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Review Article

Pharmacological potential of ferulic acid for the treatment of metabolic syndrome and its mechanism of action: Review

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ABSTRACT

Recently, obesity causes vital mortality around the globe. Last decade, obesity-related diseases increased significantly worldwide. Even though, effective drugs are not available to treat metabolic diseases such as cardiovascular diseases, Parkinson's, obesity, and hypertension. Emergence and identifying new drug moieties to treat such metabolic diseases became imperative. Nature is a vital source of remedies and isolates new effective and nontoxic drug candidates. Ferulic acid is a significant phenolic compound that is abundant in various fruits, rice oil, and vegetables. This study highlighted the beneficial effects of ferulic acid for the treatment of metabolic syndrome or obesity. Similarly, in this study, we have highlighted the therapeutic purpose of ferulic acid in treating metabolic syndrome, its mechanism of action as well as its potential pharmacological effect using animal models. Further investigations are needed to demonstrate the significant mechanism of action in clinical trials using the human species.

Keywords:
Obesity and Metabolic diseases
Lipid profiling and Glucose dysregulation
Cardioprotective
Antioxidant
Inflammation and Hepatoprotective

Introduction

Over the last few decades, metabolic diseases had become pandemic vital causes of death worldwide. Metabolic syndrome is categorized by the presence of several risk factors including insulin resistance, hyperglycemia, hypertension, obesity, and dyslipidemia. Metabolic syndrome developed primarily due to unhealthy dietary habits and a sedentary lifestyle especially saturated fat and rich carbohydrate- food intake with less exercise. This leads to cardiovascular diseases, hypertension, metabolic syndrome, and nonalcoholic fatty liver diseases (NAFLD) (Panchal and Brown, 2011; Panchal et al., 2011). Even though metabolic syndrome has exhibited complicated pathogenesis. Unfortunately, its essential mechanisms remain uncertain. There are numerous animal models for metabolic syndrome that have enhanced our pathogenesis basis insight etiology and the advance of remedies as demonstrated in the literature (Aydin et

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al., 2014; Nascimento et al., 2013).

Plants are vital sources of polyphenols which are phytochemical compounds present in various edible grains, vegetables, and fruits (Md. Reyad-ul-Ferdous et al., 2015; Yin et al., 2019). Plant polyphenols have been identified as a vital resource that leads to executing the therapeutic potential of numerous diseases such as metabolic syndrome, obesity, diabetes, cancer, and so on (Mohammad Reyad-Ul-Ferdous et al., 2014; Reyad-ul-Ferdous M et al., 2014; Williamson and Manach, 2005). Polyphenolic amalgams are categorized into regular flavonoids, phenols, coumarins, xanthones, hydroxycinnamic acids, phenylacetic acids, acetophenones, and the less common lignans and stibenes (Manach et al., 2004; Tsao, 2010). Numerous natural polyphenols have demonstrated fluctuating bioavailability as well as manifested health advances in numerous ailments (Senaphan et al., 2015). Ferulic acid (4-hydroxy-3-methoxy cinnamic acid, FA), a hydroxycinnamic acid imitative, is abundant in vegetables and fruits, including oranges, banana, citrus fruits, tomatoes, cabbage, sweet corn, carrot, cabbage, rice bran, bananas, and broccoli (Prakash et al., 2011; Zhao and Moghadasian, 2008).

Ferulic acid is esterified in several forms. It is better immersed in comparison to other flavonoid agents. Several investigations confirmed that ferulic acid has strong antioxidant properties because of its potency in scavenging free radicals. It also improves cell stress response by upregulation of the cytoprotective system (Bourne et al., 2000). Additionally, it has been reported that ferulic acid enhances endothelial activity in 2 kidney-1 clip (2K-1C) hypertensive rats and high-fat diet rabbits (Mancuso and Santangelo, 2014; Suzuki et al., 2007) and diminishes systolic blood pressure in instinctively hypertensive rats model (Ardiansyah et al., 2008). Also, ferulic acid treatment significantly reduces blood glucose, total cholesterol, free fatty acid, and plasma triglyceride, in both diabetic mice and rats (Jin Son et al., 2010; Sri Balasubashini et al., 2003). Previous studies demonstrated that treatment with ferulic acid significantly reduced little inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and prostaglandin E2 (Ou et al., 2003), enhanced NO synthesis and bioavailability (Suzuki et al., 2007). So, it seems that ferulic acid can be considered a potential drug molecule to treat several diseases associated with inflammation and oxidative stress including metabolic syndrome, diabetes, Alzheimer's, cancer, and cardiovascular diseases (Mancuso and Santangelo, 2014).

Several studies demonstrated that phenolic compounds implement divergent beneficial properties, containing anti-inflammatory, antioxidant (Perez-Ternero et al., 2017), anti-diabetic, and hepatoprotective properties (Narasimhan et al., 2015a; Yuan et al., 2016). Furthermore, many biological endeavors of arabinoxylans were validated and found to contain ferulic acid (Fadel et al., 2018; Qiu et al., 2018). Recently ferulic acid has been proved safe against acute kidney disease (AKI) persuaded by lipopolysaccharide (LPS) and gentamicin (El-Ashmawy et al., 2018; Mir et al., 2018). Numerous studies mentioned that rodent models of metabolic syndrome mimic the foremost symptoms of metabolic disorder in humans, mainly dyslipidemia, diabetes, hypertension, impaired glucose tolerance, insulin resistance, and obesity (Panchal and Brown, 2011). Earlier studies revealed that chronic consumption of high-fat diets and extreme sugar intake lead to the development of dyslipidemia, insulin resistance, fibrosis, vascular dysfunction, heart structural transformation, and inflammation in a rodent model (Nascimento et al., 2013). Drug moieties that avert metabolic syndrome and chronic vascular exertions, like vascular renovating, dyslipidemia, and insulin resistance can be high constructive to health elevation.

The purpose of this review is expounding recent therapeutic findings of ferulic acid in treating metabolic diseases such as obesity, diabetes, Non-alcoholic fatty liver disease (NAFLD), and obesity-related comorbidities among others.

Ferulic acid alleviates changes in metabolic syndrome

Previous studies indicated the effect of ferulic acid by abating vascular dysfunction and insulin resistance in a high-carbohydrate diet rat model. This model induces metabolic vagaries and is a similar analog to metabolic disease in humans. Oral administration of ferulic acid (30 or 60mg/kg) in Sprague-Dawley male rats demonstrated significant improvement in insulin sensitivity and lipid profiles as well as a decrease in high blood pressure compared with the control group rats (Senaphan et al., 2015).

a high carbohydrate, high fat (HCHF) diet mimics metabolic syndrome in rats. HCHF leads to oxidative stress and vascular remodeling. The previous investiga-

tion revealed that oral gavage of ferulic acid improves HCHF-prompted metabolic syndrome, decreases blood pressure, enhances insulin sensitivity, vascular endothelial function, lipid profiles, and inflammation as well as reduces oxidative stress. Ferulic acid has demonstrated a strong antioxidant effect both in *in-vivo* and *in-vitro* studies by up-regulating the powerful heme oxygenase-1 (HO-1), cytoprotective enzyme, protein kinase B (Erbil et al., 2019), and heat shock protein 70 (HSP70). Also, ferulic acid decreases inflammation and oxidant formation by reducing cyclooxygenase-2 (COX-2). Moreover, ferulic acid inhibits angiotensin-converting enzyme activity (Ardiansyah et al., 2008).

These healing effects of ferulic acid are probably due to its anti-inflammatory and antioxidant properties. So, this study highlighted additional proof of the medical importance and utilization of ferulic acid.

Ferulic acid expands glucose-lipid homeostasis in the liver

Ferulic acid has exhibited antihyperglycemic and anti-inflammatory activities. Previous studies demonstrated that ferulic acid significantly reduced glucose and lipid metabolism in a high-fat diet prompted obese mice model. The 25 and 50mg/kg ferulic acid treatment was used for eight weeks in which ferulic acid significantly reduced serum leptin and elevated blood glucose levels. The effect of daily oral gavage of ferulic acid (25 and 50 mg/kg) in high-fat diet (HFD) (45 kcal% fat) induced obese mice (eight weeks of age) on glucose and lipid metabolism was investigated (Reyad-ul-Ferdous et al., 2022a; Reyad-ul-Ferdous et al., 2022c; Reyad-ul-Ferdous et al., 2015a; Reyad-ul-Ferdous et al., 2020). The results demonstrated that ferulic acid significantly lowered the serum leptin levels and high blood glucose, reduced insulin resistance, and enhanced the serum adiponectin level. Similarly, the liver cholesterol, triglyceride, and serum lipid levels decreased. A histological study exhibited a significant reduction of lipid droplet size both in the liver and adipose tissue in an obese mouse. In a similar study, ferulic acid lowered the expression of hepatic lipogenic genes such as sterol regulatory element-binding protein 1c (SREBP1c), Acetyl-CoA carboxylase (ACC), and fatty acid synthase (FAS) as well as upregulated the peroxisome proliferator-activated receptor alpha (PPARa) proteins and hepatic carnitine palmitoyltransferase 1a (CPT1a) gene expression. Treatment with ferulic acid also lowered protein expressions of glucose-6-phosphatase (G6Pase), hepatic gluconeogenic enzymes, and phosphoenolpyruvate carboxylase (PEPCK). In summary, ferulic acid improves the glucose and lipid homeostasis in HFD-promoted obese mice possibly via regulating the expression of gluconeogenic and lipogenic genes in liver tissues (Naowaboot et al., 2016).

Furthermore, earlier studies revealed that insulin and leptin are best known for regulating long-acting signals in modulating energy storage and energy homeostasis in fat tissue of mice model (Enriori et al., 2006; Sohn et al., 2013).

Previous studies confirmed that the serum leptin level in the obese group was multiple times expanded as compared with the ferulic acid-treated group. In this manner, the decrease in body weight and food consumption in the ferulic acid-treated group might be identified with the improvement of leptin work. Obesity and insulin resistance lead to the development of fatty liver (DeFronzo and Tripathy, 2009; Tailleux et al., 2012). Peroxisome proliferator-activated receptors-α (PPARα) notably regulates hepatic lipid metabolism by modulating the translation of PPARa-controlled genes like CPT (Tailleux et al., 2012).

It has been demonstrated that PPARa inadequate mice have significantly higher liver weight, fat masses, and total glyceride (TG) levels (Knauf et al., 2006; Patsouris et al., 2006). Non-alcoholic fatty liver disease (NAFLD) and steatosis development were significantly reduced. Strikingly, the ferulic acid treatment enhances hepatic PPARa expression and diminishes the serum TG, Total Cholesterol (TC), as well as NEFA levels. Ferulic acid treatment leads to improved mitochondrial oxidation by free fatty acid (FFA) transport which is generated by up-regulation of hepatic PPARa protein, trailed by (I) expansion of the CPT1a gen (Suzuki et al., 2008) as well as smothering of the expanded acetyl-CoA carboxylase (ACC), sterol regulatory element-binding protein 1c (SREBP1c), and fatty acid synthase (FAS). Along these lines, ferulic acid has lipid lowing activity by downregulating lipid-associated genes and upregulating fat oxidation engaged gene levels (Naowaboot et al., 2016).

Ferulic acid regulates enzymatic, hormonal, and inflammatory changes in the high-fat diet-induced obesity in the rat model

In recent studies, it was established that the ingestion of fat-rich diets may trigger an inflammatory response in the hypothalamus that blunts the thermogenic and anorexigenic signals produced by the hormones such as leptin, insulin, and ghrelin. So that, it leads to abnormal bodyweight regulation (Velloso et al., 2008). Meanwhile, ferulic acid shows several pharmacological effects includinganti-inflammatory properties (Das et al., 2014), anti-oxidant properties (Srinivasan et al., 2007), glucose, and lipid metabolism (Mancuso and Santange-lo, 2014; Naowaboot et al., 2016) operties.

Several drugs have been banned due to inducing severe toxicity. Ferulic acid has shown a health-benefitting effect by diminishing the cardiovascular complications generated by metabolic syndrome (Senaphan et al., 2015). HFD-induced mice demonstrated an elevated level of alanine aminotransferase (Seo et al., 2019) and aspartate aminotransferase (AST) in the liver that were reduced by ferulic acid treatment (Kamei et al., 1986). Importantly, ferulic acid did not alter circulating urea and creatinine levels which confirms the safety of this compound for the liver and kidneys. In addition, ferulic acid demonstrated a protective effect against glycerol-induced nephrotoxicity and diosbulbin B-induced hepatotoxicity (Wang et al., 2014).

The promising anti-obesogenic effects of ferulic acid (10mg/kg) in HFD-induced male Swiss mice have been reported. At the end of the treatment of visceral fat accumulation, factors including plasma levels of insulin hormone and glucose, lipase, and amylase activities, bodyweights of animals, the satiety hormones leptin and ghrelin, monocyte chemoattractant protein-1 (MCH-1), and tumor necrosis factor-a (TNF-a) were evaluated. HFD results demonstrated that ferulic acid could efficiently reduce HFD-mediated increase in adipocyte size, visceral fat accumulation, and body weight gain. Similarly, ferulic acid significantly reduced HFD-induced increase in serum lipid profiles such as lipase, amylase, insulin, and blood glucose levels. Ferulic acid treatment could neutralize the elevated leptin and reduced ghrelin levels in HFD-induced obese mice. Furthermore, ferulic acid verified significant restraint of inflammatory mediators of MCH-1 and TNF-a in serum levels of mice (de Melo et al., 2017). In this context, ferulic acid prominently reduced the threat of HFD-promoted obesity through variation of inflammatory, hormonal and enzymatic activities (de Melo et al., 2017).

Ferulic acid alleviates lipid peroxidation in diabetic rats

Previous research highlighted the function of oxidative stress, the implications and etiology of diabetes complications, aging, and long-standing issues as the leading causes of death and morbidity (Reyad-Ul-Ferdous etal., 2014; Reyad-Ul-Ferdous etal., 2015b;). Hyperglycemia is a renowned cause of prominent free radical concentration, and this can prime to amplified lipid peroxidation (hydroperoxides and TBARS). Given Randle's glucose-unsaturated fat hypothesis, extraordinary free unsaturated fat discharged from the fat tissue for oxidation causes the development of metabolites that restrain glucose utilization by the tissues. These metabolites of unsaturated fat oxidation, which are embroiled in the glucose-unsaturated fat cycle, are receptive oxygen species and hydrogen peroxide. These substances may harm the cell structures and impede glucose digestion. Raised free extreme fixation and lipid peroxidation decline the cancer prevention resistance agent in natural frameworks. The significant antioxidants are (a) GPx, which catalyzes the evacuation of hydrogen peroxide to non-dangerous items by using the decreased glutathione (GSH), (b) SOD, which ensures the tissues against oxygen free radicals, and changes over these superoxides to hydrogen peroxide and in this manner predicts any harm to the layer and organic framework and (c) Catalase, that is a significant chemical in detoxification of hydrogen peroxide shaped from SOD. Several studies suggested that ferulic acid treatment reduces glucose, TBARS, FFA, and hydroperoxides, also it upregulates GSH in diabetic rats. Additionally, ferulic acid enhances the development of pancreatic islets and the function of SOD, GPx, and CAT. The impact was greatly articulated with lower portion treatment. As a result, subsequent studies have shown that administering ferulic acid as a cancer prevention medication limits these diabetic mice by destroying the free radicals formed, thereby lowering the power of diabetes (Reyad-ul-Ferdous et al., 2022b. Qiu et al., 2018). Earlier investigations demonstrated that ferulic acid reduces the oxidative pressure caused by diabetes, thus, diminishing the oxidative pressure which corresponded with the decrease in the levels of TBARS, hydroperoxides, and FFA in the liver in diabetes rats. The levels of GSH and the activities of cancer-prevention chemicals such as GPx, SOD, and CAT were increased in the liver, and the effect was more pro-

nounced with a low dose of Ferulic acid (10mg/kg body weight) than with a high dose (40mg/kg body weight). (Reyad-Ul-Ferdous et al., 2014).

Ferulic acid treatment against DNA damage and oxidative stress in kidney and testes of rats

Reactive oxygen species (ROS) are produced in the cells due to an imbalance between antioxidants and free radicals. Oxygen radicals released from ROS interact with additional fragments in the biological system. In the last decades, lead acetate (Pb(C2H3O2)2) has been used in several products such as cosmetics, insecticides, and hair dyes as an additive. Using this compound leads to irritating skin, mucous membranes, and eyes. Previous studies demonstrated that treatment with ferulic acid inhibits lead acetate toxicity which is mediated by the antioxidant and anti-inflammatory effects of ferulic acid. Also, it has been reported that ferulic acid (25mg/kg) reduces total testosterone, follicle-stimulating hormone (FSH), serum luteinizing hormone (LH) (de Melo et al., 2017), ROS, total antioxidant capacity (Gogoi et al., 2014), lipid peroxidation (LPO), and catalase activities produced by lead acetate toxicity both in kidney and testes tissues. These results illustrate the protective function of ferulic acid against lead acetate-induced toxicity in rats. In summary, ferulic acid may have impending therapeutic application against lead acetate-induced renal and testicular toxicity in rats (Kelainy et al., 2019) as demonstrated in Figure 1.

Anti-wrinkle and whitening activities of ferulic acid in b16f10 melanoma and ccd986sk fibroblast cells

Several complicated factors associated with skin aging include multiplex connections among the subcutaneous, dermis, epidermis, fat, as well as extracellular substrates triggering asteatosis, wrinkle formation, and pigmentation, induced by oxidative stress (Chiang et al., 2012; Kim et al., 2011). Consequently**,** drug moieties with high anti-inflammatory activity and anti-oxidative activity inhibit wrinkle and pigment development by interrupting the biosynthesis of collagen as well as melanin.

Several exterior stress factors lead to the formation of ROS in the body including UV. ROS fade fibroblast activity and shrinkage development of elastin, collagen, and hyaluronic acid thus diminishing skin elasticity (Chaudhary et al., 2019). Furthermore, ROS-enhanced matrix metalloproteinases (MMPs) expression leads to trigger wrinkles by the breakdown of the structure of elastin as well as collagen (Park et al., 2010).

Previous studies revealed that ferulic acid shows an anti-wrinkle and whitening effect on the CCD-986sk,

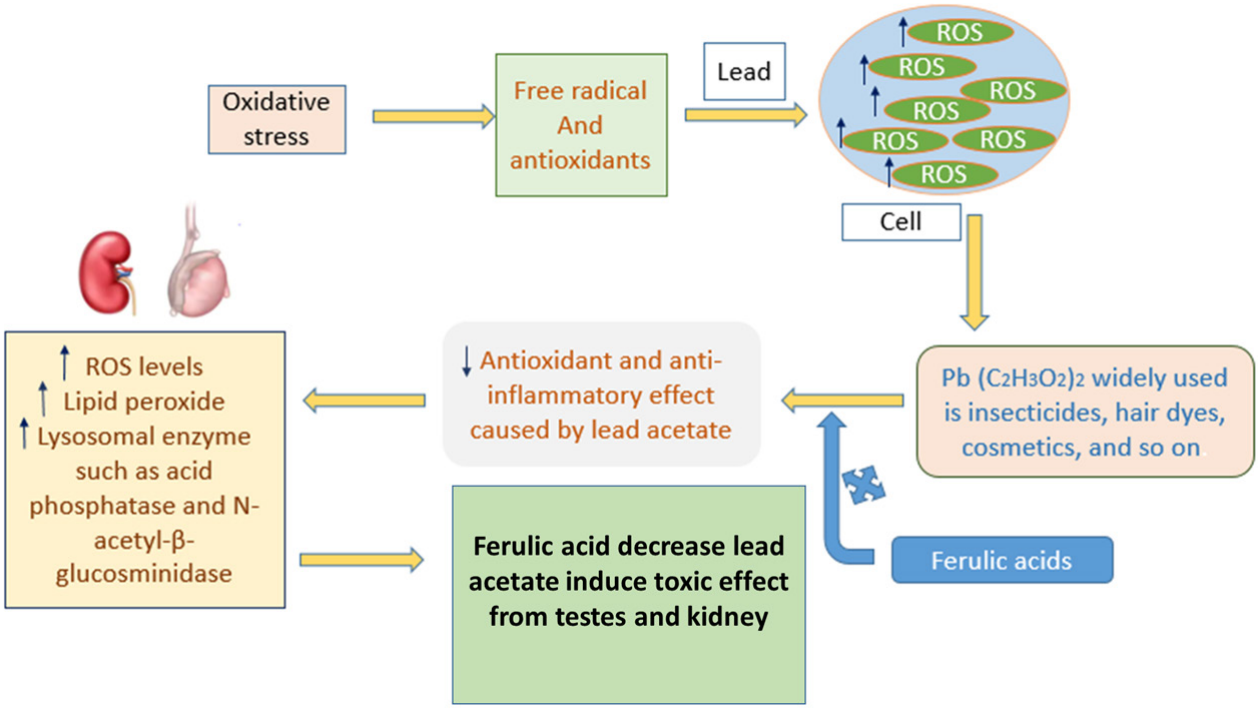

FIGURE 1. Ferulic acid reduces deleterious effects caused by lead acetate in both kidney and testes tissues of rats.

a human fibroblast dermal cell line, by inhibiting hyaluronic acid synthesis, as well as the expression of matrix metalloproteinases (MMP) 1and 9. Ferulic acid exhibited whitening effect against B16F10 melanoma cell line (mouse). Ferulic acid isolated from *T. tetragonioides* blocks melanin synthesis, tyrosinase, and the transcription factor of microphthalmia expression in B16F10 cells and is accelerated with the a-melanocyte invigorating hormone. In Figure 2, ferulic acid was demonstrated as a potential therapeutic compound with anti-wrinkle and whitening activities. It can be consumed as a functional food (Park et al., 2018).

Ferulic acid ameliorates inflammation, glucose homeostasis, and dyslipidemia in an obese rodent model

Prolonged use of HFD increases the production of major cytokines such as IL-1β, IL-10, IL-6, and IL-4 in the animal serum. Antioxidant effects are significantly reduced in obesity and excess weight conditions which is one of the vital factors that contribute to recruiting and developing non-communicable diseases. The plasma antioxidant ability was measured using the Oxygen Radical Absorbance Capacity Assay (ORAC) and Trolox Equivalent Antioxidant Capacity (TEAC) assays (Seo et al., 2019). However, the plasma antioxidant bulk was significantly higher in the ferulic acid group compared to the HFD control group.

Furthermore, ferulic acid considerably impacted the proliferation of adipocytes in comparison to the control group rats. Ferulic acid treatment of HFD receiving rats resulted in a reduction in adipocyte average size (by 43%) as well as a reduction in size range (6000-1000 m2) (Azam et al., 2022; Li et al., 2022). Due to the intake of HFD, the hexagonal structure is changed in the normal adipocyte. The abdominal adipocytes tissue showed clear hypertrophy (cell size increase) and hyperplasia (cell number increase) which distinguishes increased fat accumulation in adipose tissue. Ferulic acid significantly reduces blood glucose and insulin level in the HFD group compared with the control group (Loos et al., 2008). The potential effect of ferulic acid on insulin resistance type 2 diabetes, dyslipidemia, and antioxidant properties have been summarized in Figure 3.

Ferulic acid inhibits the progression of chronic non-communicable diseases caused by excessive HFD consumption. The consumption of HFD enhances fat accumulation in adipocytes and subsequently enhances the abdominal fat tissue (Loos et al., 2008), and body weight as well as leads to hypertrophy and hyperplasia in abnormal fat tissue (AFT) (Loos et al., 2008). The reasons declared overhead promoted imbalance of glucose homeostasis and dyslipidemia. The alteration of

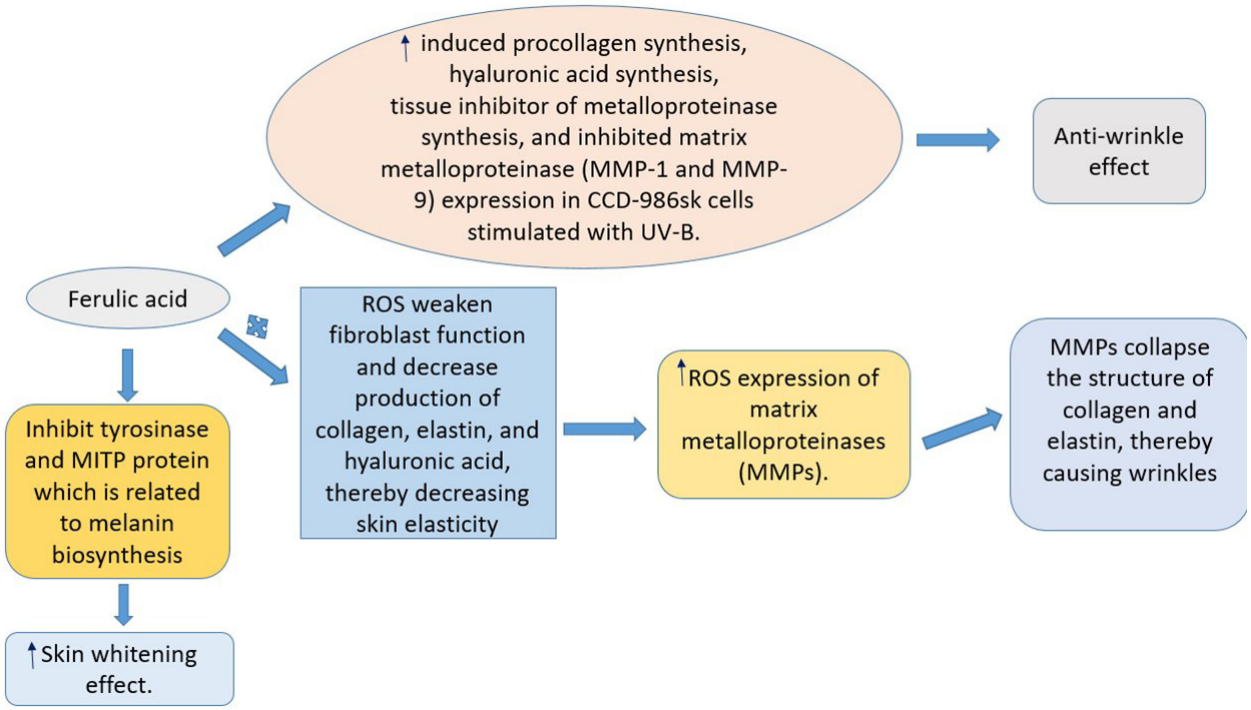

FIGURE 2. Anti-wrinkle and whitening effect of ferulic acid

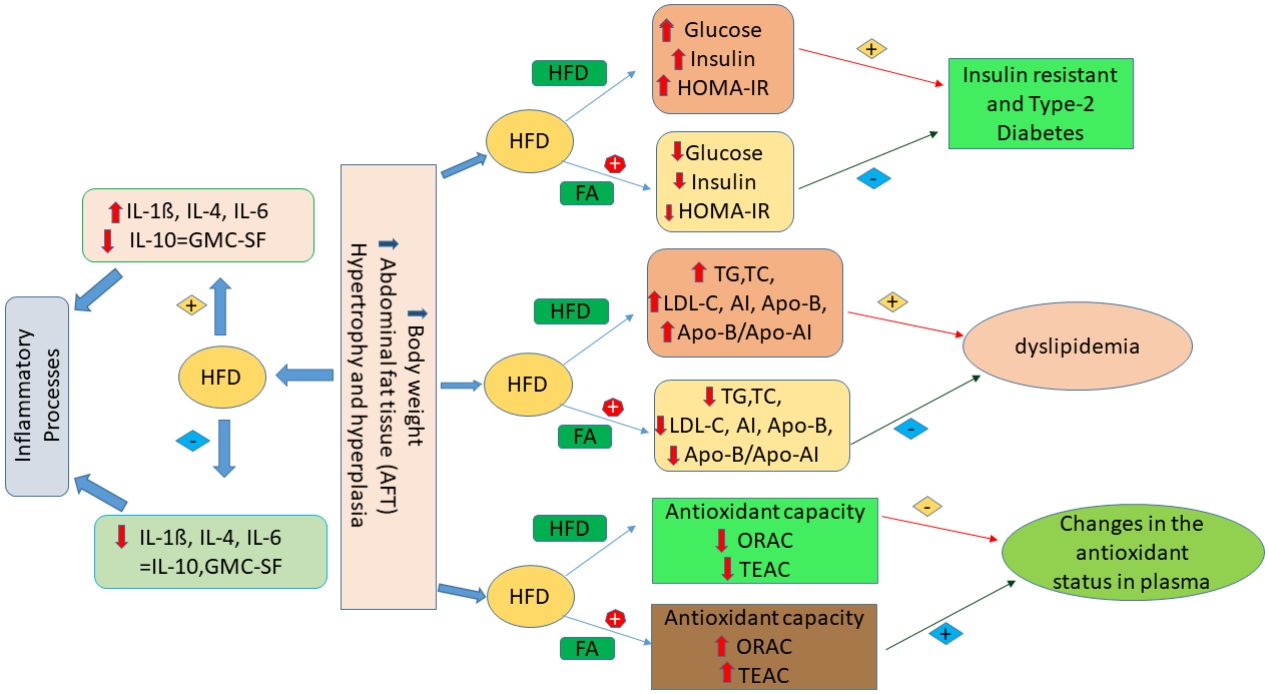

FIGURE 3. Effect of ferulic acid on dyslipidemia, inflammation, and glucose homeostasis in rats

adipocyte activity due to the excessive level of pro-inflammatory cytokines leads to a decrease in antioxidant levels that promote chronic low-grade inflammation, insulin resistance, cardiovascular diseases, type 2 diabetes, and coronary heart disease risks. The intake of ferulic acid decreases fat storage and pro-inflammatory cytokines production and improves antioxidant levels. consequently, ferulic acid may decrease the progression of obesity and overweight-related diseases. Ferulic acid revealed essential anti-oxidant, anti-inflammatory, and anti-obesity effects on the HFD rodent model. The above-mentioned findings lead to consider ferulic acid as a potent drug candidate for the treatment of obesity-related comorbidity (Salazar-López et al., 2017).

Nevertheless, investigations demonstrated that ferulic acid has a significant effect on glucose homeostasis, antioxidant capacity, inflammatory biomarkers, lipid homeostasis, and abdominal adipose tissue in the HFD-induced obese rats model.

Ferulic acid indicated hostility to adipogenic properties since it diminishes the fat index, hypertrophy, abdominal fat tissue, and hyperplasia compared to HFD treated group.

Such effects were obtained because ferulic acid suppressed lipid accumulation and hindered adipocyte differentiation in the cells (Fan et al., 2016) Thus consumption of ferulic acid could be significant against atherosclerotic development in cardiovascular diseases and associated risk features, such as abdominal obesity indices or related diseases (Xu et al., 2015).

The consumption of HFD leads to the presence of distinctive dyslipidemia categorized by reduced HDL-C and an enhanced number of LDL-C, triglycerides, free fatty acid, and ApoB. In that respect, it has been reported that ferulic acid treatment in the HFD-receiving group diminished TC and TG levels. Furthermore, ferulic acid consumption decreased the LDL-C, ApoB, and ApoB/ApoA1 ratio without affecting the HDL-C levels. In this manner, intake of ferulic acid leads to diminishing obesity-related coronary heart disease and overweight via the decreased level of LDL-C and ApoB/ApoA1 proportion. Thus, ferulic acid has exhibited potent therapeutics for atherogenic activities (Klop et al., 2013).

Moreover, a previous study demonstrated that the consumption of HFD leads to modulating normal adipocyte function through the generation of free fatty acids, adipokines (IL-6, TNF-α), free radicals, and monocyte chemoattractant protein-1 (MCP-1). Also, a positive correlation between lipid markers and inflammatory markers which is a vital factor to pledge glucose and

lipid homeostasis has been reported. (Jung and Choi, 2014; Kahn et al., 2006).

Previous studies demonstrated that ferulic acid modulated high-fat diet induces glucose dyshomeostasis by dropping the insulin, glucose, and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) levels, which prevent type 2 diabetes and insulin resistance. Ferulic acid treatment also improves glucose and lipid homeostasis by lowering the expression of lipogenesis genes (SREBP1c, FAS, ACC) as well as promoting gluconeogenic enzymes (PEPCK and G6Pase) and β-oxidation genes (CPT1a, PPARα) (Naowaboot et al., 2016).

Additionally, ferulic acid regulates hepatic GLUT2 gene expression through the modulation of transcription factors, which has been observed in high-fat and fructose-induced type-2 diabetes in adult male rats (Narasimhan et al., 2015b).

Our reports are consistent with previous reports, which showed that ferulic acid has anti-inflammatory properties because of the decrease in the expression of the transcription factor inhibitor of kappa B (IκB), and the increase of the nuclear translocation of the p65 subunit of nuclear factor kappa B (NFκBp65). Furthermore, ferulic acid may contribute to the modulation of inflammatory processes through suppression of NO production by downregulating the expression of the NF-κB-mediated iNOS gene (Niu et al., 2016).

The ferulic acid treatment enhances the number of antioxidants in the rodent serum measured by ORAC and TEAC assays. Finally, ferulic acid demonstrated the potential therapeutic effect for the treatment of diseases associated with glucose and lipid homeostases such as hypertension, cardiovascular and diabetic diseases by triggering anti-inflammatory and anti-oxidant effects (Kim et al., 2012).

Cardio-protective role of ferulic acid against isoproterenol-induced cardiac toxicity

Over the last decades, myocardial infarction (MI) has become a regular medical demand allied with considerable mortality and morbidity. This clinical complaint was categorized as myocardial necrosis due to ischemia of coronary heart muscle which leads to irregular cardiovascular activities (Anderson and Morrow, 2017). In high concentrations, ROS contributes to the establishment of numerous degenerative illnesses of aging, atherosclerosis, Parkinson's, and so on. ROS are markedly involved in instigating biological action, containing energy depletion, dysfunction, and cellular damage. Equally, ROS facilitates necrosis and cellular apoptosis. Chemically synthesized catecholamine is isoproterenol (ISO). This β-adrenergic agonist goes about as a significant controller of myocardial metabolism and contractility. ROS further prompts the arrangement of deviations in myocardial structure, biochemical parameters, and functions (Anderson and Morrow, 2017).

ISO infusion leads to enhanced heart weight, and heart rate ratio with a huge decline in body weight. It has been demonstrated that treatment with ferulic acid significantly reversed ISO-induced heart weight, heart rate, and body weight at a dose of 20 mg/kg and 40 mg/kg whereas was ineffective when administrated at a dose of 10 mg/kg, practically equivalent with standard medication metoprolol (Jain et al., 2018).

ISO-induced severe cardio-toxic results exhibited a decline in PR interim, shrinkage in QRS interim, shrinkage in QT interim, and decrease in RR interim. Accordingly, treatment with ferulic acid at a dose of 40 mg/kg could normalize ST fragment, enhance PR interim, enhance QRS interim ($P < 0.01$), and enhance QT and RR interim.

By Impact on serum heart marker enzymes, in the ISO-treated rodent group, raised levels of CK-MB, AST, lactate dehydrogenase (LDH), and ALT were detected that were preventable by ferulic acid pretreatment. Low dose treatment with ferulic acid demonstrated a decreased level of cardiovascular marker catalysts. In any case, a portion of 20 mg/kg indicated exceptional repressed ALT, AST, LDH, and CK-MB levels. Impact on total cardiac protein and oxide-nitrosative stress plays a vital role in cardiac disease. ISO-induced cardiotoxicity represses activities of GSH and SOD levels which are reversible by treatment with ferulic acid (20mg/kg).

Treatment with ferulic acid at 40 mg/kg demonstrated a similar effect to standard medication, metoprolol, by reducing cardiovascular biomarkers such as ALT, AST, LDH, and CK-MB. In this manner, ferulic acid assumes an exhaustive job in anticipating biochemical varieties, free radical scavenging activity, and cardio-protective effect.

In an experimental study, after treatment of mice with ISO increased levels of cytokines such as TNFα, IL-1β, and TNFα were reported which were reversed by ferulic acid treatment at 40 and 20 mg/kg.(Lim et al., 2013; Na-

goor Meeran et al., 2015).

Previous studies demonstrated that ferulic acid exhibits a cardioprotective role against isoproterenol-induced cardiac toxicity by augmenting the endogenous antioxidant system, alleviating oxidative stress, and normalization of serum cardiac biomarkers (Jain et al., 2018).

Isoproterenol-induced acute cardiotoxicity elevates serum levels of creatinine kinase (CK-MB), alanine transaminase (Seo et al., 2019), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST). A low dose of ferulic acid exhibited a weak inhibitory effect on cardiac marker enzyme levels and gradually demonstrated significant suppression on CK-MB, AST, ALT, and LDH at a dose of 40mg/kg compared with standard drug metoprolol (Sasaki et al., 2019).

As a result, ferulic acid considerably reduces metabolic abnormalities, resulting in a cardioprotective effect. The therapeutic effect of ferulic acid on cardiotoxicity remains poorly defined. Further studies are in urgent demand to elucidate the mechanism of action and therapeutic application of this compound.

Effect of ferulic acid on Alzheimer's disease

Last several years, a wide assortment of synthetic or natural, aromatic compounds were known as amyloid fibril development inhibitors. Several aromatic compounds exhibit potent free radical scavenging and antioxidant properties which are abundant in vegetables, drinks, grains, and so on.

The development of little particle amyloid peptide buildings may likewise be supported by powerless, non-covalent powers, for example, hydrophobic, van der Waals, solvophobic and electrostatic forces. The development of amyloids is a vital reason for causing Alzheimer's disease**.** Previous experimental data demonstrated that the anti-amyloidogenic properties of phenols may work in 3 probable paths: (1) inhibition of the underlying phase of the self-assembly procedure, prompting oligomeric classes; (2) inhibition of both extending protofibrils and fibril augmentation; (3) disaggregation, fragmentation, and/or destabilization of the settled fibrils, as well as their transformation to amorphous arrangements. Among these moieties, ferulic acid consists of the phenolic group and exhibits significant anti-inflammatory and antioxidant activities that improve oxidative stress and Alzheimer's disease. Ferulic acid comprises one of the phenolic rings inhibits Aβ fibril formation as well as shows anti-inflammatory and anti-oxidative functions (Sgarbossa et al., 2015). Because the structure of ferulic acid is similar to that of curcumin, it was suggested that ferulic acid is an efficient moiety for precisely binding A fibril and limiting fibril formation. Previous investigations suggested that ferulic acid inhibits destabilized and extension pre-formed fibrils as well as fibril formation in a dose-dependent manner. The fibril-destabilizing and anti-amyloidogenic properties of ferulic acid have demonstrated a marginally lower effect compared with curcumin (Okuda et al., 2019). Based on the results, it was revealed that ferulic acid inhibits the progress of Alzheimer's Disease development not only by direct restraint of fibril accumulation in the brain but also through scavenging reactive oxygen species (Ono et al., 2005).

A recent investigation demonstrated the role of mitochondrial dysfunction which leads to the development of neurodegenerative diseases such as Huntington's disease, Parkinson's disease, and Alzheimer's disease (Anis et al., 2019).

Another study found that ferulic acid inhibits A deposition by using relationship docking analysis between the amyloid peptide and ferulic acid. It was also discovered that ferulic acid interacts with Ap1'42q primarily through Glu22 and His14 with hydrogen bonding, interfering with -sheet development (Cui et al., 2013).

Previous investigations have shown a potential effect of ferulic acid against Aβ-actuated memory and learning shortages in the *in-vivo* murine model (Kim et al., 2004; Yan et al., 2001). Also, the ferulic acid protective effect against neurotoxicity and Aβ-initiated oxidative pressure has been shown in the *in-vitro* murine model (Sultana et al., 2005). However, in another study, no significant effect of oral ferulic acid administration on Aβ deposition or Aβ oligomers was reported (Hamaguchi et al., 2009). Whereas, ferulic acid has exhibited an optimistic effect against neurodegeneration damage triggered by Alzheimer's disease and restraint of neurotoxic total Aβ in vivo and in vitro murine models. Additionally, ferulic acid inhibits apoptotic programmed cell death prompted by oxidative stress due to Aβ mass and inflammation. The above-mentioned outcomes empower the utilization of ferulic acid as potent drug moieties for the treatment of neurodegenerative diseases (Sgarbossa et al., 2015).

Effect of ferulic acid on antioxidants

A few discoveries on the onset of various diseases linked with free radical development remain to be illustrated. Stress causes several diseases that are allied with an unhealthy lifestyle, pollution, cigarette smoking, illness, exposure to chemicals, stress, drugs, and so on. Oxygen performs a crucial function in biological systems. Excessive oxidative stress leads to cell damage. Oxygen promoted mitochondrial adenosine triphosphate (ATP) production in terms of free radicals and as an energy source.

The cellular redox process generates ROS and reactive nitrogen species (Li et al., 2016). Contingent upon their sensitive equalization inward the cells,These reactive species might be toxic or beneficial depending on their sensitivity equalization inside the cells. Reactive species have a vital impact on immune function and cellular redox signaling at small or mild concentrations but promoted oxidative stress has a toxic effect on cells' structure and function. Antioxidants protect the cell and cellular redox homeostasis by scavenging free radicals and decreasing oxidative stress (Bao et al., 2019).

Traditionally herbal medicine and dietary nourishments are used to protect against inflammation and injury caused by free radicals. Current investigation revealed that the antioxidant consumption from natural, mineral and animal sources exerts a protective effect against free radical related diseases such as neurodegenerative disorders. The antioxidant treatment enhances interest to develop new medicine and treatment of an oxidative stress-related disorder. Abundant antioxidant compounds found from plant sources include flavonoids, folic acid, cinnamic acids, ascorbic acid, benzoic acids, carotenoids, tocotrienols, and tocopherols which avert oxidation of the liable substrate. compared with synthetic antioxidants, natural antioxidants improve biological function due to the presence of herbal phytoconstituents in the human body (Chaudhary et al., 2019).

Synthetic antioxidants are intensively used as a preservative to prevent lipid peroxidation. These antioxidants primarily function in two ways: as chelating agents, oxygen scavengers, and radical terminators, or by separating the hydroperoxides formed during lipid oxidation into stable end products. Midst the varied classes of amalgams, natural phenols, particularly ferulic acid has been received considerable attention due to its safety and positive effect on several oxidative stress-related disorders such as diabetes, Parkinson's diseases, and so on. cytoprotective effect of ferulic acid is modulated in part by the upregulation of enzymes including oxygenase-1, serine/threonine kinase, heat shock protein (Erbil et al., 2019), and extracellular signal-regulated kinase (Huang et al., 2005) ½ to exhibit (Erbil et al., 2019). Besides, ferulic acid hinders the activity and expression of cytotoxic enzymes including inducible cyclooxygenase-2, caspases, and nitric oxide synthase. This proof has urged researchers to consider ferulic acid protective against several diseases such as neurodegenerative disorders, and various age-related diseases, like cardiovascular diseases, diabetes, and cancer (Erbil et al., 2019).

Ferulic acids attenuate liver fibrosis

A previous study revealed the hepatoprotective activity of ferulic acid aligned with the transforming growth factor-β1(TGF-β1) and CCl4-induced hepatic fibrosis. It was revealed that ferulic acid decreases the expression of TGF-β1that initiated liver fibrosis in the human hepatic stellate cell line (HSC) and impeded the TGF-β1/Smad signaling pathway in the LX-2 cells line. Treatment with TGF-β1, significantly enhanced fibronectin, collagen I, α-SMA, Smad4, p-Smad3, and p-Smad2 levels in the LX-2 cells line. Ferulic acid significantly reduced collagen I, TGF-β1induced α-SMA, and fibronectin, upregulation in LX-2 cell line treated by TGF-β1. Also, ferulic acid significantly decreased fibronectin expression in the LX-2 cell line treated by TGF-β1 (Hernandez-Gea and Friedman, 2011; Li et al., 2015). These results revealed the potential effect of ferulic acid on TGF-β1-instigated liver fibrosis in LX-2 cells. Likewise, CCl4 has been broadly used to initiate hepatic damage, hepatic cirrhosis, and liver fibrosis (Yao et al., 2013). Besides, the initial induction of liver damage by CCL4 increases liver enzymatic markers level including HA, ALT, AST, and Hyp in liver tissue and plasma. Ferulic acid treatment significantly reversed p-Smad2 and p-Smad protein levels which were enhanced with CCL4 treatment (Mu et al., 2018). This result endorses the therapeutic potential of ferulic acid against CCL4-induced fibrosis by the interruption of the TGF-β1/Smad pathway both in the *in-vivo* and *in-vitro* model. These discoveries gave proof of the potential utilization of ferulic acid to treat or avert liver fibrosis (Mu et al., 2019) mentioned in Figure 4.

Ferulic acid defends against methotrexate-induce

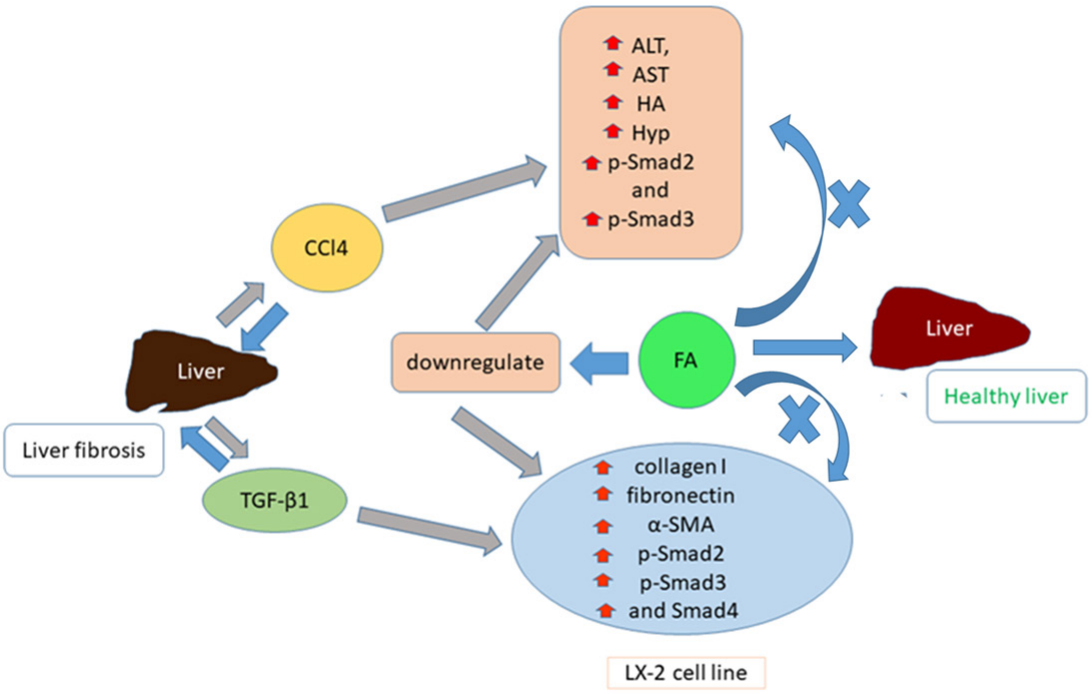

FIGURE 4. Effect of ferulic acid on liver fibrosis by downregulation of fibrosis markers via TGF-β1/Smad signaling pathway in-vivo and in-vitro

nephrotoxicity in a rodent model

Ferulic acid amends necessary kidney function markers and averts histological modifications by increasing antioxidant function and repressing ROS generation. Also, it has been reported that ferulic acid has exhibited a protective effect against MTX-induced inflammasome activation by diminishing expression of NLRP3, phosphorylation of NF-κB, IL-1β, and caspase-1. an earlier study also revealed that ferulic acid upregulates PPARγ expression and Nrf2/ARE/HO-1 signaling in the kidney of MTX-induced rats. In conclusion, ferulic acid revealed a new mechanism of MTX nephrotoxicity via activation of NLRP3 inflammasome. Ferulic acid seems protective against MTX-induced nephrotoxicity by suppressing apoptosis, ROS production, NF-κB/NLRP3 inflammasome axis, and upregulation of Nrf2 signaling and PPARγ expressions (Mahmoud et al., 2019).

In this review, we investigated ferulic acid activities for the treatment of metabolic diseases and their pharmacological effect. Ferulic acid could be an alternative drug for the treatment of metabolic-related diseases due to its several pharmacological effects in animal models.

In this review, we focused on the effects of ferulic acid in treating metabolic syndrome and the mechanism of action as well as its potential pharmacological effect. Further investigation will demonstrate a significant mechanism of action in clinical trials on the human species.

Pharmacokinetics and pharmacodynamics of ferulic acid

Curcumin byproducts generate ferulic acid along with other byproducts both in human and rodent models (Ghosh et al., 2017). Absorbability is defined as the fraction of administrated dose which crosses the intestinal mucosal barrier and reaches systemic circulation. The structure of ferulic acid has been shown in Figure 5. It reflects the bioavailability of ferulic acid. Thus, the physiological importance of ferulic acid depends on its availability for absorption and subsequent interaction with target tissues. In perfused rat intestine, net ferulic acid absorption has been reported to be proportional to the perfused dose, and once absorbed. ferulic acid gets completely recovered as conjugated forms in bile and plasma secretion. Studies have shown that ferulic acid absorption is quite efficient because approximately 50% of the ingested dose gets recovered in urine (Adam et al., 2002).

The total ferulic acid intake through consumption of food may reach a level of about 150 to 250 mg per day. Serum albumin is reported to be a major carrier of feru-

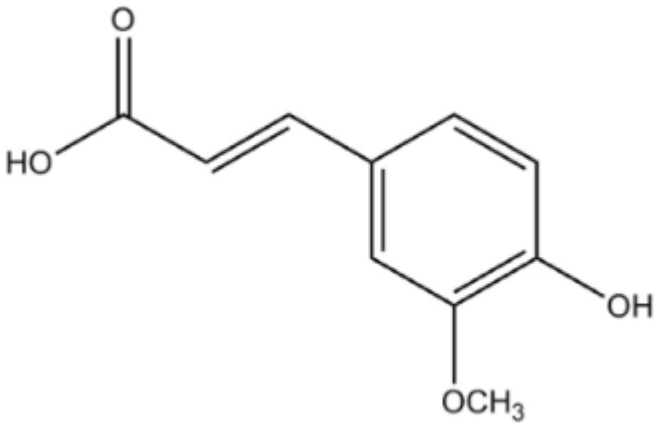

FIGURE 5. Structure of ferulic acid

lic acid. It has been reported that free ferulic acid is recovered in the kidney (~82 mg/g wet tissue), liver (~28 mg/g), lung (~34 mg/g), heart (~14 mg/g), spleen (~22 mg/g), uterus (~15 mg/g) and brain (~2.6 mg/g) within 30 min from the oral administration of 521 mmol/kg BW of ferulic acid in rats. It has been shown that 92% of the ingested ferulic acid is excreted through urine as free ferulic acid and its glucuronic conjugates after consumption of free ferulic acid. It is estimated that the half-life of ferulic acid ranges from 10-30 min approximately in rats depending on the dose and the route of administration. Free ferulic acid is reported to be detected in the plasma of humans, 10 min after an oral administration of sodium ferulate, indicating that free ferulic acid is absorbed quickly in humans. Plasma concentrations of free ferulic acid reach the maximum levels at 24 min after the oral administration, with a half-time of 42 min (Zhao and Moghadasian, 2008).

In a particular study related to the investigation of the effects of ferulic acid on interleukin 1 beta (IL-1b) based on pharmacodynamics in rats, blood samples were collected at different time intervals after ferulic acid administration. HPLC and ELISA methods were used to detect the concentration of the drug and expression of IL-1b respectively.

Computation of pharmacokinetic parameters of ferulic acid confirmed that ferulic acid inhibits the expression of IL-1b. Changes in the level of IL-1b in the plasma were observed to follow an opposing trend to the plasma concentration tendency after the maximum concentration was attained. The pharmacokinetics of ferulic acid was found to be closely related to its pharmacodynamics in treating injuries (Zhao and Moghadasian 2008).

Absorption, distribution, metabolism, and excretion (ADME) of ferulic acid

The previous *in-situ* and *ex-vivo* study revealed that ferulic acid was absorbed from the stomach and jejunum. After a 25-min incubation of ferulic acid in the rat stomach, >70% of the ferulic acid disappeared from the stomach and was recovered in the gastric mucosa, blood, bile, and urine which suggests a fast gastric absorption of ferulic acid (Zhao et al., 2003). Similarly, perfusion of ferulic acid in an isolated rat intestine showed that it quickly disappears from the jejunum and to a significantly lesser extent fades from the ileum. Only 0.5–0.8% of ingested ferulic acid was found in the feces of rats, indicating a very efficient absorption rate (Zhao and Moghadasian, 2008).

Metabolic studies have shown that ferulic acid can be metabolized in vivo into several metabolites including ferulic acid-glucuronide, ferulic acid-sulfate, ferulic acid-diglucuronide, ferulic acid-sulfoglucuronide (ferulic acid-diconjugate with sulfate and glucuronide), m-hydroxyphenylpropionic acid, feruloylglycine, dihydro ferulic acid, vanillic acid, and vanilloylglycine. Conjugated ferulic acid including ferulic acid-glucuronide, ferulic acid-sulfate, and ferulic acid-sulfoglucuronide are the major metabolites in the plasma and urine of rats. These results suggest that the conjugation reaction with glucuronic acid and/or sulfate is the principal pathway of in vivo ferulic acid metabolism.

The conjugation of ferulic acid takes place mainly in the liver (Zhao et al., 2004) through the activities of

sulfotransferases (EC 2.8.2.1) and UDP glucuronosyl transferases (EC 2.4.1.17). Intestinal mucosa (Kern et al., 2003; Spencer et al., 1999) and kidney (Chang et al., 1993; Zhao et al., 2003) may also, at least in part, contribute to this conjugation process. Conjugation of ferulic acid may be dose-dependent. high doses of ferulic acid may saturate the conjugation enzymes, leading to the accumulation of free ferulic acid in plasma. This was evidenced by the recovery of free ferulic acid in the plasma of rats after administration of just higher doses (up to 70 mol/ kg) and not lower doses (up to 7 mol/kg) (Adam et al., 2002; Rondini et al., 2002; Zhao et al., 2003).

Distribution

Serum albumin seems to be the major carrier of ferulic acid (Ghosh et al., 2017). It is estimated that approximately 4%, 10%, and 53% of the orally administered ferulic acid can be found in the gastric mucosa, blood, and other tissues including the liver and kidney, respectively. Adam et al. (2002) also showed that 49% of perfused ferulic acid in the rat intestine might be distributed in the liver and peripheral tissues. Chang et al. (1993) reported that free ferulic acid was recovered in the kidney (82 lg/g wet tissue), lung (34 lg/g), liver (28 lg/g), spleen (22 lg/g), heart (14 lg/g), uterus (15 lg/g) and brain (2.6 lg/g) at approximately 30 min after an oral administration of 521 mol/kg of Ferulic acid in rats. The concentrations of free ferulic acid in most tissues decreased by 20% in the kidneys, 80% in the lungs, and 50% in other tissues. It was observed that 60 min after the i.p. injection of ferulic acid in rats <1% of the radioactivity of 14C- ferulic acid remained in the liver, small intestine, cecum, and skin for up to 24 h (Ghosh et al., 2017; Rondini et al., 2004; Zhao and Moghadasian, 2008).

Ferulic acid is excreted mainly through urine in rats in free and conjugated forms. Ferulic acid is also excreted through bile, which accounts for about 4–6% of the oral dose (Rondini et al., 2004). Ferulic acid conjugates were found in the bile only in the beginning period after the i.p. injection (0–5 h). So, this indicates that high circulating levels of ferulic acid are needed for biliary secretion. The bile excretion explains the presence of ferulic acid and its derivatives in the feces of rats treated with i.p. ferulic acid (Zhao and Moghadasian, 2008). It is estimated that the half-life of ferulic acid can range from 10 to 30 min in rats depending on the dose and the route of administration. The short half-life of ferulic acid may suggest its low toxicity. The acute oral LD50 of ferulic acid in female and male F344 rats is 2.1 and 2.4 g/kg, respectively (Zhao and Moghadasian, 2008). No significant sub-chronic toxicity was found in female and male F344 rats after long-term (13 weeks) consumption of dietary FA at 0.16 g/kg per day (Zhao and Moghadasian, 2008).

Bioavailability of ferulic acid

Generally, the bioavailability of free ferulic acid is very low due to its rapid conjugation process in the liver. Ferulic acid bound with arabinose or arabinoxylan from corn bran showed a lower bioavailability compared with free ferulic acid. In contrast, ferulic acid in wheat bran (96% bound with heteroxylans) showed a higher bioavailability in comparison to free ferulic acid (Rondini et al., 2004). The difference may be due to the existing forms of ferulic acid and the oral dose, which affect the fate of dietary ferulic acid in the gastrointestinal tract and its systemic concentrations (Zhao et al., 2003). On the other hand, absorbability is used to describe the fraction of an administered dose of the agent that crosses the intestinal mucosa. The cumulative urinary excretion of total ferulic acid may be used to estimate the absorbability of dietary ferulic acid because absorbed ferulic acid is excreted mainly through urine (Rondini et al., 2002; Zhao et al., 2003; Zhao and Moghadasian, 2008).

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Conflict of interest

None

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