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A Review On Ferulic Acid and Its Pharmacological Activities

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ABSTRACT

Ferulic acid (FA), a common plant compound, has been of great interest in recent years because of its multifaceted pharmacological activities. In this review, the pharmacological activity of ferulic acid has been thoroughly explored, encompassing its antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, hepatoprotective, and cardioprotective, anti-diabetic, and photoprotective effects. The molecular mechanisms of these activities have been elaborately discussed, along with possible therapeutic potentials in different disease conditions. Recent developments in drug delivery systems to improve FA bioavailability and clinical trials assessing its efficacy are also discussed. Although with encouraging preclinical results, hurdles are still present in extensing these observations to clinical use, and additional research is required to maximally exploit the therapeutic potential of this strategic phytochemical.

Keywords: Ferulic acid, anti-inflammatory, antimicrobial, anticancer.

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INTRODUCTION

Ferulic acid (4-hydroxy-3-methoxycinnamic acid), a phenolic acid found to be extensively distributed throughout the walls of plant cells, has become a compound of great therapeutic interest. First found in Ferula foetida, FA is present in high concentrations in a number of grains, fruits, and vegetables such as rice, wheat, oats, pineapples, oranges, and coffee beans. Being a hydroxycinnamic acid derivative, FA has a phenolic ring and a long conjugated side chain that provides a resonance-stabilized phenoxy radical, responsible for its high free radical scavenging activity. The structural feature coupled with its abundance in nature and low toxicity has made FA an attractive candidate for a number of therapeutic uses.

The last two decades have seen FA's pharmacological activity research increasing exponentially. Aside from its firmly established antioxidant property, FA has also shown anti-inflammatory, antimicrobial, anticancer, neuroprotective, hepatoprotective, cardioprotective, antidiabetic, and photoprotective activities. These widespread biological activities result from FA's potential to interact with various signal transduction pathways such as nuclear factor kappa B (NF-ÎºB), mitogen-activated protein kinases (MAPKs), and nuclear factor erythroid 2-related factor 2 (Nrf2), among others .

This review is intended to present a detailed overview of the pharmacological attributes of FA, explaining the associated molecular mechanisms and highlighting possible therapeutic uses in diverse disease states. Recent developments in drug delivery systems for improving FA bioavailability and clinical trials assessing its efficacy are also discussed. By integrating the existing body of knowledge on FA, this review hopes to spur further research and development towards harnessing the complete therapeutic potential of this multifaceted phytochemical.(6–9)

CHEMICAL PROPERTIES AND BIOAVAILABILITY

Chemical Structure and Properties

Ferulic acid contains a phenolic core and an elongated conjugated side chain that produces a resonance-stabilized phenoxy radical. Its chemical structure makes the largest contribution to its antioxidant and free radical scavenging ability. Its carboxylic acid functionality with a pKa of 4.58 results in weak solubility in water (0.78 g/L at 25°C) but improved solubility in organic solutions and alkaline aqueous media. Its melting point varies between 168-172Â°C, and it also exhibits high stability towards different conditions of processing, including heat treatment.

Absorption, Distribution, Metabolism, and Excretion

Bioavailability of FA plays a major role in its pharmacological action. After oral consumption, FA gets absorbed in the small intestine in both passive and active modes mediated by monocarboxylic

acid transporters (MCTs). When present in its esterified form, the more common form of most foodstuffs, FA must be hydrolyzed by intestinal esterases prior to absorption. The colonic microbiota is also an important participant in FA metabolism, hydrolyzing bound FA and further metabolizing it to give rise to various compounds such as vinylphenol and vanillin derivatives.

After being absorbed, FA is subjected to extensive phase II metabolism in the liver, mainly by glucuronidation, sulfation, and methylation. The conjugation reactions increase FA's water solubility, making it easy to excrete via urine and bile. Human pharmacokinetic studies have shown that FA attains peak plasma concentration (Cmax) after 1-2 hours of oral administration and has a half-life of 0.9-5.9 hours, depending on formulation and dose.

In spite of these observations, FA's modest bioavailability (about 20-30% in Free State) is a major obstacle for its therapeutic use. This is due to a combination of factors, such as low aqueous solubility, extensive first-pass metabolism, and fast elimination. As a result, numerous drug delivery systems have been explored to improve FA bioavailability, including nanoparticle preparations, lipid-based delivery systems, and chemical derivatization, which will be addressed in later sections .(6–9)

Figure 1: Healing effect of Ferulic acid

ANTIOXIDANT PROPERTIES

REE Radical Scavenging Mechanisms

The antioxidant activity of ferulic acid is arguably its best-characterized pharmacological property, and it arises from its distinct chemical structure. FA potently quenches many reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as hydroxyl radicals, superoxide anions, peroxynitrite, and lipid peroxyl radicals. The phenolic ring of FA easily donates a hydrogen atom to free radicals and produces a relatively stable phenoxy radical stabilized by resonance. The

conjugation by the extended side chain of FA stabilizes this radical further, also attributing to its strong antioxidant activity.

In vitro experiments have proven that FA has greater antioxidant activity than other phenolic acids, such as p-coumaric acid and vanillic acid. The 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay has indicated FA to possess an € value of around 10-20 Î¼M, reflecting its strong antioxidant activity. FA also efficiently inhibits lipid peroxidation in different model systems, such as liposomes and microsomes, € values of 5-10 Î¼M.

Promotion of Cellular Antioxidant Defense Mechanisms

In addition to the direct free radical scavenging, FA maximally increases cellular antioxidant defense systems through modulating the activity and expression of diverse antioxidant enzymes. FA activates Nrf2 pathway, a master sensor of cellular antioxidant response. Under healthy conditions, Nrf2 is retained in the cytoplasm by Keap1. FA inhibits this interaction, enabling Nrf2 translocation to the nucleus, where it interacts with antioxidant response elements (AREs) in the promoter regions of target genes.

Through Nrf2 activation, FA increases the expression of many antioxidant enzymes, such as:

- Superoxide dismutase (SOD), which catalyzes the dismutation of superoxide radicals to hydrogen peroxide and oxygen
- Catalase (CAT), which decomposes hydrogen peroxide to water and oxygen
- Glutathione peroxidase (GPx), which reduces lipid hydroperoxides and hydrogen peroxide
- Heme oxygenase-1 (HO-1), which catalyzes the breakdown of heme into biliverdin, carbon monoxide, and iron
- NAD (P) Quinone oxidoreductase 1 (NQO1), which guards against quinone toxicity
- Î³-glutamylcysteine synthetase (Î³-GCS), the glutathione synthetic rate-limiting enzyme
- *In vivo* experiments using different animal models of oxidative stress, such as carbon tetrachloride-induced hepatotoxicity, streptozotocin-induced diabetes, and ischemia-reperfusion injury, has all shown FA to restore redox homeostasis by increasing antioxidant enzyme activities and glutathione levels and decreasing lipid peroxidation and protein oxidation markers.(9–15)

ANTI-INFLAMMATORY PROPERTIES

Anti-inflammatory Signaling Pathway Inhibition

Ferulic acid has strong anti-inflammatory efficacy through regulation of various signaling pathways that mediate inflammatory processes. The nuclear factor kappa B (NF-Îºb) signaling pathway, a master controller of inflammation, is a major target of FA's anti-inflammatory activity.

NF-ÎºB is normally restrained in the cytoplasm by binding with inhibitory proteins (IÎºBs). Different inflammatory inducers induce IÎºB kinase (IKK) activation, resulting in IÎºB phosphorylation and subsequent degradation, releasing NF-ÎºB for nuclear translocation and transcription activation of pro-inflammatory genes.

FA efficiently blocks several steps in this cascade, including:

1. Inhibiting IKK activation
2. Blocking IÎºB phosphorylation and degradation
3. Preventing NF-ÎºB nuclear translocation
4. Decreasing NF-ÎºB DNA binding activity

Furthermore, FA also modulates mitogen-activated protein kinase (MAPK) signaling pathways, such as p38 MAPK, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK), which are involved in inflammatory responses. Lipopolysaccharide (LPS)-activated macrophages and microglia studies have shown that FA can suppress MAPK phosphorylation, hence reducing downstream pro-inflammatory mediator production.

Modulation of Inflammatory Mediators

By inhibiting these signaling pathways, FA efficiently decreases the synthesis of several pro-inflammatory mediators, such as:

1. Cytokines: FA markedly suppresses the synthesis of tumor necrosis factor-alpha (TNF-Î±), interleukin-1 beta (IL-1Î²), IL-6, and IL-8 in different in vitro and in vivo models of inflammation [49, 50]. In LPS-stimulated RAW 264.7 macrophages, FA (50-200 Î¼M) dose-dependently inhibited TNF-Î± and IL-1Î² production by 30-70% .
2. Chemokines: FA suppresses the production of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1Î±), and regulated upon activation, normal T cell expressed and secreted (RANTES), thus inhibiting immune cell recruitment to inflammatory areas.
3. Inflammatory enzymes: FA inhibits expression and activity of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), decreasing the production of prostaglandins (notably PGEâ‚‚) and nitric oxide (NO), respectively. FA (10-50 mg/kg) decreased COX-2 expression by some 40-60% below untreated controls in carrageenan-induced paw edema models.
4. Adhesion molecules: FA suppresses the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selection on endothelial cells, thus preventing leukocyte adhesion and transmigration.

5. In vivo experiments using different animal models of inflammatory conditions, such as colitis, arthritis, and allergic airway inflammation, have repeatedly shown FA's anti-inflammatory activity. For example, in dextran sulfate sodium (DSS)-induced models of colitis, FA treatment (20-50 mg/kg) notably inhibited colon shortening, histological damage scores and pro-inflammatory cytokine levels and enhanced disease activity indices.(16–22)

ANTIMICROBIAL ACTIVITY

Antibacterial Activity

Ferulic acid is a broad-spectrum antibacterial agent against both Gram-positive and Gram-negative bacteria, though with varying effectiveness between different bacterial species. Against Gram-positive bacteria, FA has been shown to be most effective against Staphylococcus aureus, including methicillin-resistant strains (MRSA), with minimum inhibitory concentrations (MICs) of 250-1000 Î¼g/mL. FA also shows activity against other Gram-positive species such as *Bacillus subtilis*, *Listeria monocytogenes*, and certain Streptococcus species.

Against Gram-negative bacteria, FA exhibits a moderate activity against Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, and Helicobacter pylori. MIC ranges for these pathogens are usually 500-2000 Î¼g/mL, reflecting relatively lower sensitivity relative to Gram-positive species.

Antibacterial actions of FA include:

1. Interruption of bacterial cell membrane stability
2. Inhibition of critical bacterial enzymes
3. Disruption of bacterial quorum sensing mechanisms
4. Bacterial adherence to host tissue reduced
5. Inhibition of bacterial biofilm

Interestingly, FA has been found to show synergistic effects in combination with standard antibiotics, potentially providing a way to combat antibiotic resistance. For example, a combination of FA and ampicillin caused a notable reduction in MIC against MRSA relative to each drug used individually, with possible utility in combination therapy strategies.

Antifungal Activity

FA shows antifungal activity against many pathogenic fungi, such as Candida species, dermatophytes, and plant pathogens. Experiments on FA's activity against *Candida albicans* have yielded MIC values between 750-1500 Î¼g/mL. FA also shows activity against dermatophytes like *Trichophyton rubrum* and *Microsporum gypseum*, with MIC values usually between 500-1000 Î¼g/mL.

The antifungal actions of FA are:

1. Disruption of fungal cell membrane integrity
2. Inhibition of ergosterol biosynthesis
3. Production of reactive oxygen species inside fungal cells
4. Disruption of fungal cell wall formation
5. Inhibition of fungal virulence factors such as hyphal growth in *C. albicans*

Antiviral Properties

While less well researched than its antibacterial and antifungal activities, FA has also shown good antiviral activity against a range of viruses, including the influenza virus, HIV, and herpes simplex virus (HSV). Inhibition of influenza virus neuraminidase activity has been demonstrated in vitro by FA with € values of around 100-200 Î¼M, which may interfere with viral release from infected cells.

Against HIV, FA has been found to inhibit HIV integrase, a critical enzyme for viral replication, with € values of 40-150 Î¼M in cell-free assays. FA has also exhibited activity against HSV-1 and HSV-2, with mechanisms postulated to involve blocking viral attachment and entry into the host cells, and disruption of viral replication.

The comparatively low antimicrobial activity of FA as a monotherapy agent indicates the possibility of its use in combination therapies, preservatives, or as a structural template for more active antimicrobial derivatives.(23–29)

ANTICANCER PROPERTIES

Anti proliferative and Cytotoxic Effects

Ferulic acid has been found to have anti-proliferative and cytotoxic activities against several cancer cell lines, albeit with varying potency across cancers. FA's growth inhibitory activity in in vitro experiments was shown against breast, colon, prostate, liver, cervical, and pancreatic cancer cell lines, and € values were usually around 300-1000 Î¼M, indicating modest cytotoxic activity .

The mechanisms of FA's anti proliferation are:

1. Cell cycle arrest, mainly at the G0/G1 or G2/M stages
2. Induction of apoptosis by both intrinsic (mitochondrial) and extrinsic (death receptor) pathways
3. Modulation of major signaling pathways that regulate cell proliferation and survival, such as PI3K/Akt/mTOR and MAPK pathways Inhibition of telomerase activity, which may restrict cancer cell replicative capacity

4. In MCF-7 and MDA-MB-231 breast cancer cells, FA treatment has been found to suppress the expression of cyclin D1 and CDK4 and enhance the expression of p21 and p27, resulting in G1 phase arrest [95]. In addition, FA induces apoptosis in cancer cells by enhancing the Bax/Bcl-2 ratio, promoting cytochrome c release, and activating caspase-3 and caspase-9.

Anti-metastatic Effects

In addition to its anti-proliferative effects, FA also shows strong anti-metastatic activity through its inhibition of several steps in the metastatic cascade, such as:

1. Cell adhesion: FA inhibits cancer cell adhesion to components of the extracellular matrix by down regulating several adhesion molecules, including integrins.
2. Invasion and migration: FA suppresses cancer cell invasion and motility by inhibiting the expression and activity of matrix metalloproteinases (MMP-2 and MMP-9) and urokinase-type plasminogen activator (uPA) [98, 99]. In highly invasive MDA-MB-231 breast cancer cells, FA (50-200 Î¼M) inhibited cell invasion by 30-70% in Matrigel invasion assays.
3. Epithelial-mesenchymal transition (EMT): FA inhibits EMT, an important process in metastasis initiation, by regulating the expression of EMT markers such as E-cadherin, N-cadherin, and vimentin [101]. FA also inhibits important EMT transcription factors, such as Snail, Slug, and Twist.

Anti-angiogenic Activity

Angiogenesis, or the generation of new blood vessels, is an important aspect of tumor growth and metastasis. FA exhibits strong anti-angiogenic activity through various mechanisms:

1. Suppression of vascular endothelial growth factor (VEGF) expression in cancer cells
2. Inhibition of VEGF receptor signaling in endothelial cells
3. Inhibition of endothelial cell proliferation, migration, and tube formation
4. Suppression of hypoxia-inducible factor-1 (HIF-1) expression and activity
5. Modulation of matrix metalloproteinase activity in vascular remodeling

In chick chorioallantoic membrane assays, FA (50-100 Î¼g/mL) inhibited blood vessel formation by about 40-60%, supporting its anti-angiogenic activity

Chemosensitizing and Radioprotective Effects

FA exhibits chemosensitizing activity, increasing the effectiveness of standard chemotherapeutic drugs but perhaps diminishing their toxicity. For example, FA synergistically augments the cytotoxicity of doxorubicin in several cancer cell types with the ability to reduce the dose without compromising the therapeutic effect. Synergism could result from FA's capacity to regulate drug

efflux transporters such as P-glycoprotein and increase cellular oxidative stress selectively within cancer cells

Ironically, FA also demonstrates radioprotective activity in normal tissues but may increase radiosensitivity in cancer cells. The differential effect can be due to the selective antioxidant action of FA in normal cells versus the induction of pro-oxidant effects in cancer cells with dysfunctional redox homeostasis. FA pretreatment significantly attenuated oxidative stress markers and histopathological changes but enhanced survival in animal models of radiation-induced tissue injury.

In spite of these encouraging preclinical results, it must be mentioned that the anticancer activity of FA when used alone is fairly weak as compared to typical chemotherapeutic agents, hinting at the possibility of using it in conjunction with other therapies or as a chemopreventive but not as an isolated treatment against advanced cancers.(30–41)

NEUROPROTECTIVE PROPERTIES

Protection against Oxidative Stress-Induced Neuronal Damage

The brain is particularly susceptible to oxidative stress owing to its high oxygen metabolism, rich content of polyunsaturated fatty acids, and relatively incomplete antioxidant defenses. Ferulic acid's strong antioxidant activity provides remarkable neuroprotection against neuronal damage caused by oxidative stress. In numerous in vitro models involving neuronal and glial cell cultures, FA is an effective inhibitor of hydrogen peroxide, glutamate, and Î²-amyloid-induced oxidative stress and cytotoxicity.

FA's neuroprotective actions against oxidative stress involve:

1. Direct scavenging of reactive oxygen and nitrogen species
2. Augmentation of endogenous antioxidant defenses by Nrf2 activation
3. Maintenance of mitochondrial function and membrane potential
4. Antioxidant protection against lipid peroxidation in neuronal membranes
5. Regulation of cellular glutathione levels

In vivo models involving diverse neurotoxicity models, such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced parkinsonism and kainic acid-induced excitotoxicity , have illustrated FA's potential to decrease markers of oxidative damage, such as lipid peroxidation, protein carbonylation, and DNA oxidation, and maintain neuronal structure and function.

Anti-inflammatory Effects in the Central Nervous System

Neuroinflammation is a key feature in the pathogenesis of neurodegenerative diseases. FA exhibits potent anti-neuroinflammatory activity, mainly by modulating microglial and astrocyte activation.

In LPS-activated microglia, FA (10-100 Î¼M) dose-dependently suppresses pro-inflammatory mediator synthesis, such as TNF-Î±, IL-1Î², NO, and prostaglandins, and suppresses NF-ÎºB and MAPK signaling pathway activation.

Secondarily, FA decreases the activation of microglial markers such as ionized calcium-binding adapter molecule 1 (Iba-1) and CD11b and instead initiates a differentiation toward the anti-inflammatory M2 microglia phenotype. FA has also been observed to decrease in astrocytes reactive astrogliosis with decreased levels of glial fibrillary acidic protein (GFAP) and S100Î², activation markers for astrocytes.

In vivo experiments using other neuroinflammation models, such as LPS-induced neuroinflammation and experimental autoimmune encephalomyelitis (EAE) , have all proved that FA can inhibit neuroinflammatory reactions, such as microglia activation, production of pro-inflammatory cytokines, and disruption of blood-brain barrier.

Impacts on Neurotrophic Factors and Neuroplasticity

Apart from its antioxidant and anti-inflammatory activities, FA has favorable impacts on the expression of neurotrophic factors and neuroplasticity. FA increases the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), important controllers of neuronal survival, differentiation, and synaptic plasticity. The neurotrophic action is mediated by various mechanisms, such as the phosphorylation and activation of cAMP response element-binding protein (CREB), an important transcription factor that controls the expression of neurotrophins.

FA also encourages neuroplasticity by increasing long-term potentiation (LTP), a cellular process underpinning learning and memory, in hippocampal slices. FA also induces neurogenesis in the dentate gyrus and subventricular zone, which may help improve cognitive function in neurodegenerative and neuropsychiatric diseases.

Applications in Neurodegenerative Disorders

FA's varied neuroprotective mechanisms make it a valuable candidate for neurodegenerative disorders:

1. Alzheimer's disease (AD): FA prevents Î²-amyloid fibrillation and aggregation effectively, decreases tau hyperphosphorylation, blocks Î²-amyloid-mediated neurotoxicity, and diminishes AD-linked neuroinflammation. In a model of transgenic AD mice, FA treatment (30-100 mg/kg/day) drastically improved cognitive functions in Morris water maze and Y-maze experiments as well as lowering amyloid plaque load and markers of neuroinflammation.

2. Parkinson's disease (PD): FA rescues dopaminergic neurons from MPTP, 6-hydroxydopamine, and rotenone-induced neurotoxicity by antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. FA (50-100 mg/kg/day) in MPTP-treated mice maintained striatal dopamine content, saved tyrosine hydroxylase-positive neurons of the substantia nigra, and restored motor function.
3. Stroke: FA shows robust neuroprotection in ischemia-reperfusion injury models by several mechanisms, such as attenuation of oxidative stress, reduction of excitotoxicity, suppression of neuroinflammation, and maintenance of blood-brain barrier integrity [148,149]. In MCAO models, pretreatment with FA greatly decreased infarct volume, neurological deficit scores, and brain edema but enhanced functional recover.

These preclinical results indicate FA's therapeutic potential in neurodegenerative diseases, but additional clinical trials are needed to confirm its efficacy and safety in human patients.(42–51)

HEPATOPROTECTIVE PROPERTIES

Antidrug and Chemical-Induced Hepatotoxicity

Ferulic acid shows potent hepatoprotective action against several hepatotoxicants, such as drugs, chemicals, and environmental pollutants. In models of carbon tetrachloride -induced hepatotoxicity, FA pretreatment (50-100 mg/kg) caused remarkable inhibition of liver enzyme elevation (ALT, AST, ALP), decreased lipid peroxidation markers (MDA), restored the activity of antioxidant enzymes (SOD, CAT, GPx), and maintained hepatic architecture, as confirmed by histopathological examination .

In the same way, FA also efficiently guards against acetaminophen (APAP)-caused hepatotoxicity, a major cause of acute liver failure. Mechanistically, FA counteracts APAP toxicity by inhibiting CYP2E1-catalyzed conversion of APAP to its toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), increasing glutathione content for NAPQI detoxification, and reducing subsequent oxidative stress and inflammation.

FA also shows hepatoprotection against other hepatotoxins, such as ethanol, D-galactosamine, thioacetamide, and heavy metals, mainly by virtue of its antioxidant, anti-inflammatory, and anti-apoptotic activities.

Impact on Hepatic Steatosis and Non-alcoholic Fatty Liver Disease

Hepatic steatosis and non-alcoholic fatty liver disease (NAFLD) are major global health problems with few therapeutic options. FA has good effects on several models of hepatic steatosis and NAFLD by several mechanisms:

1. Modulation of lipid metabolism: FA adjusts the important enzymes and transcription factors that play significant roles in lipid metabolism in the liver, such as sterol regulatory element-binding protein-1c (SREBP-1c), fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and peroxisome proliferator-activated receptor alpha (PPARÎ±) . FA (50-100 mg/kg/day) in high-fat diet (HFD)-induced steatosis models decreased the hepatic accumulation of triglyceride and cholesterol by 30-50% and also normalized serum lipid profiles.
2. Increased insulin sensitivity: FA enhances hepatic insulin sensitivity by activating the IRS/PI3K/Akt signaling pathway, possibly blunting the evolution from simple steatosis to steatohepatitis.
3. Blunting of oxidative stress and inflammation: FA reduces oxidative stress and inflammation of NAFLD progression, such as lowering lipid peroxidation, inhibiting NF-ÎºB signaling, and down regulating pro-inflammatory cytokine expression.
4. Modulation of gut microbiota: There is emerging evidence that FA may modulate gut microbiota composition, enhancing beneficial bacteria (e.g., Lactobacillus, Bifidobacterium) and decreasing pathogenic species, which may affect the gut-liver axis in NAFLD pathogenesis.
5. In methionine-choline deficient (MCD) diet-induced non-alcoholic steatohepatitis (NASH) models, FA treatment markedly enhanced histological features such as steatosis, inflammation, and fibrosis scores, and decreased NASH activity scores by about 40-60%.

Anti-fibrotic Effects

Hepatic fibrosis, defined by the excessive deposition of extracellular matrix (ECM), is a shared pathway in chronic liver diseases. FA exhibits potent anti-fibrotic activities by various mechanisms:

1. Inhibition of HSC activation: FA inhibits HSC activation, a pivotal event in hepatic fibrogenesis, by blocking transforming growth factor-beta (TGF-Î²) signaling and down regulating alpha-smooth muscle actin (Î±-SMA) expression.
2. Modulation of ECM remodeling: FA controls the ratio between ECM synthesis and degradation by suppressing collagen production, lowering TIMPs expression, and increasing MMP activity.
3. Attenuation of oxidative stress: FA counteracts oxidative stress-mediated HSC activation and fibrogenic signaling due to its strong antioxidant action.

4. Inhibition of pro-fibrotic cytokines: FA inhibits the expression of some pro-fibrotic cytokines, such as TGF-Î², platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF).

Treatment with FA has been shown in several experimental fibrosis models, such as bile duct ligation, and thioacetamide-induced fibrosis, to significantly decrease collagen deposition (on the basis of hydroxyproline content and Sirius red staining), reduce Î±-SMA expression, and enhance liver function parameters without lessening the histopathological changes .

These results together indicate FA's therapeutic potential in many liver diseases, such as drug-induced liver injury, NAFLD/NASH, and hepatic fibrosis, though clinical trials are required to confirm these preclinical findings.(52–60)

CARDIOPROTECTIVE PROPERTIES

Effects on Lipid Metabolism and Atherosclerosis

Ferulic acid demonstrates significant beneficial effects on lipid metabolism and atherosclerosis development through multiple mechanisms:

1. Improvement of lipid profiles: FA effectively reduces total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) while increasing high-density lipoprotein cholesterol (HDL-C) in various hyperlipidemia models. In apolipoprotein E-deficient mice, FA supplementation (50-100 mg/kg/day) reduced plasma cholesterol and triglyceride levels by approximately 20-40% while increasing HDL-C by 15-25%.
2. Inhibition of cholesterol synthesis: FA suppresses 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity, the rate-limiting enzyme in cholesterol biosynthesis, potentially contributing to its cholesterol-lowering effects.
3. Enhancement of reverse cholesterol transport: FA promotes reverse cholesterol transport by up regulating ATP-binding cassette transporters A1 and G1 (ABCA1 and ABCG1) and scavenger receptor class B type I (SR-BI) expression in macrophages.
4. Attenuation of foam cell formation: FA inhibits oxidized LDL (ox-LDL) uptake by macrophages through down regulation of scavenger receptors, including CD36 and lectin-like oxidized LDL receptor-1(61)

CONCLUSION:

Ferulic acid is identified as a compound of outstanding scientific interest and therapeutic potential from multi-disciplinary research with a broad body of evidence. The studies gathered here illustrate its extraordinary diversity in biological systems with powerful antioxidant, anti-inflammatory, neuroprotective, anticancer, and metabolic regulating activities. The scientific

environment that encompasses ferulic acid identifies a molecule bridging basic biochemistry and practical medical science. Its extensively documented molecular mechanisms and biological activities place it as an ideal candidate to develop new therapeutic interventions, preventive health strategies, and alternative therapy modalities for multifactorial diseases. Although the existing body of evidence is considerable, there are still a number of research gaps to be filled. Future research will need to include large human clinical trials, newer delivery systems, synergistic uses, and long-term metabolic effects. Translating laboratory work into clinical use is the next important area of research for ferulic acid. As scientific knowledge progresses, ferulic acid is an intriguing illustration of nature's complexity a single molecule with multiple biological interactions with profound implications for human disease and health. On-going rigorous research will be critical to fully achieve its therapeutic potential and establish evidence-based applications in medical, pharmaceutical, and nutritional arenas.

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