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The effect of ellagic acid on the metabolic syndrome: A review article

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ABSTRACT

Objective: (s): Metabolic syndrome is a collection of metabolic abnormalities that includes hyperglycemia, dyslipidemia, hypertension, and obesity. Ellagic acid is found in various fruits and vegetables. It has been reported to have several pharmacological properties, such as antibacterial, antifungal, antiviral, anti-inflammatory, hepatoprotective, cardioprotective, chemopreventive, neuroprotective, gastroprotective, and antidiabetic. Our current study aims to shed light on the probable efficiency of ellagic acid in managing metabolic syndrome and its complications.
Materials and methods: To prepare the present review, the databases or search engines utilized included Scopus, PubMed, Science Direct, and Google Scholar, and relevant articles have been gathered with no time limit until March 2023.
Results: Several investigations indicated that ellagic acid could be a potent compound for the treatment of many disorders such as diabetes, hypertension, and hyperlipidemia by various mechanisms, including increasing insulin secretion, insulin receptor substrate protein 1 expression, regulating glucose transporter 4, triglyceride, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), attenuating tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), reactive oxygen species (ROS), malondialdehyde (MDA), and oxidative stress in related tissues. Furthermore, ellagic acid ameliorates mitochondrial function, upregulates uncoupling protein 1 (found in brown and white adipose tissues), and regulates blood levels of nitrate/nitrite and vascular relaxations in response to acetylcholine and sodium nitroprusside.
Conclusion: Ellagic acid can treat or manage metabolic syndrome and associated complications, according to earlier studies. To validate the beneficial effects of ellagic acid on metabolic syndrome, additional preclinical and clinical research is necessary.

1. Introduction

Recently, researchers have paid attention to and attended studies on the efficacy of herbal medications in the treatment of chronic diseases such as cancer, cardiovascular disease, and metabolic syndrome (MetS) [1,2]. MetS, also known as syndrome X and insulin

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resistance, is a metabolic disorder characterized by metabolic abnormalities such as hypertension [3], central obesity [4], insulin resistance [5], hyperglycemia, and atherogenic dyslipidemia [6]. Smoking, age, obesity, low socioeconomic level, ethnicity, post-menopausal status, physical inactivity, sugary drinks, soft drinks, and excessive alcohol use are all involved in the etiology of MetS [7–9]. Several substances, including antihypertensive, antihyperlipidemic, and insulin-stimulated medicines, have been utilized to treat MetS [10–13]. Herbal medicines and natural chemicals have recently appeared among scientists as a safe strategy for MetS treatment [14–16]. Because there is no existing treatment for MetS, healthcare professionals' options are severely limited, prompting researchers to seek novel targets and medicines for MetS treatment.

Ellagic acid (EA) (Fig. 1) is a well-known natural compound found in many fruits and vegetables, including pomegranate, persimmon, plum, strawberry, peach, raspberry, and nuts, and has been linked to antibacterial, antifungal, antiviral, anti-inflammatory, hepatoprotective, cardioprotective, chemopreventive, neuroprotective, gastroprotective, and antidiabetic properties [17–20]. EA has the potential to be a powerful molecule for the treatment of a wide range of illnesses, including diabetes, hypertension, and hyperlipidemia [21–23]. It has been observed that EA possesses antibacterial [24], antifungal [25], antiviral [26], and anti-inflammatory [27] properties that might be related to its antioxidant effect. Previous research has shown that EA can treat and manage MetS through a variety of mechanisms, including blood glucose and pressure regulation, weight loss, control of serum lipid profile, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and pro-inflammatory cytokines, increasing insulin secretion [28], and enhancing the amount of high-density lipoprotein (HDL) [29]. According to Zhou et al. [31], EA treatment in streptozocin-treated mice decreased blood glucose, tumor necrosis factor-alpha (TNF-α), serum creatinine levels, increased antioxidant enzyme activity, altered renal pathology, downregulated the expression of toll-like receptors-4, interleukin 1 receptor-associated kinase 4, tumor necrosis factor receptor-associated factor 6, an inhibitor of nuclear factor-kappa B (NF-κB), NF-κB p65, and high mobility group box protein 1.

Our team conducted a literature review on the effects of EA on hypertension, high blood glucose, obesity, and dyslipidemia, all of which play essential roles in the development of MetS. This work, on the other hand, sheds light on the significant potential pharmacological effects of EA against a wide range of disorders, but further research is needed to define its benefits, particularly in humans (Fig. 2).

1.1. Pharmacokinetics, metabolism, safety, and dose translation in humans

Not EA-containing foods, but free EA is absorbed primarily in the stomach and can be detected in the plasma 2 h after ingestion. Urolithin derivatives are the most prevalent EA-derived metabolites produced by human intestinal microbiota, and urolithin A and B conjugates are the most detectable forms in plasma, urine, and various tissues in humans after phase 1 and 2 metabolic activity. Enterohepatic circulation (up to 48–72 h) aids their long-term persistence in plasma and urine [30]. Lei et al. used HPLC to analyze the presence of EA after oral administration of pomegranate leaf extract (0.8 g/kg/day). They observed an open, two-compartment system with a lag time and a plasmatic C_{max} of 213 ng/mL (0.55 h) after oral administration of the extract, with poor absorption and rapid elimination [31]. Murugan et al. [32] investigation in Wistar rats indicated that the pharmacokinetics of an EA-phospholipid complex (equivalent to 80 mg/kg/day of EA) and serum concentration of EA obtained from the complex were higher ($C_{max} = 0.54$ μg/mL) than when the equivalent dose of the free form (80 mg/kg/day) was used ($C_{max} = 0.21$ μg/mL). The plasmatic concentration of the complex was maintained over a long time.

Following EA intake, a small number of free compounds can be absorbed in the stomach, whereas the remainder is absorbed in the small intestine [28]. Ellagitannins, on the other hand, are resistant to gastric metabolism; their hydrolysis occurs in the small intestine

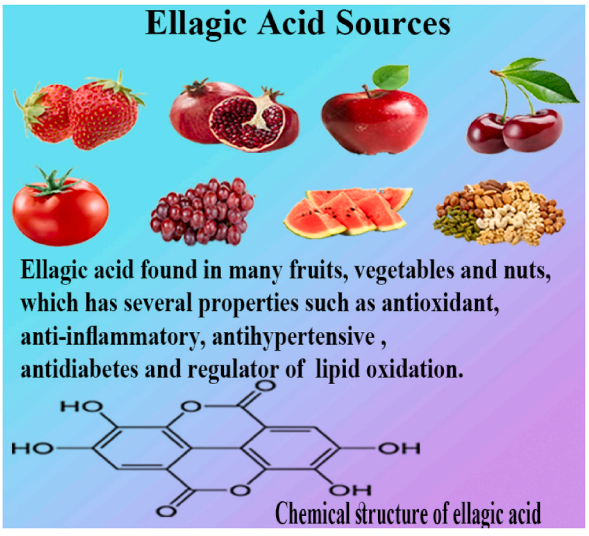

Fig. 1. Chemical structure and natural sources of EA.

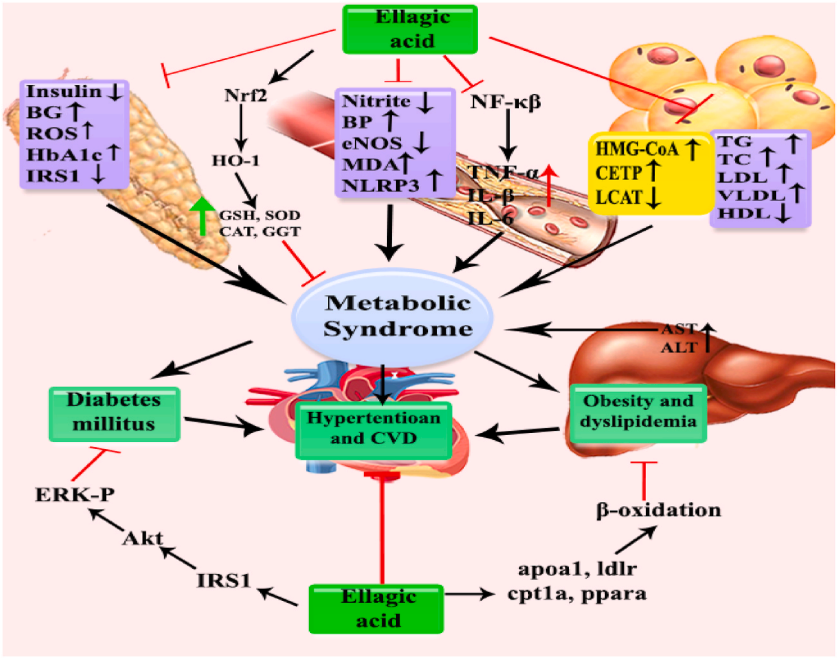

Fig. 2. Schematic description showing the mechanisms of EA on metabolic syndrome.

at a neutral to slightly basic pH, resulting in free EA that can be absorbed in the small intestine. The effective plasma concentration of the complex was maintained for a longer time [21]. González-Sarrías et al. [33] described the absorption saturation in the small intestine when high doses of EA were used. Indeed, in a crossover study with humans receiving either 130 mg punicalagin plus 524 mg free EA (high dose) or 279 mg punicalagin plus 25 mg free form (low dose), the authors found that the high dose of the free form had no more bioavailability than the low dose. Another intriguing hypothesis based on EA pharmacokinetic data is that primary absorption occurs in the stomach and upper part of the small intestine (short T max) and that rapid elimination is due to efficient first-pass metabolism and weak enterohepatic recirculation [34]. Unabsorbed EA and ellagitannins are metabolized to urolithins in the colon by the gut microbiota, whereas absorbed EA is transformed into methyl esters, dimethyl esters, and glucuronides, which are excreted in

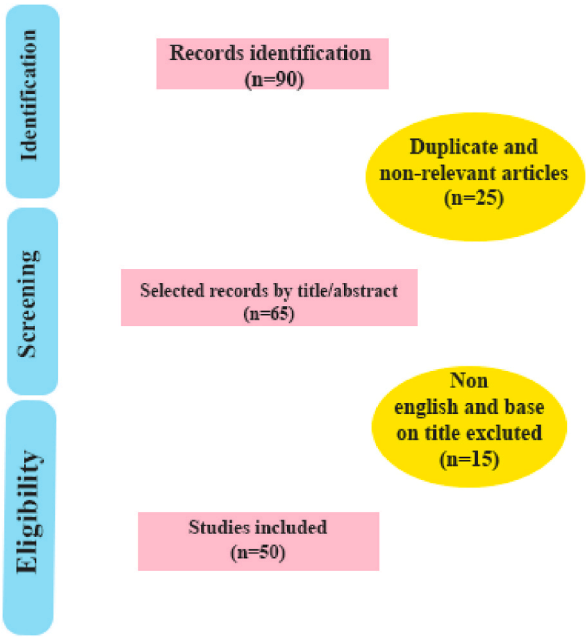

Fig. 3. The diagram of the search strategy.

urine 1–5 h after administration [35].

When this substance was ingested as a nutrition supplement or as part of a diet by people, no adverse effects were reported [30]. An investigation showed that a high dose of ellagitannins (10 g/kg/day), a complex form of EA, has antinutritional effects because it inhibits β-galactosidase and binds to various dietary proteins, fibers, and minerals, perhaps leading to malabsorption [36].

The toxicological effects of this compound have not been thoroughly investigated. The LD_{50} of EA following intraperitoneal injection in rats has been reported to be 630 mg/kg/day. Male rats had no visible alterations in a 90-day subchronic investigation of EA, while female rats had a small drop in body weight. According to this study, the no-observed-adverse-effect level (NOEL) for male rats is 3011 mg/kg/day and 778 mg/kg/day for female rats. Meanwhile, the NOEL for female rats was estimated to be 3254 mg/kg/day [37]. The translation of doses from animals to humans is based on an indirect formula normalized by body surface area (BSA): Human equivalent dose (mg/kg) = animal dose (mg/kg) * (animal Km/human Km), where Km is determined by dividing body weight (kg) by BSA (m2). Thus, 50 mg/kg in mice [28,38–40] whose weight and BSA are 0.02 kg and 0.007 m2, respectively, equates to about 4 mg/kg in a 60 kg adult human with 1.6 m2 BSA [41]. In this regard, for starting a clinical trial in healthy adult volunteers based on animal studies, the human equivalent dose is calculated using the BSA normalization of the safe animal dose [41].

2. Method

Several databases or search engines, including PubMed, Science Direct, Scopus, and Google Scholar, were used in this review. All of the articles have been gathered with no time limit until March 2023. The search items included "metabolic syndrome", "hyperlipidemia", "atherosclerosis", "hypertension", "hyperglycemia", "obesity", "antidiabetic", "anti-hyperlipidemic", "hypoglycemic", and "*ellagic acid*". Duplicate, irrelevant, or written in a language other than English articles were eliminated. We discovered 65 publications in online databases using these search parameters, 15 of which were removed, leaving the remaining 50 articles for the current study (Fig. 3). Additionally, some relevant papers (about EA and an introduction) were added to the previously listed publications.

2.1. The effects of EA on diabetes mellitus

Diabetes is a non-communicable metabolic disease that is spreading rapidly around the world. Diabetes affects over 200 million people and is expected to double by 2030 [42]. Type 1 diabetes, which is an autoimmune disorder characterized by an absolute or nearly total loss of insulin secretion, and diabetes mellitus type 2 (DMT2), which is associated with loss of insulin sensitivity and relative insulin deficiency, have been reported [43]. It has been shown that diabetes increases the risk of hypertension [44], cardiomyopathy [45], nephropathy [46], retinopathy [47], neuropathy [48], and hepatic steatosis [49]. Several investigations indicated that various natural agents, including crocin [50], *Ginkgo biloba* [51], and alpha-mangostin [52], have shown anti-diabetic properties.

In a prior study, EA administration (0.1 % in the diet, p.o.) in mice reduced fasting blood glucose while increasing serum adiponectin. Urolithin A, a microbial metabolite of EA, improved insulin-mediated glucose-lowering effects and lowered blood TG and free fatty acids (FFA) during the intraperitoneal insulin tolerance test in 15–120 min [28]. Guo et al. found that EA (*Lagerstroemia speciosa* leaf extracts contain EA 4 g/day, p.o.) administration in rats reduced antidiabetic effects by regulating fasting blood glucose, body weight, serum biomarkers such as urea, total protein, uric acid, albumin (ALB), TG, and increased final insulin content [53]. It has been shown that insulin receptor substrate protein 1 (IRS1) expression was decreased in rat skin exposed to ultraviolet A (UVA) and ultraviolet B (UVB) irradiation, which was ameliorated with EA (50 mg/kg/day, p.o.) administration [54]. It was also illustrated that EA (50 μM, 24 h) decreased lipid accumulation (lipogenesis) through gene regulation of glucose transporter type (GLUT) 4 and adiponectin. Furthermore, EA inhibits TNF-α, inducible nitric oxide synthase (iNOS), interleukin 6 (IL-6), and monocyte chemoattractant protein-1 in murine 3T3-L1 preadipocytes [55].

Diabetes mellitus is a chronic metabolic disorder characterized by behavioral and psychological symptoms such as anxiety [56], depression [57], tension, and a poor intelligence quotient [47,58]. A previous study found that EA (50 mg/kg/day, p.o.) supplementation ameliorated cognitive deficits in diabetic rats by decreasing blood glucose content, suppressing inflammation status, improving neurotrophic support, and reducing neuronal loss [58].

Another investigation revealed that EA (30 μM, 12 h) upregulated glucose consumption, IRS-1, protein kinase B (Akt), extracellular signal-regulated kinase (ERK) phosphorylation under insulin secretagogues, attenuated reactive oxygen species (ROS), O_2 production, malondialdehyde (MDA) level, and enhanced superoxide dismutase (SOD) function in high glucose-treated HepG2 cells [59]. IRS1 is an important modulator of the insulin receptor tyrosine kinase, which transduces downstream enzymes such as Akt and ERK for hormonal control of metabolism [60]. Moreover, EA ameliorated insulin resistance by increasing miR-223 expression, downregulating of mRNA and protein levels of keap1, and enhancing nuclear factor erythroid 2–related factor 2 (Nrf2), heme oxygenase-1 (HO-1), SOD1, and SOD2 protein levels [59]. Polce et al. found that EA (50 mg/kg, p.o.) treatment significantly reduced insulin resistance by regulating the homeostasis model assessment index of insulin resistance, hepatic lipid accumulation, and oxidative stress by downregulating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunit p47-phox and upregulating Nrf2 in diabetic rats. In addition, EA stimulated the insulin signaling pathway in the hepatic tissue via an increase in Akt phosphorylation [61]. High glucose conditions exhibited exacerbated ROS generation, impairment of endothelium-dependent vasodilation, and endothelial dysfunction, all of which were reduced by EA (20 μM before high glucose condition exposure) treatment by increasing ERK1/2 activation and suppressing NADPH Oxidase 4 (NOX4) expression, which was one of the major sources of vascular ROS in human aortic endothelial cells [62]. Non-obese DMT2 rats received EA (50 mg/kg/day, p.o.), and the results showed a decrease in the fasting blood glucose, increased serum insulin, β-cells size, β-cells number, total antioxidants and glutathione (GSH), diminished liver thiobarbituric acid reactive substances (TBARS), and glucose intolerance in rats [63]. NF-κβ is a nuclear transcription factor that regulates the

expression of several genes that are essential for cellular apoptosis, proliferation, tumorigenesis, inflammation, and various autoimmune diseases [64]. According to *in vitro* and *in vivo* studies, EA induced the nuclear factor erythroid 2-related factor 2 expression and HDL formation. It also inhibited the synthesis of the NF-κβ, TNF-α, MDA, and ROS formation as important biomarkers in inflammation [27,65]. The nuclear factor erythroid 2-related factor 2 protein signaling pathways decrease Bcl-2, NF-κβ, and TNF-α protein signaling pathways, directing damaged cells to apoptosis. It has been observed that oxidative stress and inflammation are risk factors for the initiation of damaging body organs and diseases such as MetS, which EA considerably protects by managing these pathways [66,67].

It has been shown that EA (10 mg/kg/day, p.o.) and repaglinide treatment in DMT2 rats reduced glucose, fructosamine, aldose reductase, TG, TC, FFA, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, ammonia, manganese levels, suppressed serum MDA, TNF-α, IL-6, leptin, resistin, and visfatin contents, and increased GSH, catalase (CAT), SOD, adiponectin, and sRAGE levels. The diabetic group treated with both drugs (EA + repaglinide) presented a highly significant decline in all these parameter levels compared to the diabetic control group or with either treatment alone groups, except for its effect on the aldose reductase enzyme, which was the same as repaglinide. Remarkably, the combined treatment of both EA and repaglinide displayed a more pronounced effect than either treatment alone. Furthermore, EA downregulated the hepatic NF-κβ, cytochrome C, GLUT2, myeloperoxidase (MPO), caspase-3/8, matrix metallopeptidase 9, and hypoxia-inducible factor 1- A levels and upregulated adipo R1, adipo R2, tyrosine kinase, and phosphoinositide 3-kinase levels [68]. A previous study reported that EA (0.2 % and 2 % in the diet) administration to diabetic rats inhibited the glycation-mediated red blood cell-immunoglobulin G cross-links, hemoglobin A1c (HbA1c), and N-carboxymethyl lysine accumulation, which are predominant advanced glycation end products in the diabetic kidney. Moreover, EA diminished urinary ALB and creatinine content, ameliorated renal tissue damage, and suppressed the expression of transforming growth factor-β in glomeruli as an important regulator in advanced diabetic renal disease [69].

The investigation by Goswami et al. [70] indicated that EA (50 mg/kg/day, p.o.) co-administration with sildenafil improved the

Table 1
Summary of the effects of EA on diabetes mellitus.

Dose and duration of EA treatment	Experimental model	Results	References
0.1 % EA in a diet, for 4 days, p.o.	Diabetic male DBA/2J mice	↑ insulin secretion ↓ blood TG and FFA	[28]
Lagerstroemia speciosa leaf extracts contain EA 4 g, for 21 days, p.o.	Diabetic male mice	↓ blood glucose, body weight, body fat ↑ insulin	[53]
50 mg/kg, for 30 days, p.o.	Female Wistar albino rats	↑ IRS1 in rat skin exposed to UVA/B	[54]
50 μM, for 24 h	Murine 3T3-L1 cells	Regulated GLUT4 and adiponectin ↓ TNF-α, iNOS, IL-6	[55]
50 mg/kg, for 8 weeks, p.o.	Diabetic male Wistar rats	↓ cognitive deficits and neuronal loss ↑ neurotrophic support ↓ blood glucose	[58]
30 μM, for 12 h	HepG2 cells	↓ ROS and O_2^{0-} generation and MDA level Improved IR by increasing miR-223 expression level ↑ Nrf2, HO-1, SOD1, and SOD2 protein contents.	[59]
50 mg/kg, for 28 days, p.o.	Goto-Kakizaki female rats	Regulated FBG, ↓ IR lipid accumulation and oxidative stress ↑ insulin signaling pathway in the liver	[61]
20 μM before exposure	Human aortic endothelial cells treated with 30 mM high glucose for 24 h	↓ROS generation and endothelial dysfunction ↑ERK1/2 activation and NOX4 expression	[62]
50 mg/kg, for 28 days, p.o.	Non-obese type 2 diabetic rats	↑ serum insulin, β-cell size, β-cells number ↓ liver TBARS and glucose intolerance in rats	[63]
10 mg/kg, for 14 days, p.o.	Type 2 diabetic male Wistar albino rats	↓ glucose, fructosamine, aldose reductase, TG, TC, FFA, AST, ALT, GGT ↓ the hepatic and pancreatic NF-κB, cytochrome C, GLUT 2, MPO ↑ adipo R1, Adipo R2, tyrosine kinase, and phosphoinositide 3-kinase levels	[68]
0.2 % and 2 % in the diet, for 12 weeks, p.o.	Male Wistar rats	↓ HbA1c and N-carboxymethyl lysine accumulation ↓ urinary ALB and creatinine levels	[69]
50 mg/kg, for 28 days, p.o.	Diabetic male Wistar rats	Improved sexual function of diabetic rats	[70]
50 mg/kg, for 28 days, p.o.	Diabetic male Sprague Dawley rats	↓ Blood glucose levels inflammatory cytokines such as TNF-***α***, IL-6, and MDA ↑ CAT and SOD activities, thin collagen fibers and FGF-2	[71]
50 mg/kg, for 21 days, p.o.	Female Wistar Albino rats	↑Paraoxonase 1, CAT, and TAS levels ↓ TOS, OSI, MDA and NO. ↓ Neural degeneration	[72]
2 % in the diet, for 12 weeks, p.o.	Diabetic Male Balb/c mice	↑ Plasma insulin ↓plasma glucose, TG, MDA, IL-6 and TNF-α content in the heart tissue	[65]
180 mg, for 8 weeks, p.o.	44 patients	↓ BS, IR, HbA1c, TC, TG, MDA and TNF-α ↑ TAC level and activity of GPx, SOD	[74]

sexual function of diabetic rats by regulating blood glucose and ameliorating their sexual behavior. Moreover, diabetic rats were treated with EA (50 mg/kg/day, p.o.) after tooth extraction, and the results revealed that EA improved bone healing and formation, increased fibroblast growth factor-2 (FGF-2) as an important protein in fracture healing, reduced blood glucose levels and inflammation markers such as TNF-α and IL-6 in the serum, enhanced antioxidant parameters (CAT and SOD), decreased MDA, ameliorated insufficient connective tissue, thin collagen fibers, and incomplete or abortive efforts for bone development (osteogenesis), with prominent blood vasculatures and red blood cell extravasations and a smaller amount of osteoblasts [71].

The study by Uzar et al. [72] indicated that significant depletion in paraoxonase 1, CAT, total antioxidant levels, increased total oxidant status, oxidative stress index, MDA, and nitric oxide (NO) in the sciatic nerve tissue and brain of diabetic rats was reversed by EA (50 mg/kg/day, p.o.) treatment. Their findings revealed that diabetic rats' brains had neuronal hydropic changes and disorganized fibrillary degeneration, which was improved by EA administration. ATP-sensitive potassium channels in pancreatic beta cells play an important role in diabetes mellitus by stimulating insulin secretion and serving as a powerful target for the regulation of postprandial glucose levels in the body. The results of molecular docking showed that EA has a high affinity for ATP-sensitive potassium channels as well as common drugs like nateglinide and glimepiride [73]. The investigation by Pei-Chun et al. suggested that EA (2 % in the diet) treatment in diabetic rats reduced body weight loss, enhanced plasma insulin, and diminished plasma glucose and TG levels in cardiac tissue and plasma. Furthermore, they reported that EA increased plasma antithrombin-III and protein C activities and significantly suppressed cardiac levels of MDA, ROS, IL-1β, IL-6, TNF-α, and monocyte chemoattractant protein-1 in the heart tissue of diabetic rats [65]. In a clinical trial study by Ghadimi. et al., it was shown that in patients with DMT2, the prescription of EA (180 mg/kg/day, p.o.) significantly decreased blood glucose, insulin resistance, HbA1c, TC, TG, LDL, HDL, MDA, C-reactive protein, TNF-α, IL-6, and also enhanced total antioxidant capacity (TAC), glutathione peroxidase (GPx), and SOD activities [74].

Inflammation is a consequence of hyperglycemia; it can be diagnosed by the elevation of several inflammatory key factors such as high sensitivity C-reactive protein (hs-CRP), TNF-α, IL-6 and interleukin-18 (IL-18) [75]. Previous research found that EA protects against pancreatic injury in the STZ murine model of T2DM by increasing insulin sensitivity, as well as having an anti-inflammatory effect by suppressing signaling pathways linked with IL-6 and TNF-α [76].

Saheem Ahmad et al. [77] study explored the anti-diabetes and antiglycation properties of EA in both *in vitro* and *in vivo* systems. Interestingly, EA supplementation in diabetic rats reversed the increase in fasting blood sugar (FBS) and HbA1c levels. EA administration also exhibited an inhibitory role against glycation intermediates, including dicarbonyls, as well as AGEs. Additionally, EA treatment suppressed LPO and conjugated dienes (CD). Furthermore, EA demonstrated an antioxidant capacity by raising plasma GSH levels and facilitating the reduction of histological alterations in animal kidney tissues [77].

Another study indicated that the supplementation of BC2000 with EA in mice enhanced EA-transforming potential and induced the activation of the hepatic autophagy pathway [78]. In addition, BC2000+EA regulated the insulin-signaling pathway (P13K/AKT/mTOR), which plays an extremely important role in cellular autophagy and metabolic processes, thereby slowing down the prevention of high-fat-induced insulin resistance in mice. Furthermore, BC2000 and EA significantly regulated liver pathways of fatty acid metabolism, cholesterol metabolism, bile acid metabolism, retinol metabolism, and PPAR signaling, thereby assisting EA in playing a role in the prevention of insulin resistance due to high-fat diets [78].

In summary, these findings show that EA is a powerful regulator of fasting blood glucose, increasing insulin secretion and RS1 expression, regulating GLUT4 gene expression, and suppressing lipid accumulation and inflammation in adipose tissue (Table 1). According to these studies, the effective dose of EA for treating diabetes in most *in vivo* studies could be 50–200 mg/kg/day p.o [54,58,59]. However, more research is required in both *in vivo* and *in vitro* investigations, as well as clinical trials, to verify these findings.

2.2. The effects of EA on blood pressure and the cardiovascular system

Hypertension (high blood pressure) is a common cause of morbidity and mortality and increases the risk factor for cardiovascular diseases, including stroke and coronary artery diseases [79]. Hypertension is the main reason for chronic renal failure, peripheral vascular disease, cognitive dysfunction, and premature death [80]. A previous study reported that the redox imbalance accounts for cardiovascular diseases through ROS generation, which leads to a decrease in NO bioavailability, inflammation, and imbalance in salt and water homeostasis, and disturbances of the renin-angiotensin-aldosterone system [81].

EA (30 mg/kg/day, p.o.) treatment restored blood levels of nitrate/nitrite, ameliorated vascular reductions to acetylcholine and sodium nitroprusside, contraction to phenylephrine, decreased alkaline phosphatase activity, aortic wall thickening, calcification, and improved heart and kidney weight in hypertensive rats [82]. A previous study indicated that EA (50 mg/kg/day, p.o.) attenuated the right ventricle systolic pressure, the right ventricular hypertrophy, and the wall thickness/external diameter ratio of the lung arteries, which were induced by monocrotaline in rats. Also, EA treatment decreased oxidative stress, caspase-1, NLR family pyrin domain containing 3 (NLRP3) as a key activator of IL-1β which has a critical role in inflammation in the pulmonary tissue, suppressing the brain natriuretic peptide level and inflammatory markers in serum [83]. Both cardiac arrest and global cerebral ischemia contributed to an increase in heart rate. The possibility of cardiac arrest or global cerebral ischemia as a possible cause of decreased parasympathetic cardiac regulation increased sympathetic activity, or intrinsic heart rate should be considered as a different reason for the raised heart rate [84]. It has been shown that in ischemic rats, the blood pressure, the voltage of QRS and the PR interval were significantly reduced and electrocardiogram waves impaired, whereas EA (100 mg/kg/day, p.o.) pretreatment prevented these alterations, ameliorated cardiovascular hemodynamic factors such as blood pressure and heart rate, and diminished MDA enzyme in serum [85]. Moreover, it was shown that co-administration of EA (15 mg/kg/day, p.o.) with L-N^G-Nitro arginine methyl ester in rats improved the reduced high systolic blood pressure and heart rate, upregulated endothelial nitric oxide synthase (eNOS) protein production, attenuated oxidative stress, plasma MDA content, NADPH oxidase subunit p^{47}phox expression, and increased plasma

nitrate/nitrite levels [86].

High-carbohydrate, high-fat diet-fed rats showed cardiovascular remodeling, ventricular dysfunction, reduced glucose tolerance, and non-alcoholic fatty liver disease with an elevation of NF-κB protein levels and a decline in protein levels of Nrf2 and carnitine palmitoyltransferase 1A in the heart and the liver, which all these changes reversed with EA (800 mg/kg/day, p.o.) administration [8].

Isoproterenol-treated rats showed arrhythmias, hypertrophy, elevated myoglobin levels, creatine kinase-MB, lipid peroxidation, ventricular hypertrophy, and myocardial necrosis, which were ameliorated with EA (15 mg/kg/day, p.o.) supplementation [87]. A former study demonstrated that pretreatment of the human endothelial cell line with EA inhibited NADPH oxidase, suppressed the release of NO by iNOS down-regulating, increased cellular antioxidant defenses, and attenuated oxidatively modified low-density lipoprotein-induced lectin-like oxidized up-regulation of LDL receptor 1 and eNOS down-regulation. Thus, it was suggested that the EA (20 μM, 2 h before exposure) prescription can act as a potent compound for preventing atherosclerosis through underlying mechanisms [88] (Table 2).

In conclusion, these studies suggest that EA with a dose of 50 mg/kg/day p.o. for *in vivo* treatment could be useful in the treatment of high blood pressure [79,82,85]. It modulates the circulatory system by relaxing blood vessels, acting as an antioxidant, and producing NO, but more reliable research is needed to improve our understanding of EA's role in the prevention and treatment of cardiovascular diseases.

2.3. The effects of EA on obesity and hyperlipidemia

Nowadays, the use of herbal medicines has become popular besides chemical synthetic drugs for the treatment of a variety of diseases such as diabetes [89], hypertriglyceridemia [90], and hypertension [91]. Excessive body weight, or obesity, is a known global public health issue, and during the past 30 years, it has increased steadily worldwide and the world health organization (WHO) investigation in 2015 indicated there were over 1 billion overweight people around the world [92]. According to the WHO investigations, obesity is one of the most common risk factors for cardiovascular diseases, cerebral ischemia, DMT2, and reproductive disorders for both men and women through various metabolic pathways and their complications, such as elevated blood pressure, plasma glucose, and dyslipidemia [93,94].

A study found that EA (4 mg/kg/day, p.o.) reduced TC in the liver and serum, enhanced hepatic 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) and cholesteryl ester transfer protein activities, and decreased hepatic lecithin cholesterol acyltransferase. EA inhibited HMG-CoA reductase activity by phosphorylating AMP-activated protein kinase, reduced the activation and nuclear translocation of sterol regulatory element-binding protein-2, a key transcription factor in cholesterol biosynthesis, and significantly reduced serum AST and ALT levels [95]. Overweight, elevated glucose levels and white adipocyte hypertrophy were observed in high-fat diet rats, which were alleviated by EA (10 mg/kg/day, p.o.) treatment. EA supplementation attenuated serum resistin levels, mRNA expression of Zfp423 and aldehyde dehydrogenase 1 family member A1 (ALDH1A1) as critical factors for white adipose tissue plasticity, ameliorated liver steatosis and serum lipid profile, and also upregulated brown adipocyte markers including uncoupling protein 1, PRDM16, cell death-inducing DNA fragmentation factor-like effector A (CideA), PPARγ coactivator 1-α, and PPARα [96]. In another study, EA (88 mg/kg/day, p.o.) treatment in hamsters enhanced the expression of liver X receptor, peroxisome proliferator-activated receptor alpha (PPARα), PPARγ, and their downstream gene adenosine triphosphate-binding cassette transporter A1, with no effect on retinoid X receptor, and enhanced TC elimination by increasing fecal bile acid and up-regulation of the two pathways, LXR/PPAR-ABCA. Furthermore, EA suppressed TG, TC, and LDL and enhanced plasma HDL concentration [97]. An earlier study found that isoproterenol raised TG, LDL, VLDL, FFA, phospholipids, and HMG-CoA reductase function in rats while decreasing HDL levels, which were reversed by EA (15 mg/kg/day, p.o.) supplementation [29]. It has been shown that EA (25 mg/kg/day, p.o.) and coenzyme Q10

Table 2
Summary of the effects of EA on the cardiovascular system.

Dose and duration of EA treatment	Experimental model	Results	References
30 mg/kg, for 6 weeks, p.o.	Male Wistar rats	↑ Blood levels of nitrate/nitrite, ↑ vascular relaxations ↓ BP, ALP activity, aortic wall thickening, and calcification	[21]
50 mg/kg, for 4 weeks, p.o.	Male Sprague-Dawley rats	Improved ventricular hypertrophy and the wall thickness/external diameter ratio of the pulmonary arteries	[83]
100 mg/kg, for 1 week, p.o.	Male Wistar rats	Regulated BP, the voltage of QRS and PR interval, and improved ECG waves	[85]
15 mg/kg, for 7 days, p.o.	Male Sprague-Dawley rats	↓ high SBP and HR ↑ eNOS ↓ oxidative stress, plasma MDA content, and NADPH oxidase	[86]
800 mg/kg, for 8 weeks, p.o.	High-carbohydrate, high-fat diet-fed male Wistar rats	↓ cardiovascular remodeling, ventricular dysfunction, NF-κB and glucose intolerance ↑ levels of Nrf2 and carnitine palmitoyltransferase 1A in the liver and heart	[8]
15 mg/kg, for 10 days, p.o.	Male albino Wistar rats	↓ arrhythmias, hypertrophy ↑ levels of myoglobin, creatine kinase-MB	[88]

ALP: alkaline phosphatase; BP: Blood pressure; ECG: electrocardiogram; eNOS: Endothelial nitric oxide synthase; iNOS: Inducible nitric oxide synthase; HR: Heart rate; MDA: Malondialdehyde; NADPH: Nicotinamide adenine dinucleotide phosphate; NO: Nitric oxide; SBP: systolic blood pressure.

co-treatment prevented high-fat diet-induced hyperlipidemia in rats by decreasing levels of plasma glucose, TC, LDL, TG, and enhanced HDL content [2]. Furthermore, EA (1 % in the diet) administration in rabbits with high-fat diet intake prevented the elevation of LDL, TG, TC, and TBARS, free-radical scavenging activities, reduced LDL oxidation, and significantly declined the amount of 8-hydroxy-2′-deoxyguanosine production in the aorta [98]. It has been shown that EA (0.1 % in the diet, p.o.) supplementation diminished serum resistin and ameliorated liver steatosis and serum lipid profile in mice with a high-fat diet. Moreover, EA upregulated mRNA expression of apolipoprotein A–I (ApoA1), low-density lipoprotein receptor (LDLR), carnitine palmitoyltransferase 1A, and PPARα genes in the liver, which have an important role in fatty acid β-oxidation [99].

EA has been reported to affect cellular lipid metabolism during benzoyl peroxidation. Furthermore, EA significantly prevents lipid peroxidation, which leads to the inhibition of membrane damage and the release of FFA from the membrane [100]. Because FFA is a substrate for other lipids, its decrease may have an impact on their levels. EA has been demonstrated to have some preventive benefits against LDL oxidation in previous studies [64,98]. However, the precise mechanism of EA on other lipid levels is unknown; however, it can be expected that EA may decrease the activity of β-Hydroxy β-methylglutaryl-CoA reductase or increase the rate of the lipid degradative process, thereby increasing hepatic bile acids and fecal neutral sterol and thus decreasing the levels of other lipids [101].

EA and *Weizmannia coagulans* BC2000 supplementation prevented HFD-induced hypercholesterolemia and promoted fecal cholesterol excretion. Transcriptome analysis indicated that primary bile acid biosynthesis in the liver was meaningfully activated by EA and *W. coagulans* BC2000 treatments [102]. EA and *W. coagulans* BC2000 treatment also obviously increased the intestinal *Eggerthellaceae* abundance and the liver EA metabolites, iso-urolithin A, Urolithin A, and Urolithin B. Furthermore, *W. coagulans* BC2000 administration promoted the intestinal transformation of EA, which led to the upregulation of liver bile synthesis, thus preventing hypercholesterolemia [102].

A clinical trial investigation disclosed that EA (50 mg/kg/day, p.o.) administration in middle-aged overweight males improved the levels of blood lipid metabolism, declined TC, TG, LDL, increased HDL, and also attenuated saliva cortisol levels [103] (Table 3). Hence, these findings support the fact that EA is a bioactive compound that can be used as an alternative agent to regulate blood TC, TG, LDL, HDL, and hepatic steatosis, but more *in vivo* research and clinical trials are needed to understand the mechanisms involved. According to the *in vivo* findings, the most effective dose of EA for treating obesity could be 30–50 mg/kg/day p.o [97,103].

Overall, more randomized clinical trials are needed to confirm the effects and probable side effects of EA. To the best of our knowledge, there are limited clinical trials in this area, and more research projects should be conducted to reveal more about these mechanisms in humans to link the bench to the bed of the patient.

2.4. Molecular target of EA in MetS

EA has significant effects on multiple pathways, including: (i) activation of the antioxidant response through Nrf2, inhibition of NF-kB downstream, regulation of the insulin-signaling pathway (P13K/AKT/mTOR), IRS1 expression, modulation of several cell survival/cell-cycle genes, including Bcl-2 and Bax, regulation of kinases such as MAPK and PI3–K (99–101). EA has inhibitory effects on α-glucosidase, α-amylase, and angiotensin I-converting enzyme, the suppressed concentration of glucose in plasma, along with insulin, HbA1c, and hexokinase activity, and simultaneously diminished glycogen (liver and muscle), while enhancing glucose-6-phosphatase and fructose-1,6-bisphosphatase activity in the liver and kidney, all in diabetic rats (102, 103).

EA also could inhibit inflammatory cytokines, and adipokines in serum and tissues (liver, pancreas, adipose tissue, and brain) while improving insulin signaling, adiponectin receptors, glucose transporters, and inflammatory mediators (104). A previous study also indicated that EA decreased oxidized LDL uptake and cholesterol influx while suppressing both scavenger receptor class B type 1 (SRB1) induction and foam cell formation in murine oxidized-LDL-stimulated macrophages, enhanced expression of PPARγ and ABCA1, all of which are for cholesterol modulation (105).

Table 3
Summary of the effects of EA on obesity and dyslipidemia.

Dose and duration of EA treatment	Experimental model	Results	References
10 mg/kg, for 24 weeks, p.o.	Male Sprague-Dawley rats with a high-fat diet	↓ serum resistin levels, mRNA expression of Zfp423 and ALDH1A1 ↓ hepatic steatosis and serum lipid profile	[96]
15 mg/kg, for 12 days, p.o.	Male albino Wistar rats	↓ TG, LDL, VLDL, free fatty acid ↑ HDL	[29]
0.1 % in the diet, for 68 days, p.o.	KK-A^y mouse	↓ serum resistin and hepatic steatosis ↑ ApoA1, LDLR, carnitine palmitoyltransferase 1A, and PPARα genes in the liver	[99]
25 mg/kg, for 2 weeks, p.o.	Male Sprague–Dawley rats	↓ TC, LDL, TG ↑ HDL	[2]
1 % in the diet, for 8 weeks, p.o.	New Zealand white rabbits	↓ TG, TC, LDL, TBARS, free-radical, and 8-hydroxy-2′-deoxyguanosine production	[98]

ALDH1A1: Aldehyde dehydrogenase 1 family member A1; ALT: Alanine transaminase; ApoA1: Apolipoprotein A1; AST: aspartate transaminase; HDL: High-density lipoprotein; HDL-C: HDL cholesterol; LDL: low-density lipoprotein; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-CoA; mRNA: messenger ribonucleic acid; PPARα: peroxisome proliferator-activated receptor-α; PPARγ: peroxisome proliferator-activated receptor-γ; TBARs: Thiobarbituric acid reactive substances; TC: total cholesterol; TG: Triglyceride; VLDL; Very low-density lipoprotein.

2.5. Antioxidant properties of EA

EA has important antioxidant properties, that have been attributed to its free radical scavenging activity, like the essential vitamins. It has been indicated that EA has scavenging activity against a variety of ROS formations. The four hydroxyl and two lactone functional groups act respectively as hydrogen bond acceptors and donors, enabling EA to scavenge $O_2^{\bullet-}$, $HO^{\bullet}$, H_2O_2 and $ONOO^{\bullet}$ [104]. Furthermore, EA showed an indirect protective effect against oxidative stress through the expression of Nrf2 and the downregulation of Kelch-like ECH-associated protein 1 (Keap1), which plays an important role as a detoxifying enzyme in the induction of phase I and phase II metabolism [105].

Previous investigations reported that lactone groups in the EA molecule are the portions essential for the activation of phase II enzymes, but it has not been determined if EA could induce Nrf2 phosphorylation via upstream kinases PI3K/Akt and MAPK. Low contents of ROS or electrophiles induce the oxidation or covalent alteration of cysteine residues contained in Keap1, reducing its affinity to Nrf2 and releasing it for nuclear translocation [106,107]. Whereas, Nrf2 activation is due to its release from inhibitors and phosphorylation at Ser-40 by kinases such as extracellular-signal-regulated kinases (ERK), protein kinase C (PKC), and PI3–K; in addition, EA upregulates NADPH: quinone oxidoreductase 1 (NQO1), HO-1, SOD, CAT, GPx, and GST [108].

3. Conclusion

This review explains the potential pharmacological effects of EA for the treatment of MetS-related diseases. EA is beneficial for lowering TC, TG, LDL, and inflammation, and increasing HDL and bile acid secretion. Furthermore, EA demonstrates beneficial effects in the treatment of hypertension, diabetes, and obesity via underlying mechanisms such as decreasing blood glucose and pressure, increasing NO in the blood vessels, improving pancreatic insulin secretion, and decreasing inflammatory cytokines in the body that cause cardiovascular diseases. Although herbal medicines and natural compounds are thought to be safe due to a lack of evidence for adverse effects, there are many medicinal plants with serious side effects, therefore, more research is needed to gain a better understanding of EA properties and mechanisms on the MetS, particularly in humans (Fig. 4).

Declarations

Ethical approval

Not applicable.

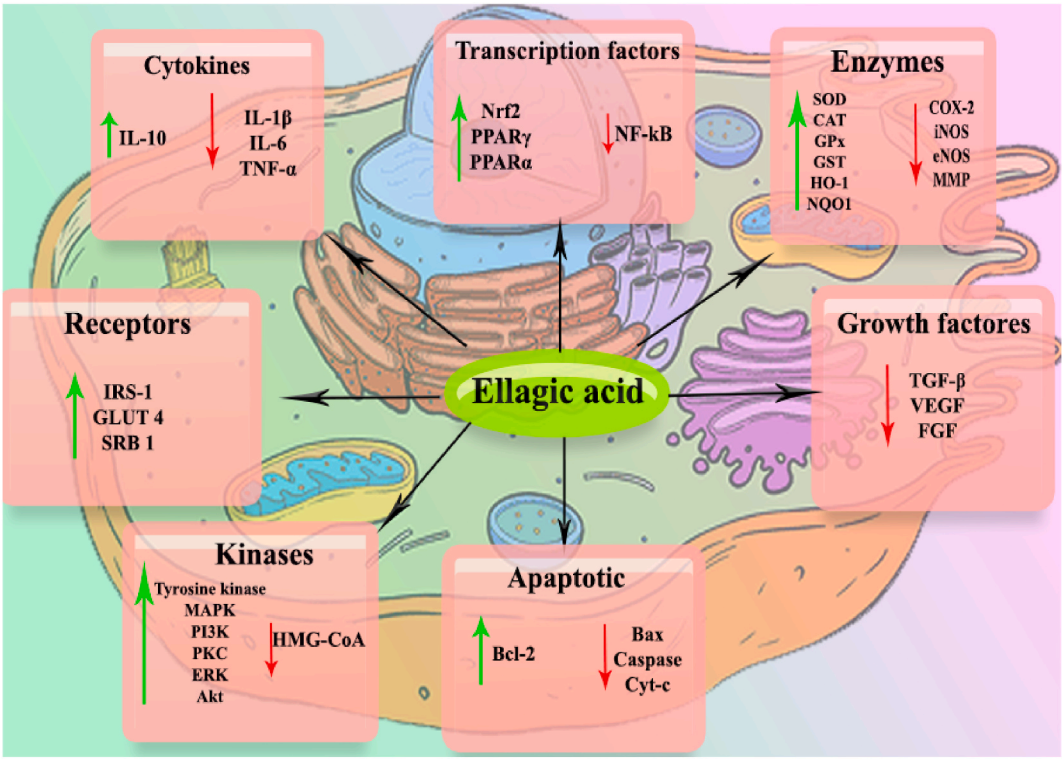

Fig. 4. Ellagic acid upregulates (↑) or downregulates (↓) several molecular targets in Metabolic Syndrome.

3.1. Competing interests

The authors declare no competing interests.

3.2. Consent to participate

Not applicable.

3.3. Consent to publish

Yes.

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No datasets were generated or analyzed during the current study.

ALB: Albumin; ALT: Alanine transaminase; ApoA1: Apolipoprotein A1; AST: aspartate transaminase; CAT: Catalase; ERK: Extracellular signal-regulated kinase; FBG: Fasting blood glucose; FFA: Free fatty acids; FGF-2: Fibroblast growth factor-2; GGT: gamma-glutamyl transferase; GLUT2: glucose transporter 2; GLUT4: Glucose transporter type 4; GPx: Glutathione peroxidase; HbA1c: hemoglobin A1c; IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; iNOS: Inducible nitric oxide synthase; IRS1: Insulin receptor substrate protein 1; LDLR: Low density lipoprotein receptor; MDA: Malondialdehyde; MPO: Myeloperoxidase; NF-κβ: nuclear factor-kappa β; NO: Nitric oxide; NOX4: NADPH Oxidase 4; Nrf2: Nuclear factor erythroid 2–related factor 2; OSI: Oxidative stress index; PPARα: peroxisome proliferator-activated receptor-α; ROS: reactive oxygen species; SOD: Superoxide dismutase; TAC: Total antioxidant capacity; TAS: Total antioxidant status; TBARS: Thiobarbituric acid reactive substances; TC: total cholesterol; TG: Triglyceride; TNF-α: Tumor necrosis factor-alpha; TOS: Total oxidant status; UVA: Ultraviolet A; UVB: Ultraviolet B.

CRediT authorship contribution statement

Karim Naraki: Data curation, Writing – original draft. **Mahboobeh Ghasemzadeh Rahbardar:** Data curation, Writing – original draft. **Basiru Olaitan Ajiboye:** Supervision, Writing – review & editing. **Hossein Hosseinzadeh:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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