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FERULIC ACID – A COMPREHENSIVE PHARMACOLOGY OF AN IMPORTANT BIOFLAVONOID

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ABSTRACT

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is an phenolic compound and an antioxidant found in many staple foods, such as fruits, vegetables, cereals, coffee and in plant constituent exhibiting a wide range of therapeutic effects such as anticancer, antidiabetic, cardio protective and neuroprotective, anti-inflammatory activity. The present review summarizes the most recent literature on FA including its pharmacological actions, preclinical and clinical studies, reported mechanisms of actions, pharmacokinetic profile, precautions and safety parameters and its interaction with other drugs and plasma protein. The article also deals with the latest research updates as well as avenues for further research to elucidate the positive effects of this widespread phenolic compound for a better understanding of its potential applications in health and disease. It may subsequently help in the development and design of suitable pharmaco-active compounds.

INTRODUCTION: There has been an emerging interest in the use of naturally occurring antioxidants derived from dietary components for their potential therapeutic usage in minimizing the risk of a wide range of ailments including cardiovascular disease, cancer, diabetes, neurodegenerative diseases, cataracts, age-related functional decline, endothelial dysfunction, and cellular proliferation.

Ferulic Acid is one of the most abundant phenolics arising from the metabolism of phenylalanine and tyrosine by Shikimate pathway and distributed in plants especially cereals, fruits and vegetables, with a close resemblance to cinnamic acid. FA is a natural polyphenol extracted from rice bran that is approved as a food additive in Japan. FA occurs most frequently as ester cross-links with polysaccharides in the cell wall, e.g. as arabinoglycans in grasses, pectin in spinach and sugar beet and xyloglycans in bamboo and it is difficult to facilitate its release from the polysaccharides and its subsequent purification. The molecular structure of Ferulic Acid is shown in **fig. 1**[13].

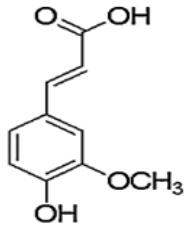

FIG. 1: MOLECULAR STRUCTURE OF FERULIC ACID

Pharmacological activity:

***In vitro*:**

Antioxidant activity: Superoxide anion radical (SAR) scavenging activity of FA (at 60 and 120 µM) was first observed in murine peritoneal macrophages with SAR induced by phorbol-12-myristate-13-acetate. In these study subsequently showed that FA upregulated the SAR scavenging activity induced by benzoyl peroxide of cultured murine peritoneal macrophages by measuring the proportion of formazan-positive cells [1].

It has been reported that FA inhibited lipid peroxidation in rat liver microsomal membranes, and the production of ROS in cultured fibroblasts [2]. Another study focused on superoxide anion scavenging activity, xanthine oxidase inhibition activity, and chain-breaking activity. The combined antioxidant activity from radical scavenging and xanthine oxidase inhibition of ferulic acid was much weaker than that of (-) epigallocatechin gallate (EGCG) and ascorbic acid. On the other hand, EGCG, ascorbic acid and ferulic acid exhibited chain-breaking activity and prevented ischaemia-reperfusion-associated intestinal injury. Chain-breaking activity may play a contributory role in the protective effect of ferulic acid on oxidative injury in humans and *in vivo* studies [3].

Anti-inflammatory Effect: It has been reported that FA on account of its antioxidant potential, can decrease the levels of inflammatory responses mediated by prostaglandin E_2 and tumor necrosis factor-alpha and iNOS expression and function in cells stimulated by the bacterial endotoxin lipopolysaccharide [4, 5]. Moreover, western blotting analysis identified the antiproliferative effects of FA in the mitogen-activated protein kinases pathway. Further examination of the cell cycle regulatory proteins showed that FA inhibited vascular smooth muscle cell (VSMC) proliferation by regulating cell progression from G(1) to S phase [6].

Anticancer Effect: A recent study had shown that Ferulic acid could inhibit ultraviolet-B (UVB) induced carcinogenesis. The human keratinocyte HaCaT cells were treated by UVB irradiation and ferulic acid. Along with these the cellular viability, secretion of IL-6 and TNF-α, apoptosis and cell cycle, formation of Cyclobutane Pyrimidine Dimers (CPDs), mRNA expression of p53, p21 and c-fos, protein expression of p53, proliferating cell nuclear antigen (PCNA), and replication protein A (RPA) were also investigated.

Ferulic acid treatment inhibited the UVB-induced cytotoxicity, apoptosis and CPDs formation. Ferulic acid also attenuated the mRNA levels of apoptosis-regulatory gene (p53- p21 and c-fos) the protein levels of p53, PCNA and RPA and the secretion of cytokines (IL-6 and TNF-α). Hence these results shows that Ferulic acid may have the potential anti-carcinogenic properties on the UVB induced epidermic tumor development by blocking therelevant cytokine secretion and expression of p53, p21, c-fos, PCNA and RPA genes [7]. Radiotherapy may be effectively combined with plant derived radiosensitizers. Ferulic acid, a naturally occurring phenolic acid, has been reported to have free radical producing properties. In this study, the radio sensitisation potential of ferulic acid has been tested in two cervical cancer cell lines (HeLa and ME-180) *in vitro*. Percentage of growth inhibition (MTT assay), colony survival, levels of lipid peroxidation (TBARS, CD and LHP), antioxidant status (SOD, CAT, GPx and GSH), oxidative DNA damage (% tail DNA, tail length, tail moment and Olive tail moment), apoptotic morphological changes (AO/EtBr staining) and intracellular ROS levels (DCFH-DA) were estimated.

The results show that ferulic acid (FA) enhances radiation effects by increasing lipid peroxidative markers in HeLa and ME-180 cells. Significant enhancement of ROS levels were observed during ferulic acid plus radiation treatment. FA treatment alone increased intracellular ROS levels indicate its prooxidant nature. Similarly, there was also observed enhanced oxidative DNA damage and apoptotic morphological changes in FA plus radiation treated cells. Hence data suggest radiation sensitizing property of FA in cervical cancer cells [8].

Neuroprotective Effects: Oxidative stress has been recognized as accountable for the pathology and neurotoxicity associated with age and many neurodegenerative diseases, especially the Alzheimer's disease (AD), wherein the free ROS and reactive nitrogen species (RNS) generated in the brain can lead to protein, DNA and RNA oxidation, lipid peroxidation and neuronal dysfunction or even death. FA is reported to be a potent scavenger of ROS and RNS, thereby reducing the chances of free radical attack on proteins and hence preventing their oxidative modification [9].

The study was aimed to evaluate the therapeutic effects of FA on hydrogen peroxide-induced oxidative stress nucleus pulposus cells (NP) and the potential for early treatment in intervertebral disc (IVD) degeneration. The results showed that 500 µM of FA might be the threshold dose to treat NP cells without cytotoxicity. Post-treatment of FA on hydrogen peroxide induced oxidative stress NP cells significantly up regulated the expression of aggrecan, type II

collagen and BMP-7 and down regulated the expression of MMP-3 in mRNA level. Post-treatment of FA on hydrogen peroxide-induced oxidative stress NP cells could restore the production of sulfated-GAGs and inhibit the apoptosis caused by hydrogen peroxide. From the results of the study, FA could be used as a therapeutic agent for NP regeneration in the very near future [10].

Effects on Angiogenesis: Angiogenesis (3rd Phase of Wound healing) involves the growth of new blood vessels from pre-existing vessels to provide sufficient nutrients and oxygen, plays an important role in embryonic development, wound healing and cardiovascular diseases such as myocardial infarction and stroke [11]. A study was done to investigate the augmenting effect of FA on angiogenesis through functional modulation of Human Umbilical Vein Endothelial Cells (HUVECs) via cell migration and tube formation studies and found that FA (10^{-6}–10^{-4}M) was able to induce significant angiogenesis in HUVECs *in vitro* without cytotoxicity.

The results showed that FA exhibits significant stimulatory effects on cellular migration and tube formation, a typical response to angiogenic stimulation [12]. FA at a range of concentrations from 0.1µg/mL to 10µg/mL could markedly improve cell proliferation and DNA synthesis in a dose-dependent manner. Flow cytometry revealed a significant decrease in the percentage of cells in the G0/G1 phase and a significant increase in the percentage of cells in the S phase. Furthermore, we found that FA enhanced cyclin D1 and VEGF mRNA expression in ECV304 cells. FA was able to promote ECV304 cells proliferation *in vitro*. This effect might be observed through the modulation of cyclin D1 and VEGF [13].

***In vivo*:**

Anti-diabetic Effect: In hyperglycaemia, auto-oxidation of glucose increases the formation of free radicals beyond the capacity of the body's defence system to neutralize it thereby causing oxidative stress, the major cause and consequence of diabetes mellitus [14]. Hence, dietary supplementation with antioxidants like FA has been suggested as a plausible means of controlling diabetic complications. The hypoglycaemic and antioxidant activity of FA in two mouse models of diabetes, streptozotocin (STZ) and spontaneously diabetic KK-Ay mice was investigated [15]. FA at 0.01% and 0.1% of basal diet showed to suppress significantly blood glucose levels in STZ-induced diabetic mice. In KK-Ay mice 0.05% FA suppressed blood glucose levels effectively. In addition, FA significantly reduced the lipid peroxidation (determined as TBARS) in brown adipose tissue of diabetic mice. These findings indicated that dietary FA may be useful in alleviating oxidative stress and attenuating the hyperglycaemic response associated with diabetes.

The anti-diabetic activity of FA was again investigated in further studies by using female Wistar rats with STZ-induced diabetes. The results showed that FA supplementation (10 and 40 mg/kg body weight; PO) for 45 days resulted in increased body weight gain (by 52% at highest dose (HD) and 61% at lowest dose (LD) and lowering of blood glucose (by 40% at HD and 60% at LD), relative to untreated diabetic rats. In the liver, TBARS, hydroperoxides and FFAs were significantly reduced at both dose levels. Activities of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione Peroxidase (GPx) and glutathione (GSH) were increased in the liver of FA-treated (LD and HD) diabetics relative to the untreated diabetic group [16].

In another study, rice derived ferulic acid was administered to diabetic mice form17 days and results showed an increase in plasma insulin level while blood sugar level decreased significantly compared to control [17]. The collective results from another study indicated that oral supplementation of FA (50 mg/kg body weight/day on alternate days) for 4 weeks can significantly mitigate diabetes-associated oxidative impairments in the testis by restoring the STZ-induced depletion of reduced glutathione (GSH) and elevated protein carbonyl content.

Furthermore, STZ induced oxidative impairments in the liver were also abrogated significantly by FA treatment [18]. A very recent study investigated the inhibitory activity of FA against rat intestinal alpha-glucosidase and porcine pancreatic alpha-amylase *in vitro*. The results showed that ferulic acid was one of the most potent inhibitors against intestinal maltase and sucrase. However, FA was found to be inactive in pancreatic alpha-amylase inhibition. This study could

provide a new insight into the use of FA as a naturally occurring intestinal alpha-glucosidase inhibitor that could be useful for treatment of diabetes and its related complications [19]. The effects of FA in obese diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats and non-diabetic control Long-Evans Tokushima Otsuka (LETO) rats were studied.

Diabetic nephropathy was assessed based on urinary protein excretion and pathological changes which were scored based on the percentages of extracellular matrix area in the glomerular area. Furthermore, renal messenger RNA (mRNA) expression of intercellular adhesion molecule-1 (ICAM-1), cyclooxygenase-2 (COX-2) and transforming growth factor-b1 (TGF-b1) was quantified by real-time polymerase chain reaction. After 12 weeks of FA supplementation, urinary protein in untreated-OLETF group was significantly higher than that in LETO group, thus FA-supplementation significantly decreased urinary protein excretion.

Pathological scores in FA-supplemented group were significantly lower than those in untreated OLETF group. Supplementation with either FA significantly prevented the elevation of TGF-b1 mRNA expression caused by diabetes. Treatment with FA had no any significant effect on COX-2 or ICAM-1 mRNA expressions. Thus, the preventative effect of FA on diabetic nephropathy was studied via suppression of TGF-b1 upregulation [20].

Hepatoprotective Effect: The protective role of ferulic acid on alcohol and PUFA-induced liver toxicity and reported that FA protected rats against alcohol and thermally-oxidised sunflower oil-induced hepato-toxicity when administered PO at 20 and 40 mg/kg body weight for 45 days. The activities of the liver marker enzymes (alkaline phosphatase, gamma glutamyl transferase, alanine transaminase, and aspartate transaminase) were decreased significantly on treatment with FA.

The results suggested that FA is an effective anti-hepatotoxic agent without side effects and may serve as a potential candidate in the current search for a natural hepatoprotective agent [21]. It has been reported that FA protects against carbon tetrachloride (CCl_4) induced toxicity in an experimental animal model, wherein, the liver marker enzymes in plasma and lipid peroxidative index in liver and kidney were decreased significantly on treatment with FA. The antioxidants (superoxide dismutase, catalase, glutathione peroxidase and reduced glutathione), which were depleted in CCl_4-treated groups, were improved significantly by FA treatment.

The result explains the antioxidant potential for the hepatoprotective activity of FA [22]. It was also evaluated that the effect of FA supplementation (20 mg/kg body weight) on D Galactosamine (GalN) provoked hepatotoxicity in male Wistar rats [23]. The toxicity produced by GalN is of clinical significance because there is a close resemblance between the multifocal necrosis produced by GalN and the lesion produced by viral hepatitis in humans.

The study reported that pre-treatment with FA significantly ameliorated the increased levels of the hepatospecific marker enzymes like Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP) and Lactate Dehydrogenase (LDH). Moreover, the FA pretreated rats exhibited a significant inhibition of Lipid Peroxidation (LPO) and augmentation of endogenous antioxidants [superoxide dismutase (SOD), catalase (CAT), Glutathione Peroxidase (GPx) and Glutathione Reductase (GR)] in the liver tissue. Pre-treatment with FA also reversed the increased levels of cholesterol, triglycerides and free fatty acids to near normal.

The overall results of the study revealed that FA could afford a significant protection in the alleviation of GalN induced hepatocellular injury [24]. Ferulic acid (FA), isolated from the root of Scrophularia buergeriana, is a phenolic compound possessing antioxidant, anticancer, and antiinflammatory activities. It has been investigated that the hepatoprotective effect of FA against carbon tetrachloride (CCl_4) induced acute liver injury.

Mice were treated intraperitoneally with vehicle or FA (20, 40, and 80 mg/kg) 1 h before and 2 h after CCl_4 (20µl/kg) injection. CCl_4-treated mice showed increased nuclear translocation of nuclear factor-kB (NF-kB), and decreased levels of inhibitors of NF-kB in cytosol. Also, CCl_4 significantly increased the level of phosphorylated JNK and p38 mitogen-activated protein (MAP) kinase, and nuclear translocation of

activated c-Jun. FA significantly attenuated these changes. It has also been found that acute CCl_4 challenge induced TLR4, TLR2, and TLR9 protein and mRNA expression, and FA significantly inhibited TLR4 expression. These results suggest that FA protects from CCl_4-induced acute liver injury [25].

Anti-cancer and Anti-apoptotic Effects: Phytochemicals present in fruits and vegetables may interfere with the processes of cancer development and carcinogenesis before invasion and metastasis occur by inhibiting carcinogen activation thereby maintaining the balance between carcinogen-activating phase I enzymes and phase II detoxifying enzymes, which exhibit a protective role against xenobiotic-mediated cellular damage [26]. It has been reported the modulatory effects of phenolic acids including FA, on an antioxidant system in male Sprague-Dawley rats at a dosage of 100 mg/kg body weight for 14 consecutive days.

The activities of hepatic superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase were found to be greater after administration of FA compared to the control group ($P<0.05$). FA (100 mg/kg) could also modify the activities of phase II detoxifying enzymes, glutathione S-transferase (GST) and quinone reductase (QR) in liver and colon, suggesting that detoxifying enzymes are related to the blocking effect of FA on AOM-induced colon carcinogenesis [27].

The chemopreventive potential of orally administered FA was studied, in 7, 12-dimethylbenz[a]anthracene (DMBA)-induced skin carcinogenesis in swiss albino mice by its ability to revert the status of phase I and phase II detoxication agents, lipid peroxidaton by products and anti-oxidants to near-normal range [28]. The chemopreventive potential of FA was studied, by monitoring the tumor incidence, as well as analyzing the status of biochemical enzymatic and non-enzymatic antioxidants and phase II detoxification enzymes and molecular (p53 and bcl-2) markers during DMBA-induced mammary carcinogenesis in Sprague-Dawley rats.

Oral administration of FA at a dose of 40 mg/kg body weight to rats treated with DMBA significantly prevented the tumor formation in 80% of animal. Although the exact mechanism is still unclear, FA's anti-genotoxic and antioxidant potential as well as modulatory effect on phase II detoxification cascade could play a possible role in this regard [29]. A study explored the anti-apoptotic and radical scavenging potential of FA against H_2O_2 induced apoptosis in normal human peripheral blood mononuclear cells (PBMCs) with an assay by phosphotidylserine externalization, nucleosomal damage and DNA fragmentation. Significant inhibition of DNA damage and lipid peroxidation was also reported in the study, which indicated the involvement of free radical scavenging by FA and/or dissociation of phenolic-translocase enzyme binding due to oxidative stress [30].

Ferulic acid ethyl ester (FAEE) and ferulic acid (FA) were fed to rats to determine *in vivo* efficacy in elevating selected phase II enzyme activities and antioxidant capacity. Male Sprague–Dawley rats were fed the control diet supplemented with 1% FA, 1% FAEE, or 0.1% FAEE for 2 weeks. Quinone reductase (QR), glutathione-S-transferase (GST), thioredoxin reductase (TxR) activities, and oxidised and reduced glutathione were determined for brain, lung, liver, kidney, intestine and colon tissues.

Both FA and FAEE (1%) supplementation increased QR and GST specific activities in kidney and colon tissues by 23–38% relative to the control diet. FAEE (1%) supplementation also induced QR specific activity, by 1.46- and 1.27-fold over the control diet, in intestinal and lung tissue of animals, whereas FA did not. No effect of diet was observed on liver cytochrome P450-1A1 activity. These results demonstrate that dietary FA and FAEE induce QR activity in the colon, small intestine, lung, and kidney, and improve glutathione antioxidant status in the colon and intestine. Therefore, dietary FA and FAEE may elevate defences to oxidative- and xenobiotic-induced stress *in vivo* [31].

Neuroprotective Effect: The long term administration of FA at a dose of 300 µM provided effective protection against centrally administered β-amyloid peptide (Abeta) induced toxicity by inhibiting microglial activation *in vivo* [32]. It has been showed that 10–50 µM of FA significantly attenuated Abeta-induced cytotoxicity, intracellular reactive oxygen species accumulation, protein oxidation, lipid peroxidation and induction of inducible nitric oxide synthase.

Moreover, the FA ethyl ester treatment exerted neuroprotective effects by upregulating protective enzymes, such as hemeoxygenase-1 and heat shock protein 72 [33]. The findings from pre-treatment with FA (5mg/kg, s.c.) once a day for 6 days may attenuate the memory deficits and increase the carbonyl protein levels induced by dl-buthionine-(S,R)-sulfoximine (BSO: 3micromol/3microL/mouse, intracerebroventricular), an inhibitor of glutathione synthesis, used as a model of brain dysfunction in mice [34]. A study clarified the ameliorative effects FA against cognitive deficits and choline acetyl transferase (ChAT) activation in trimethyltin (TMT) induced memory injured mice following a 28-days FA treatment.

The finding suggested that FA might be useful for preventing cognitive dysfunction as well as for boosting the activation of ChAT in dementia related to AD [35]. Very recently, solid lipid nanoparticles (SLNs), containing ferulic acid (FA-SNL), were developed as a novel drug delivery system (NDDS) to improve its delivery to the brain to counteract the neurodegeneration in AD. FA loaded into SLNs, was found to decrease ROS generation, restore mitochondrial membrane potential and reduce cytochrome c release and intrinsic pathway apoptosis activation [36]. The neuroprotective effects of FA (100mg/kg, i.v.) were further investigated during reperfusion after 90 min of cerebral ischemia in a transient middle cerebral artery occlusion (MCAo) model in rats.

FA administered immediately after MCAo was found to inhibit intercellular adhesion molecule-1 (ICAM-1) and macrophage-1 antigen (Mac-1) mRNA expression in the striatum at 2 h of reperfusion, and reduce the number of Mac-1, 4-hydroxy-2-nonenal (4-HNE) and 8-hydroxy-2′-deoxyguanosine (8- OHdG) positive cells in the penumbra and ischemic core regions at 10, 24 and 36 h of reperfusion.

The data suggested that FA is a promising therapeutic modality that can extend the time window in transient MCAo and hence can be a potential candidate for ischemic stroke [37]. Another very recent as well as interesting study was designed to test the hypothesis whether FA could provide *in vivo* protection against noise-induced hearing loss (NIHL) in the guinea-pigs [38]. Increased production of reactive oxygen and nitrogen species and its redox-related forms, in conjunction with an imbalance of antioxidant defences, have been demonstrated to play a significant role in noise induced hearing loss (NIHL) that is characterized by inner and outer hair cell death through either apoptosis or necrosis. FA (150 mg/kg i.p. for 4 days) counteracted NIHL at days 1, 3, 7 and 21 from noise exposure coupled with a significant reduction in oxidative stress, apoptosis and increase in hair cell viability in the organ of Corti.

The neuroprotective effect of FA was also found to be functionally related to the up regulation of the cytoprotective microsomal enzyme, heme oxygenase-1 (HO-1) that increases cellular stress response by heme catabolism. These results confirmed the antioxidant properties of FA as a free-radical scavenger and activator of HO-1 in preventing noise-induced auditory loss [39]. Traditional Chinese medicine included that Chaihu–Sugan–San (CSS) can simultaneously exert anti-depression and prokinetics.

From this data, it was aimed to find a new antidepressant with polypharmacological mechanisms. *In vivo* antidepressive and prokinetic comparisons between CSS and its absorbed compound ferulic acid (FA) were made. And FA's action mechanisms involved in monoaminergic systems, HPA axis and gastrointestinal peptide ghrelin was then studied in forced swimming test (FST) of rat. Lastly, the jejuna contraction activity evoked by FA was measured *in vitro*. Compared with vehicle, FA reduced immobility time, increased locomotor activity, accelerated gastric emptying and intestinal transit similar to CSS whose absorbable component FA was identified in hippocampus and jejunum.

FA's prokinetics *in vivo* was further supported by its jejunal contraction *in vitro*. FA-induced anti-immobility was prevented by pretreated with PCPA, WAY-100635, ketanserin, sulpiride, SCH233390, haloperidol and yohimbine, respectively. CRH, ACTH and 5-HT were significantly decreased, but ghrelin was apparently increased compared with vehicle. Thus, FA induced anti-depression and prokinetics similar to CSS via inhibiting serotonin, norepinephrine and dopamine reuptakes, regulating HPA axis, increasing ghrelin and stimulating jejunal contraction simultaneously [40].

Radio protective Effect: Ferulic acid (FA) can be used as an antioxidant to prevent damage from ultraviolet (UV) radiation and skin carcinogenesis. To this end, the feasibility of the skin absorption of FA and its derivatives was evaluated in the present study. The percutaneous absorption of five compounds into/across porcine skin was measured and compared using Franz diffusion cells. The skin delivery from pH 6 and 9.9 buffers was the highest for ferulic acid ethyl ether (FAEE), followed by coniferyl aldehyde (CD), coniferyl alcohol (CA), FA, and 3-hydroxy-4-methoxycinnamic acid (HMA). According to permeation via the skin with different treatments (delipidization, ethanol, and oleic acid treatments), it was determined that the lipid bilayers in the stratum corneum (SC) comprised the predominant barrier for FA permeation.

On the other hand, FAEE could easily partition into and penetrate across the skin through intercellular pathways. Nude mouse was used as an *in vivo* animal model to examine the amount of permeants remaining in the skin. The *in vivo* skin deposition was generally correlated with the *in vitro* results. The safety study which examined transepidermal water loss (TEWL), erythema, and the skin pH value demonstrated that the topical application of FA and related compounds for up to 24 h did not cause skin irritation. It can be concluded that topical delivery may serve as an efficient and safe route for FA and its derivatives against photo damage [41].

Miscellaneous Effect: Administration of FA (10 mg, 20 mg, and 40 mg/kg body weight) in female wistar rats positively modulated the nicotine-induced changes in the micronutrients (zinc and copper) level and increased the endogenous antioxidant defense system and protected the cells from oxidative damage. The data suggested that FA exerts its preventive effects by effectively quenching the free radicals, preventing them from attacking the membrane, protecting the membrane, inhibiting the leakage of marker enzymes into circulation, and improving the antioxidant status in circulation [42].

Another investigation for the protective role of FA (20 mg/kg body weight) via intragastric intubations for 22 weeks against nicotine-induced toxicity in female albino Wistar rats revealed a positive modulation of circulatory marker enzymes (i.e. lactate dehydrogenase and alkaline phosphatase) and tissue (lung, liver and kidney) lipid levels (i.e. cholesterol, free fatty acids, triglycerides and phospholipids) by FA.[43] A very recent study assessed the effect of FA against nicotine toxicity by comparing it with the well-known antioxidant, N-acetylcysteine (NAC).

The results indicated that FA and NAC co-treated rats showed a significant decrease in the activities of circulatory lactate dehydrogenase and alkaline phosphatase, the levels of lipid peroxidative markers (in circulation, lung and liver), DNA single stranded breaks (comet parameters), micronuclei frequency (in the whole blood) and expression of cyclooxygenase-2 and Nf-κB (in lung and liver tissues), and a significant increase in antioxidant status (in circulation, lung and liver). The protection of FA against nicotine-induced toxicity was merely equal to the effect of NAC [44].

Clinical data for FA: Cytovector™ FA, a cationic liposome encapsulating FA with elevated, intracellular penetration capacity has been launched by the BASF chemical company, US. Evidences from clinical studies in two groups of 25 subjects each with pigment spots and non-uniform complexion, have suggested that the product can visibly reduce the number and surface of skin spots and improve the overall complexion in 28 days [45]. Feru-guard (3g/day) may be effective and valuable for treating the behavioral and psychological symptoms of dementia in frontal temporal lobar degeneration and dementia with Lewy bodies [46].

Ferulic acid (FA) of Chuanxiong Rhizoma could promote gastrointestinal motor has been reported. However, its pharmacokinetic characteristics in patients with functional dyspepsia (FD) have never been investigated. This study was designed to evaluate and compare the pharmacokinetics of FA in patients with FD and healthy volunteers following oral administration of Chaihu-Shugan-San (CSS). The pharmacokinetic parameters showed that FD reduced the absorption of FA after oral administration of CSS [47].

Preclinical Pharmacokinetic properties of FA:

Absorption: *In situ* absorption models suggest a fast absorption of FA from the stomach before reaching the cecum [48]. Similarly, FA quickly disappeared from the jejunum and to a significantly lesser extent from the

ileum, when it was perfused in an isolated preparation of jejunum and ileum from the small intestine of rat. Moreover, ~20% of the FA was conjugated with glucuronide or sulfate, while transportation across the isolated small intestinal section, suggesting that FA could be metabolized in the intestinal epithelial cells [49].

Distribution: It has been estimated that approximately 4%, 10% and 53% of the orally administered FA was stored in the gastric mucosa, blood pool and liver, kidney, and/or other tissues, respectively [48]. Similarly, it also been determined that ~49% of perfused FA in rat intestine might be distributed in liver and peripheral tissues [50].

Metabolism: The metabolic fate of FA has been summarized in a number of studies, wherein it was shown that FA can be metabolized *in vivo* into a number of metabolites including FA-glucuronide, FA-sulfate, FA diglucuronide, FA-sulfoglucuronide (FA-diconjugate with sulfate and glucuronide), m-hydroxyphenylpropionic acid, feruloylglycine, dihydroferulic acid, vanillic acid and vanilloylglycine [48, 50-51]. Intra-peritoneal administration of FA to the rats leads to the excretion of 3-hydroxy phenyl propionic acid as a major urinary metabolite [52].

Elimination: Several studies reported various data on the urinary excretion of FA and FA-based metabolites. FA is eliminated mainly through the urine in rats in free as well as in conjugated forms [48-50, 53]. Additionally, about 4–6% of the oral dose of FA is also excreted through bile [48, 50].

Bioavailability: Generally, the bioavailability of free FA is very low due to its rapid conjugation process in the liver [48, 51]. Several studies have investigated the bioavailability of FA, wherein the rate of urinary excretion has been quantified from low to high bioavailability (0.4–98%), depending upon the dietary source [54-56].

Clinical pharmacokinetics properties of FA: Free FA was detected in the plasma of humans at 10 min after an oral administration of sodium ferulate, indicating that free FA is absorbed quickly in humans. Plasma concentrations of free FA reached the maximum levels at 24 min after the oral administration, with a half-time of 42 min. FA, vanillic acid and caffeic acid was identified in the b-glucuronidase and sulfatase hydrolyzed human urine after ingestion of 1 g (86 µmol/kg BW) of FA [57]. It has been detected that free FA and its glucuronic conjugate in the plasma and free FA and its glycine conjugate in the urine after ingestion of FA of wheat bran (23 lmol FA/kg BW) [58]. Several studies have suggested that the absorbability of dietary FA in humans may be similar to that in animals [7]. High levels of FA are found in both free and bound forms in vegetables, fruits, cereals, and coffee. We have estimated that consumption of these foods may result in approximately 150–250 mg/day of FA intake [59].

Precautions and safety: The safety study of Ferulic acid was done which examined transepidermal water loss (TEWL), erythema, and the skin pH value demonstrated that the topical application of FA and related compounds for up to 24 h did not cause skin irritation. It can be concluded that topical delivery may serve as an efficient and safe route for FA and its derivatives against photo damage [60]. A very recent study was reported to examine the genotoxic and clastogenic potential of three phenolic compounds: caffeic, cinnamic and ferulic acids, using the comet and micronucleus assays *in vitro*.

Drug-metabolizing rat hepatoma tissue cells (HTCs) were used. Three different concentrations (50, 500 and 1500 µM) of these phenolic acids were tested on the HTCs for 24 h. The caffeic, cinnamic and ferulic acids were not genotoxic by the comet assay ($P > 0.05$). However, the micronucleus test showed an increase in the frequency of micronucleated cells for the three compounds, indicating that these substances have clastogenic effects in HTC [61].

Food and Drug interactions: Dietary polyphenols have been widely assumed to be beneficial to human health. Polyphenols are commercially prepared and used as functional foods. We report here for the first time that ferulic acid, which is widely used as a functional food, affects the transport of clinical agents. It is important to be aware of the potential of food−drug interactions and to act in order to prevent undesirable and harmful clinical consequences. Food−Drug Interaction between Ferulic Acid and Nateglinide Involving the Fluorescein/H^+ Cotransport System has been reported [62].

Food and Protein interactions: The interactions of chlorogenic acid and ferulic acid with human serum albumin (HSA) have been investigated by fluorescence and Fourier transformed infrared (FT-IR) spectrometry. Fluorescence results showed that one molecule of protein combined with one molecule of drugs at the molar ratio of drug to HSA ranging from 1 to 10, and their binding affinities (K_A) are 4.37×10^4 M^{-1} and 2.23×10^4 M^{-1} for chlorogenic acid and ferulic acid, respectively.

The primary binding site for chlorogenic acid is most likely located on IIA and that for ferulic acid in IIIA. This indicated a partial unfolding of HSA in the presence of the two acids. From the fluorescence and FT-IR results, the binding mode was discussed [63]. Ferulic acid has also been known to complex with proteins and peanut allergens. Preliminary studies indicated that ferulic acid could also complex with and inhibit IgE antibodies to peanut allergens in ELISA. It was concluded that ferulic acid (10 mg/ml), in combination with IgE, enhanced IgE binding to peanut allergens in Western blots [64].

CONCLUSION: Considering an emerging public and scientific interest in the use of phytochemicals derived from dietary components for their therapeutic usage, a wide spectrum of beneficial activity for human health has been advocated for FA, because of the strong antioxidant activities, explained by its free radical scavenging activity. However, the specific underlying mechanism(s) by which FA affects human health still remains to be exploited further. Hence, future studies must aim to adequately characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of this highly promising Nutraceutical.

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