tract: In general, gastro-intestinal 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 (Hou et al, 2014).

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 (Kikuzaki et al, 2002) and (Ohnishi et al, 2004).

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), tumour 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 (Yagi and Ohishi, 1979).

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 signalling pathways in the lungs and alleviated LPS-induced ARDS though the anti-inflammatory and antioxidant activities (Wang et al, 2017).

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) were examined. The release of pro-inflammatory cytokines such as tumour necrosis factor (TNF-), 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 (Son and Lewis, 2002) and (Pisoschi and Pop, 2015).

Action on 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 minimise nephrotic damage, renal cell death, and inflammation (Gouveia and Castilho 2011).

Furthermore, in relation to primary hepatocytes under nutrient-rich media, ferulic acid has 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 (Taweel et al, 2012).

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 reveals that ferulic acid could protect 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 a proof of its potential as anti-inflammatory agent (Raygude, 2012).

Action on liver: The flavonoid ferulic acid, which is common in plant-based foods, protects versus liver lipotoxicity via the SIRT1/autophagy pathway. Increased ferulic acid ingestion may be a useful measure to avoid and treating metabolic diseases that have lipotoxicity as a hallmark (Enadis et al, 2003).

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 (Ogiwara et al, 2001).

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-1beta. 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 (Kandhare et al, 2014) and (Kanski et al, 2004).

Action on central nervous system: Concurrent administration of a hydroxamine derivative such as ferulic acid to mice, an increase in biogenic amines was 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 (Laffey and Talmor, 2013).

A dose of 100mg/kg 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 (Koshiguchi et al, 2017).

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 in 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 (Lin et al, 2014).

Action on 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 level and also to enhance the level of NO in vascular endothelial cells of the arteries which provides hypotensive results (Ma et al, 2011).

During atherosclerosis, there is a linkage between peroxidation and production of macrophage foam

cells has been studied. In 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 suppress low density lipoprotein (LDL), which is known to be bad cholesterol as it takes up the cholesterol from liver to the cells; and increase the level of high density lipoprotein (HDL) i.e. good cholesterol which takes up the cholesterol to liver for metabolism (Das et al, 2016) and (Panneerselvam et al, 2003).

Thus, ferulic acid has much 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 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 (Nakazato et al, 2007)

The rate of generation of chemokine cells and contraction of wound was found to be reduced when ferulic acid ointment was applied in the treatment group of rats. A raise in 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 in order to study faster shrinkage of wound and over epithelialization in injured cells (Zhu et al, 2016).

Hence, in the nut shell we can say that ferulic acid itself act as a wound healer and serves as best cells regenerator in case of injury and chronic wounds. While, aesthetic techniques allows a lot more usage of advanced processes and chemicals; there are some herbal chemicals like ferulic acid that builds up a powerful profile against free radical and oxidative stress (Balasubashini et al, 2003).

Miscellaneous: Ferulic acid has variety of roles like improving immune cells and formation of antibodies that boost up the immune system (Silversides and Ferguson, 2013).

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 activity of ferulic acid against microorganisms is concerned, it acts in various ways. In a research study, it has found that ferulic acid is active against P24 antigen which is essential for virus cascade and it inhibits the replication of virus without any toxic effects on cells (Adhikari et al, 2004).

Ferulic acid act negatively for both gram negative and gram positive bacteria. An in-vitro study was performed via enzyme linked immunosorbent assay (ELISA); revealed that ferulic acid suppress murine interleukin 8 (IL-8) against influenza virus (Thyagaraju and Muralidhara, 2008).

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-alpha, interleukins, 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. (Kumar and Pruthi, 2014).

Table 2: Role of Ferulic Acid on Various Organ Systems

S.No.	System	Roles	References
1.	CNS	<ul style="list-style-type: none"> • ↑ 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 	(Luo et al., 2010; Jia et al., 2011; Dhingra & Bansal, 2015; Yuan et al., 2017; Nakhate et al., 2018)
2.	CVS	<ul style="list-style-type: none"> • ↑ Voltage based K⁺ • ↓ Ca²⁺ conc. • ↑ Diastolic tension • Triphasic inotropic retort in papillary muscles (+, - and +) • ↓ Nrf2 and NF-κB expression 	(Itoigawa et al., 1991; Floreani et al., 1996; Courboulin et al., 2012; Wang et al., 2016)
3.	Hepatic	<ul style="list-style-type: none"> • ↓ 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 • ↓Cytochrome P-450 	(Liu et al., 2013; Chen et al., 2015; Wei et al., 2015; Sumsakul et al., 2016; Wang et al., 2016; Li et al., 2017; Lu et al., 2018; Pai et al., 2019)
4.	Renal	<ul style="list-style-type: none"> • Stimulates PKC • Hinders NADPH oxidase 4 	(Ding et al.,2005; Yong et al., 2013; Kim et al., 2017)
5.	Skin	<ul style="list-style-type: none"> • Constrains the synthesis of melanin • ↓ MAPK pathway • ↓ DNA binding to AP1, NF-κB, STAT3, PERK 	(Sand et al., 2012; Oh et al., 2017; Alem et al 2020)
6.	Bone	<ul style="list-style-type: none"> • Prevents osteoclast genesis and action 	(Wang et al., 2019)
7.	Immune system	<ul style="list-style-type: none"> • Impedes IL-6 and TNF-α enlightens its immunosuppressive effects 	(Checker et al., 2010; Bae et al., 2016)
8.	Miscellaneous	<ul style="list-style-type: none"> • Persuades micronuclei • Defeats dendritic cells • ↓ GLUT 1 • ↓ PI3K/Akt pathway • ↓ expression of FOXM1 	(Sivakumar et al., 2005; Zhang et al., 2014; Niu et al., 2015; Chen et al., 2017; Na et al., 2018; Lee et al., 2020)

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 study	Findings	References
1.	To study hypoglycemic actions of ferulic acid in diabetes	Male Wistar rats	50mg/kg by oral route for 8 weeks	<ul style="list-style-type: none"> • Ferulic Acid Inhibits Hyperglycemia-Mediated MAPK Activation • Prevents programmed cell death • Ferulic Acid Inhibits IκBα degradation • Reduced Renal Cytokines, Chemokine and Adhesion Molecules 	Choudhary et al, 2019
2.	To evaluate Protective effect of ferulic acid in lipotoxicity induced autophagy in hepatocytes	Swiss albino mice	25, 50 and 100μM	<ul style="list-style-type: none"> • Reduced hepatocyte cell death induced by palmitic acid • Improved lipotoxicity-induced mitochondrial dysfunction in hepatocytes • Heals proinflammatory cytokine activation in hepatocytes 	Tiantian et al, 2021
3.	To study effects of ferulic acid on CNS enzymes	Male swiss albino mice	50 and 100mg/kg i.p administration	<ul style="list-style-type: none"> • Inhibition of monoamine oxidas^e A/B • Inhibition of acetylcholine • Inhibition of tyrosinase 	Rea et al, 2020
4.	To study the inhibitory actions of ferulic acid in Ulcerative colitis	Sprague Dawley rats	10, 20 and 40mg/kg Oral route for 14days	<ul style="list-style-type: none"> • Decreased oxido-nitrosative stress • Less alteration in colonic inflammatory expressions • Decreased ulcer area and index • Low risk of colonic apoptosis 	Sardar et al, 2016
5.	To analyze effect of ferulic acid in lipopolysaccharide-induced acute respiratory distress syndrome (ARDS)	Male Wistar rats	50mg/kg Intraperitoneal route for 30 days	<ul style="list-style-type: none"> • It helps in maintain total protein in BALF, partial oxygen level in lungs • Less secretion of IL-6, IL-8 and IL-10 in BALF • Low oxidative stress 	Zhang et al, 2017
6.	To evaluate potential of ferulic acid against cisplatin-induced nephrotoxicity	Male Wistar Albino rats	50mg/kg Oral route for 5 days	<ul style="list-style-type: none"> • 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 	Bami et al, 2017
7.	The effect of ferulic acid on experimental traumatic brain damage in rats	Wistar rats	50mg/kg and 100mg/kg Intraperitoneal route	<ul style="list-style-type: none"> • Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) enzyme activities, malondialdehyde (MDA) level were found to be reduced 	Erbil et al, 2019
8.	To analyze effects of hydroxycinnamic acid in management of depression	Male Swiss albino mice	40 and 80 mg/kg by oral route for 15days	<ul style="list-style-type: none"> • Ferulic acid supplementation in restores corticosterone level • Minimize IL-1β, TNF-α levels in hippocampus • Decreased immobility time dose dependently was noticed in tail suspension test 	Singh et al, 2017
9.	To study effect of Ferulic acid against doxorubicin-induced cardiotoxicity	Wistar rats	100 mg/kg, p.o. 50 μM	Regulation of Nrf2/ARE pathway	Yarmohamma et al, 2020; Sahu et al, 2019

10.	To evaluate potential of ferulic acid against imiquimod-induced psoriasis	BALB/cByJ mice	100mg/kg, oral route for 14days	<ul style="list-style-type: none"> Inhibition of infiltration and cytokine secretion of T helper cell, dendritic cell, and granulocyte subsets in psoriatic skin tissues. 	Hsin-Yi et al, 2019
11.	To study ferulic acid activity against placental inflammation with preeclampsia	Female nulliparous Sprague-Dawley rats	100mg/kg, oral gavage for 21 days	<ul style="list-style-type: none"> 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 	Chen et al, 2018
12.	To study protective effects of ferulic acid against glucocorticoid-induced osteoporosis	Male albino neonatal rats	10,20 and 30mg/kg via oral route for 6 weeks	<ul style="list-style-type: none"> It raises production of messenger RNA and certain proteins like sirtuin1 (SIRT1), density of bone, Ca²⁺ and phosphate in bones, but reduces NF-κB. Pixel intensity and stiffness of bones also get reduced 	Hou et al, 2019
13.	To study potential of ferulic acid against immune response induced via ovalbumin	BALB/c mice	25,50 and 100mg/kg by oral gavage for 14 days	<ul style="list-style-type: none"> Ferulic acid suppress airway remodeling, by reduction of mucus production Also decreases epithelial-derived chemokines and cytokines 	Brugiolo et al, 2017
14.	To study <i>in-vivo</i> Antithrombotic activity of ferulic acid	Swiss albino mice	10 and 20mg/kg by intravenous route for 10days	<ul style="list-style-type: none"> Doses of 2.5–40 mg/kg produces an anticoagulant effect by delaying blood coagulation Ferulic acid activates partial thromboplastin time (APTT) and thrombin time (TT), and inhibiting erythrocyte agglutination 	Choi et al, 2017
15.	To study activity of ferulic acid against atherosclerotic injury and improper lipid profile	ApoE mice	40mg/kg/day via oral gavage for 12 weeks	<ul style="list-style-type: none"> Ferulic acid alleviate atherosclerosis and regulate lipid levels Ferulic acid also reduces atherosclerotic injury via altering microbial organisms of intestine and lipid metabolism via the AMPKα/SREBP1/ACC1 pathway 	Yuyan et al, 2021

IV. CONCLUSION

Widely present 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 by 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 from various diseases but also improve physiological functioning of the body organs. Organs that plays vital role in metabolism including liver and kidney, which are more prone to the persistent diseases like cirrhosis and nephrotitis respectively, such conditions can be suppressed via intake of ferulic acid. The major

cause of infectious diseases are ingestion of antigen that stimulates antigen antibody reaction followed by free radical generation and apoptosis can also be recovered by the help of phenolic acid derivatives. Ferulic acid also helps in 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 occurs due to anti-cancer therapies in cancer patients. Ferulic acid, itself cures the generation of oxidative stress as well as inflammosomes suppression in the body in any chronic condition.

In a recent study, it was noted that, ferulic acid as an active constituent has shown maximum of its protective effects in almost every second disease

which can't be cure by synthetic drugs. Therefore, this paper summarizes the importance of this bioactive compound, ferulic acid's versatile application in improving the physiological functioning and many diseased conditions.

Conflict of interest: Author declares no conflict of interest

Abbreviations: AMPK: AMP activated protein kinase, SREBP1: Sterol regulatory element binding protein, APTT: Activated partial thromboplastin time, TT: thrombin time, NF- κ B: 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: Phosphatidylinositol-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, I κ B α , 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- γ : Peroxisome proliferator-activated gamma, MIP: Maximum inspiratory pressure, CRP: C-reactive protein, iNOS: Inducible nitric oxide synthase.

REFERENCES

1. Chowdhury S, Ghosh S, Das AK, Sil PC. Ferulic Acid Protects Hyperglycemia-Induced Kidney Damage by Regulating Oxidative Insult, Inflammation and Autophagy. *Front Pharmacol.* 2019 Feb 5;10:27.
2. Zduńska K, Dana A, Kolodziejczak A, Rotsztejn H. Antioxidant Properties of Ferulic Acid and Its Possible Application. *Skin Pharmacol Physiol.* 2018; 31 (6):332-336.
3. Xu T, Song Q, Zhou L, Yang W, Wu X, Qian Q, Chai H, Han Q, Pan H, Dou X, Li S. Ferulic acid alleviates lipotoxicity-induced hepatocellular death through the SIRT1-regulated autophagy pathway and independently of AMPK and Akt in AML-12 hepatocytes. *Nutr Metab (Lond).* 2021 Jan 19;18(1):13.
4. Rea J, García-Giménez MD, Santiago M, De la Puerta R, Fernández-Arche MA. Hydroxycinnamic acid derivatives isolated from hempseed and their effects on central nervous system enzymes. *Int J Food Sci Nutr.* 2021 Mar;72 (2):184-194.
5. Sadar SS, Vyawahare NS, Bodhankar SL. Ferulic acid ameliorates TNBS-induced ulcerative colitis through modulation of cytokines, oxidative stress, iNOS, COX-2, and apoptosis in laboratory rats. *EXCLI Journal.* 2016 ;15:482-499.
6. Li D, Rui YX, Guo SD, Luan F, Liu R, Zeng N. Ferulic acid: A review of its pharmacology, pharmacokinetics and derivatives. *Life Sci.* 2021 Nov 1; 284:119921.
7. Aziz, M. T. A., El-Asmar, M. F., El-Ibrashy, I. N., Rezq, A. M., Al-Malki, A. L., Wassef, M. A., et al. (2012). Effect of novel water soluble curcumin derivative on experimental type-1 diabetes mellitus (short term study). *Diabetol. Metab. Syndr.* 4:30. doi: 10.1186/1758-5996-4-30.
8. Bian, Z., Furuya, N., Zheng, D.-M., Trejo, J. A. O., Tada, N., Ezaki, J., et al. (2013). Ferulic acid induces mammalian target of rapamycin inactivation in cultured mammalian cells. *Biol. Pharm. Bull.* 36, 120–124. doi: 10.1248/bpb.b12-00695.
9. Bourne, L., Paganga, G., Baxter, D., Hughes, P., and Rice-Evans, C. (2000). Absorption of ferulic acid from low-alcohol beer. *Free Radic. Res.* 32, 273–280. doi: 10.1080/1071576000300281.
10. Buranov, A. U., and Mazza, G. (2009). Extraction and purification of ferulic acid from flax shives, wheat and corn bran by alkaline hydrolysis and pressurised solvents. *Food Chem.* 115, 1542–1548. doi: 10.1016/j.foodchem.2009.01.059.

11. Hou, S., Zheng, F., Li, Y., Gao, L., and Zhang, J. (2014). The protective effect of glycyrrhizic acid on renal tubular epithelial cell injury induced by high glucose. *Int. J. Mol. Sci.* 15, 15026–15043. doi: 10.3390/ijms150915026.
12. Kikuzaki, H., Hisamoto, M., Hirose, K., Akiyama, K., and Taniguchi, H. (2002). Antioxidant properties of ferulic acid and its related compounds. *J. Agric. Food Chem.* 50, 2161–2168. doi: 10.1021/jf011348w.
13. Ohnishi, M., Matuo, T., Tsuno, T., Hosoda, A., Nomura, E., Taniguchi, H., et al. (2004). Antioxidant activity and hypoglycemic effect of ferulic acid in STZ-induced diabetic mice and KK-A^y mice. *Biofactors* 21, 315–319. doi: 10.1002/biof.552210161.
14. Yagi, K., and Ohishi, N. (1979). Action of ferulic acid and its derivatives as antioxidants. *J. Nutr. Sci. Vitaminol.* 25, 127–130. doi: 10.3177/jnsv.25.127.
15. Wang S, Suh JH, Zheng X, Wang Y, Ho CT. 2017. Identification and quantification of potential anti-inflammatory hydroxycinnamic acid amides from wolfberry. *J Agric Food Chem.* 65(2):364–372.
16. Son S, Lewis B. 2002. Free radical scavenging and antioxidative activity of caffeic acid amide and ester analogues: structure-activity relationship. *J Agric Food Chem.* 50(3):468–472.
17. Pisoschi AM, Pop A. 2015. The role of antioxidants in the chemistry of oxidative stress: a review. *Eur J Med Chem.* 97:55–74.
18. Gouveia S, Castilho PC. 2011. Antioxidant potential of *Artemisia argentea* L ' Her alcoholic extract and its relation with the phenolic composition. *Food Res Int.* 44(6): 1620–1631.
19. Al-Taweel AM, Perveen S, El-Shafae AM, Fawzy GA, Malik A, Afza N, Iqbal L, Latif M. 2012. Bioactive phenolic amides from *Celtis africana*. *Molecules.* 17(3):2675–2682. Anand P, Singh B, Singh N. 2012. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. *Bioorg Med Chem.* 20(3):1175–1180.
20. Raygude KS, Kandhare AD, Ghosh P, Ghule AE, Bodhankar SL. Evaluation of ameliorative effect of quercetin in experimental model of alcoholic neuropathy in rats. *Inflammopharmacology.* 2012b; 20:331-41.
21. Enadis N, Zhang HY, Tsimidou MZ. Structure-antioxidant activity relationship of ferulic acid derivatives: effect of carbon side chain characteristic groups. *J Agric Food Chem.* 2003;51:1874-9.
22. Ogiwara T, Satoh K, Kadoma Y, Murakami Y, Unten S, Atsumi T, et al. Radical scavenging activity and cytotoxicity of ferulic acid. *Anticancer Res.* 2001;22: 2711-7.
23. Kandhare AD, Shivakumar V, Rajmane A, Ghosh P, Bodhankar SL. Evaluation of the neuroprotective effect of chrysin via modulation of endogenous biomarkers in a rat model of spinal cord injury. *J Nat Med.* 2014;68:586-603.
24. Kanski J, Aksenova M, Stoyanova A, Butterfield DA. Ferulic acid antioxidant protection against hydroxyl and peroxy radical oxidation in synaptosomal and neuronal cell culture systems in vitro: structure-activity studies. *J Nutr Biochem.* 2002;13:273-81.
25. Laffey JG and Talmor D (2013) Predicting the development of acute respiratory distress syndrome: Searching for the “Troponin of ARDS.” *American Journal of Respiratory and Critical Care Medicine* 187: 671–672.
26. Koshiguchi M, Komazaki H, Hirai S, et al. (2017) Ferulic acid suppresses expression of tryptophan metabolic key enzyme indoleamine 2, 3-dioxygenase via NFκB and p38 MAPK in lipopolysaccharide stimulated microglial cells. *Bioscience, Biotechnology and Biochemistry* 81: 966–971.
27. Lin WC, Peng YF and Hou CW (2015) Ferulic acid protects PC12 neurons against hypoxia by inhibiting the p-MAPKs and COX-2 pathways. *Iranian Journal of Basic Medical Sciences* 18: 478–484.
28. Ma ZC, Hong Q, Wang YG, et al. (2011) Ferulic acid protects lymphocytes from radiation-predisposed oxidative stress through extracellular regulated kinase. *International Journal of Radiation Biology* 87: 130–140.
29. Das U, Biswas S, Sengupta A, et al. (2016) Ferulic acid (FA) abrogates ionizing radiation-induced oxidative damage in murine

- spleen. *International Journal of Radiation Biology* 92: 806–818.
30. Panneerselvam L, Subbiah K, Arumugam A, et al. (2013) Ferulic acid modulates fluoride-induced oxidative hepatotoxicity in male Wistar rats. *Biological Trace Element Research* 151: 85–91.
 31. Nakazato T, Sagawa M, Yamato K, et al. (2007) Myeloperoxidase is a key regulator of oxidative stress mediated apoptosis in myeloid leukemia cells. *Clinical Cancer Research* 13: 5436–5445.
 32. Zhu WW, Kong GQ, Ma MM, et al. (2016) Short communication: Camel milk ameliorates inflammatory responses and oxidative stress and downregulates mitogen-activated protein kinase signaling pathways in lipopolysaccharide-induced acute respiratory distress syndrome in rats. *Journal of Dairy Science* 99: 53–56.
 33. Balasubashini, M. S., Rukkumani, R., and Menon, V. (2003). Protective effects of ferulic acid on hyperlipidemic diabetic rats. *Acta Diabetol.* 40, 118–122. doi: 10.1007/s00592-003-0099-6.
 34. Silversides JA and Ferguson ND (2013) Clinical review: Acute respiratory distress syndrome— Clinical ventilator management and adjunct therapy. *Critical Care* 17: 225.
 35. Adhikari N, Burns KE and Meade MO (2004) Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. *Cochrane Database of System Reviews* 18: CD004477.
 36. Thyagaraju BM and Muralidhara (2008) Ferulic acid supplements abrogate oxidative impairments in liver and testis in the streptozotocin-diabetic rat. *Zoological Science* 25: 854–860.
 37. Kumar N and Pruthi V (2014) Potential applications of ferulic acid from natural sources. *Biotechnology Reports* 4: 86–93.
 38. Chowdhury Sayantani, Ghosh Sumit, Das Abhishek Kumar, Sil Parames C., Ferulic Acid Protects Hyperglycemia-Induced Kidney Damage by Regulating Oxidative Insult, Inflammation and Autophagy, *Frontiers in Pharmacology*, 2019 [10].
 39. Hou T, Zhang L, Yang X. Ferulic acid, a natural polyphenol, protects against osteoporosis by activating SIRT1 and NF- κ B in neonatal rats with glucocorticoid-induced osteoporosis. *Biomed Pharmacother.* 2019 Dec;120:109205. doi: 10.1016/j.biopha.2019.109205. Epub 2019 Oct 18. PMID: 31634777.
 40. Bami, Erliasa, Ozakpinar, Ozlem Bingol, Ozdemir-Kumral, Zarife Nigar, K'oroğlu, Kutay, Ercan, Feriha, Cirakli, Zeynep, Sekerler, Turgut, Izzettin, Fikret Vehbi, Sancar, Mesut, Okuyan, Betul, Protective Effect of Ferulic Acid on Cisplatin Induced Nephrotoxicity in Rats. *Environmental Toxicology and Pharmacology* doi.org/10.1016/j.etap.2017.06.026.
 41. Erbil G, Sacik U, Yilmaz F, Kisaoglu H, Erbayraktar Z, Pekcetin C, Ozogul C. The effect of ferulic acid on experimental traumatic brain damage in rats. *Bratisl Lek Listy.* 2019;120(5):372-379. doi: 10.4149/BLL_2019_061. PMID: 31113201.
 42. Singh T, Kaur T, Goel RK. Ferulic Acid Supplementation for Management of Depression in Epilepsy. *Neurochem Res.* 2017 Oct;42(10):2940-2948. doi: 10.1007/s11064-017-2325-6. Epub 2017 Jun 12. PMID: 28608235.
 43. Yarmohammadi F, Rezaee R, Karimi G. Natural compounds against doxorubicin-induced cardiotoxicity: A review on the involvement of Nrf2/ARE signaling pathway. *Phytother Res.* 2021 Mar;35(3):1163-1175. doi: 10.1002/ptr.6882. Epub 2020 Sep 28. PMID: 32985744.
 44. Lo HY, Li CC, Cheng HM, Liu IC, Ho TY, Hsiang CY. Ferulic acid altered IL-17A/IL-17RA interaction and protected against imiquimod-induced psoriasis-like skin injury in mice. *Food Chem Toxicol.* 2019 Jul; 129:365-375. doi: 10.1016/j.fct.2019.04.060. Epub 2019 May 3. PMID: 31054998.
 45. Yuanyuan Chen, Fengxia Xue, Cha Han, Huiyun Yang, Lulu Han, Ke Li, Jie Li, Qian Xu, Zengyan Li, Bibo Yuan, Limin Yu, Xiaoli Gao & Ye Yan (2018): Ferulic acid ameliorated placental inflammation and apoptosis in rat with preeclampsia, *Clinical and Experimental Hypertension*, DOI: 10.1080/10641963.2018.1516773.

46. Hou T, Zhang L, Yang X. Ferulic acid, a natural polyphenol, protects against osteoporosis by activating SIRT1 and NF- κ B in neonatal rats with glucocorticoid-induced osteoporosis. *Biomed Pharmacother.* 2019 Dec; 120: 109205. doi: 10.1016/j.biopha.2019.109205. Epub 2019 Oct 18. PMID: 31634777.
47. Sin Singer Brugiolo A, Carvalho Gouveia AC, de Souza Alves CC, de Castro E Silva FM, Esteves de Oliveira É, Ferreira AP. Ferulic acid suppresses Th2 immune response and prevents remodeling in ovalbumin-induced pulmonary allergy associated with inhibition of epithelial-derived cytokines. *Pulm Pharmacol Ther.* 2017 Aug;45:202-209. doi:10.1016/j.pupt.2017.07.001. Epub 2017 Jul 5. PMID: 28689020.
48. Choi JH, Park JK, Kim KM, Lee HJ, Kim S. In vitro and in vivo antithrombotic and cytotoxicity effects of ferulic acid. *J Biochem Mol Toxicol.* 2018 Jan;32(1). doi:10.1002/jbt.22004. Epub 2017 Oct 27. PMID:29077251.
49. Gu Y, Zhang Y, Li M, et al. Ferulic Acid Ameliorates Atherosclerotic Injury by Modulating Gut Microbiota and Lipid Metabolism. *Front Pharmacol.* 2021;12:621339. Published 2021 Mar 25. doi:10.3389/fphar.2021.621339.