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Review Article

The improvement effect of ellagic acid and urolithins on metabolic diseases: Pharmacology and mechanism

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Abstract: Epidemiological studies have demonstrated that a range of metabolic diseases, particularly type 2 diabetes and obesity, have reached epidemic proportions. These chronic conditions not only diminish the equality of life for individuals but also impose significant financial burdens on families and healthcare systems. While various therapeutic medications can effectively manage the progression of these diseases, they often come with adverse side effects. In contrast, natural products and their metabolites, such as ellagic acid (EA) and urolithins derived from a variety of plant species, have gained attention for their wide-ranging biological activities, diverse classes, and minimal side effects. Emerging research suggests that EA and urolithins may offer promising therapeutic effects in the treatment of metabolic disorders. This review aims to provide a comprehensive overview of the therapeutic effects and associated signaling pathways of EA and its metabolite urolithins in various metabolic diseases, offering valuable insights for their clinical applications and the potential development of novel food and medicine homologous therapies.

Keywords: ellagic acid; urolithins; metabolic diseases; therapeutic effects

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1 Introduction

Metabolic diseases (MDs) encompass a range of health conditions such as type 2 diabetes mellitus (T2DM), obesity, atherosclerosis (AS), hyperuricemia, hypertension, and metabolic dysfunction-associated steatotic liver disease (MASLD), which have emerged as significant public health concerns[1]. In addition, metabolic syndrome means that the occurrence conditions of multiple diseases in MDs are interrelated and have the same mechanism and pathway of action, so metabolic syndrome can enhance the risk of metabolic diseases[2]. T2DM, the most prevalent chronic metabolic disease, is primarily attributed to insulin resistance. This resistance is often accompanied by various symptoms including hyperinsulinemia, dyslipidemia leading to atherosclerosis, hypertension, and hyperuricemia[3]. In 2017, there were 451 million individuals diagnosed with diabetes globally (aged 18-99), with a projected rise to 693 million by 2045[4]. The numerous complications associated with T2DM contribute to high mortality and disability rates, placing substantial economic burdens on families and healthcare systems[5,6]. Excessive energy intake leading to lipid accumulation is the primary cause of obesity[7] which also acts as a risk factor for various chronic metabolic diseases including T2DM, AS, hypertension, and MASLD[8-11]. Additionally, both T2DM and obesity contribute to the development of hyperuricemia, with excessive consumption of high-purine foods being another significant factor[12]. Given the interrelated nature of these chronic metabolic diseases, tailored treatment approaches are essential for effective management.

Various treatment methods are available for metabolic diseases with lifestyle changes and exercise being the primary focus for early-stage patients[13]. As the diseases progress, medications such as metformin[14], statins[15], and SGLT2 inhibitors[16] may become necessary, despite the potential side effects like lactic acidosis, blood sugar disorders, ketoacidosis, and urinary tract infections[17-20]. Phytochemicals and functional foods have gained attention for their diverse biological activities and minimal side effects[21,22], particularly in the context of metabolic diseases[23-25]. In this regard, dietary polyphenols interventions are gradually being recognized as relatively safe and effective strategy for preventing metabolic diseases. Ellagic acid (EA) is a polyphenolic compound found in pomegranates, blueberries, walnuts, tea leaves, grapes, chestnuts, and some edible fungi[26-28], has garnered increasing

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attention in recent years for its favorable effects in ameliorating and preventing various metabolic disorders. As a naturally occurring compound, EA exhibits pleiotropic effects by targeting multiple pathways, thereby conferring significant therapeutic potential through its anti-oxidant[29], anti-inflammatory[30], anti-cancer, anti-angiogenic, anti-obesity, and anti-atherogenic properties[31-34]. Foods rich in EA have shown promising effects in lowering blood glucose and lipid levels, preventing AS, and reducing uric acid levels[35-37]. However, most dietary polyphenols remain unabsorbed in the small intestine, they may accumulate in the large intestine and be metabolized into low-molecular-weight phenolic metabolites, which can be easily absorbed and benefit host health[28]. Urolithin, an intestinal metabolite of EA[38], also exhibit similar biological activities[39,40]. Although it has been shown that EA can improve various diseases by affecting the composition of intestinal flora or the receptors of intestinal cells, the low bioavailability of EA makes it difficult to enter the blood, so that it can improve diseases by targeting various organs. Urolithins, as an intestinal metabolite of EA, has been shown by multiple studies to be a key agent of EA's role in the body[41]. Therefore, many studies take urolithins as the main research object, but the key role of EA in the regulation of intestinal flora cannot be ignored[42].

The purpose of this review is to systematically analyze research articles on the effects and mechanism of EA and its metabolite urolithins on metabolic diseases, providing a basis for their subsequent clinical application.

2 Sources, metabolism and biological characteristics of Ellagic acid

EA was first discovered in the gallnut by Chevreul and described by Braconnot in 1818[43]. EA is a polyphenolic compound primarily derived from the hydrolysis of ellagitannins. It is found abundantly in various natural plants, particularly in the berries of the family Rosaceae, such as cloudberries, blueberries, raspberries and strawberries[44], EA is also present in pomegranates, *Vaccinium spp.*, *Rubus idaeus* L., *Fragaria* × *ananassa* Duch., *Rubus fruticosus* Pollich, tea, walnuts and several other tree species (summarized in Table1).

Table 1 Contents of EA in nuts, fruits, tea, tree and vegetable

	Plant species	Part	EA content (mg /kg)	Ref.
Nuts	*Carya illinoinensis* (Wangenh.) K. Koch	Meat	330 [a]	[45]
	Vigna angularis (Willd.) Ohwi & H. Ohashi	Adzuki bean	89.6 [a]	[46]
	Vigna unguiculata (L.) Walp.	Mottled cowpea	181 [a]	[46]
	Phaseolus vulgaris L.	Speckled kidney bean	95.8-183 [a]	[46]
	Pisum sativum L.	Green pea	96.8 [a]	[46]
	Glycine max (L.)Merr.	Black soy bean	456 [a]	[46]
	Glycine max (L.) Merr.	Yellow soy bean	489 [a]	[46]
	Juglans nigra Linn.	meat	590 [b]	[45]
Fruits	*Myrciaria dubia* (H.B.K.) McVaugh	Pulp	258.5 [a]	[47]
		Flours	5,657 [a]	[47]
	Punica granatum L.	Arils	700 [a]	[48]
		Mesocarp	38,700 [a]	[48]
		Peels	5,150±190 [a]	[49]
		Seed coat	14,430±210 [a]	[50]
	Rosa L. species	Rosehip	1,096 [b]	[51]
	Arctic bramble (arctic raspberry)	Berries	3,900 [b]	[52]
	Rubus chamaemorus L.	Berries	3,151 [b]	[51]
	Rubus idaeus L.	Red raspberries	10 [b]	[53]
		Rasp berry	1,500-3,309 [b]	[51]
		Boysen berry	1,684-4,960 [a]	[54, 55]
	Rubus ursinus	Blackberry	1,500 [a]	[45]
	Terminalia Ferdinandiana	Kakadu plum	8,796 [a]	[54, 56] [57]
	Vaccinium macrocarpon Ait.	Cranberry	120 [a]	[45]
	Muscadinia rotundifolia (Michx.)	Fruit	360-912 [b]	[58, 59]
	Castanea sativa Mill.	Leaf	340-500 [a]	[59]
		Bur	1,410-3,210 [a]	[59]
		Outer shell	240-900 [a]	[59]
		Inner shell	800-1,370 [a]	[59]
	Fragaria × *ananassa* Duch.	Fruit	48-55 [a]	[60]
	Hippophae rhamnoides L.	Fruit	10 [b]	[45]
	Caryocar brasiliense Cambess.	Peel flours	5,094.7-16,306.6 [a]	[61]
	Cucurbita pepo L.	Fruit	10.28-36.66 [b]	[62]
	Dimocarpus longan Lour.	Seed	8,130-1,2650 [a]	[63]

(Continued)

	Plant species	Part	EA content (mg /kg)	Ref.
	Vitis rotundifolia Michx.	Peel flours	8-162 [b]	[64]
Tea	*Camellia taliensis* (W. W. Sm.) Melch.	Leaf	15-446 [a]	[65]
Tree	*Alternanthera sessilis* (L.) R. Br. Ex DC.	Plant material	30,072.6 [a]	[66]
	Alnus cremastogyne Burkill.	Acorns	15,931.3-21,719 [a]	[67]
	Eucalyptus globulus Labill.	Fruit	-	[68]
	Rhus chinensis Mill.	Gall	-	[69]
	Trapa natans L.	Pericarp	-	[70]
Vegetable	*Geum japonicum* Thunb.	Whole plants	3,064.1-4,026.6 [a]	[71]
	Amaranthus tricolor L.	Leaf	1.24-6.23 [b]	[72]

a represents dry weight, b represents fresh weight.

Due to its polyhydroxy structure, EA is highly hydrophobic and has low bioavailability. Upon ingestion, ellagitannins are hydrolyzed into EA in the stomach, with only a small portion being absorbed in the stomach and intestines. The majority of EA reaches the colon, where it is metabolized by the colonic microbiota into urolithins, primarily urolithin A (UA) and urolithin B (UB) (Fig. 1)[73]. The *in vivo* metabolism of EA primarily involves microbial reduction of one lactone ring to an open chain carboxyl group in the colon, followed by varying degrees and positions of dihydroxylation, yielding different metabolites collectively known as urolithins (Fig. 1).

The metabolic pathway of EA begins with the loss of a lactone ring, leading to the formation of Uro-M5. Subsequent dehydroxylation of Uro-M5 results in the production oftetrahydroxy urolitin isomers, such as Uro-M6R, Uro-M6, Uro-E and Uro-D, which were respectively removed from the hydroxyl group at positions 3, 4, 9 and 10. Further dehydroxylation of these tetrahydroxy urolitin isomers yields trihydroxy urolitin isomer, with specific hydroxyl groups removed based on the isomer. For instance, Uro-D loses its fourth hydroxyl, while Uro-M loses its tenth hydroxyl. Uro-M6 and lose its nineth and fourth hydroxyl and Uro-E lose its fourth hydroxyl, and Uro-M7R loses its nineth and tenth hydroxyl after d dihydroxylation. A single dehydroxylation of the trihydroxyurolitin isomer results in the formation of Uro-C and Uro-A. Meanwhile, Uro-M7 and Uro-CR produce Uro-AR after the removal of the hydroxyl group at positions 10 and 9, respectively. Additionally, Uro-A forms the monohydroxy urolitin isomer Uro-B by losing its nineth hydroxyl group, and may also produce Uro-B by losing the eighth hydroxyl group (Fig. 1).

Previous studies have shown that EA possesses a range of biological activities, including lowering blood glucose, reducing blood lipids and blood pressure, and exhibiting anti-inflammatory effects. Its metabolite, urolithins, also exhibits various biological effects, which are associated with the development of metabolic diseases. This connection underscores the need for further investigation into EA's bio-pharmacological potential for treating such conditions. A multitude of studies have underscored the positive influence of EA on metabolic disorders. This review provides a comprehensive overview of EA's therapeutic effects and the underlying molecular mechanisms, with a focus on its potential role in managing T2DM, obesity, atherosclerosis, non-alcoholic fatty liver disease, hypertension, and hyperuricemia.

3 The effects of ellagic acid on type 2 diabetes mellitus and its mechanism

T2DM is a widespread chronic metabolic disease characterized by insulin resistance (IR) and dysfunction pancreatic β cell. Obesity is the most significant risk factor for T2DM and is closely

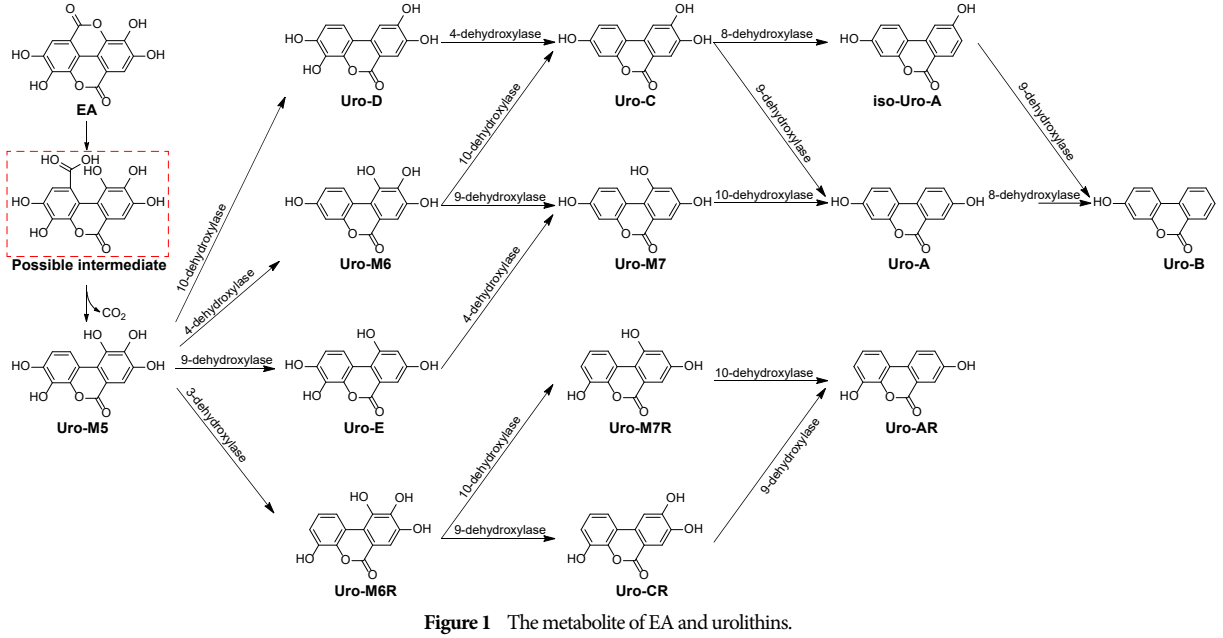

Figure 1 The metabolite of EA and urolithins.

linked to IR[74]. The impairment of insulin action and secretion leads to elevated blood glucose levels[75]. Previous study has indicated that phosphoinositide 3 -kinase (PI3K)/protein kinase B (PKB) signaling pathway enhanced the insulin action[76], while AMP -activated protein kinase (AMPK) pathway regulated β cell dysfunction[77].

Pomegranates, which are rich in polyphenols, have been shown to reduce high blood sugar levels[78] and improve insulin resistance[79]. Similarly, tea, also high in polyphenols, has demonstrated the ability to lower blood glucose levels and increase insulin sensitivity[80,81]. Both tea and pomegranate polyphenols contain significant amounts of tannic acid[26,82], which is believed to be instrumental in their anti-diabetic effects. Tannic acid is thought to contributes to these effects by promoting glucose uptake, improving insulin resistance, reducing oxidative stress, and regulating gut microbiota (Fig. 2).

3.1 Ellagic acid and urolithins promote glucose uptake and insulin secretion

Studies have shown that treatment with EA extract can decrease fasting blood glucose levels and stimulate the regeneration of insulin-producing β cells by inhibiting the expression of inflammatory proteins such as IL-6 and TNF-α[83]. Initial research suggests that EA not only exhibits hypoglycemic effects but also, when combined with sinapic acid (SA), can enhances these effects in diabetic rats, leading to a significant increase insulin expression in rat β cells compared to the control group[84]. Given EA's limited absorption rate, a study has utilized nanomaterials to enhance its oral bioavailability and biocompatibility by combining Ella nanoparticles (Ella NPs) with metformin. The group treated with Ella NPs exhibited superior outcomes in reducing blood glucose and lipid levels, along with a more pronounced improvement in the quantity and function of pancreatic β cells[85]. These findings clearly demonstrate the beneficial effects of EA in lowering blood glucose levels and enhancing insulin secretion.

Urolithin, a gut metabolite of EA, is believed to play a crucial role in EA's beneficial effects on blood glucose levels and insulin secretion. Urolithin C has been shown to enhance insulin secretion in a glucose-dependent manner by activating ERK pathway in pancreatic β cells[86]. Urolithin A has been shown to improve insulin sensitivity by enhancing mitochondrial function and biogenesis, and by activating autophagy, which protects pancreatic β cells and promotes insulin secretion[87,88]. Additionally, Urolithin A can increase glucose uptake in L6 myotube cells through the PI3K/AKT and AMPK signaling pathways, potentially improving impaired glucose tolerance in diabetic mice[89].

3.2 Ellagic acid and urolithins improve insulin resistance

Insulin resistance is pivotal in managing T2DM. EA has demonstrated the ability to mitigate oxidative stress and improve insulin resistance in HepG2 cells under high glucose conditions via the KEAP1-Nrf2 pathway through miR-223[29]. In T2DM patients, oxidative stress and insulin resistance are often associated with MASLD. EA treatment has been shown to activate insulin signaling in the liver, enhancing hepatic insulin sensitivity in T2DM rats, reducing HIF-α levels, upregulating NRF2, and lowering blood glucose levels, effectively combating MASLD[90]. EA's beneficial effects extend to gestational diabetes mellitus, where it has been shown promise in improving insulin resistance in T2DM[35]. Both EA and the microbial metabolite urolithin A have been shown to improve insulin resistance caused by high-fat, high-sucrose diets, primarily through enhancing mitochondrial metabolism in muscle and liver tissues[91].

3.3 Ellagic acid and urolithins inhibit inflammation and oxidative stress

Inflammation is a significant contributor to T2DM development by inducing insulin resistance, highlighting the importance of targeting inflammation pathways for diabetes prevention and management[92,93]. Biomarkers of inflammation are crucial for assessing diabetes progression and complications[94]. Reactive oxygen species (ROS) production during oxidative stress

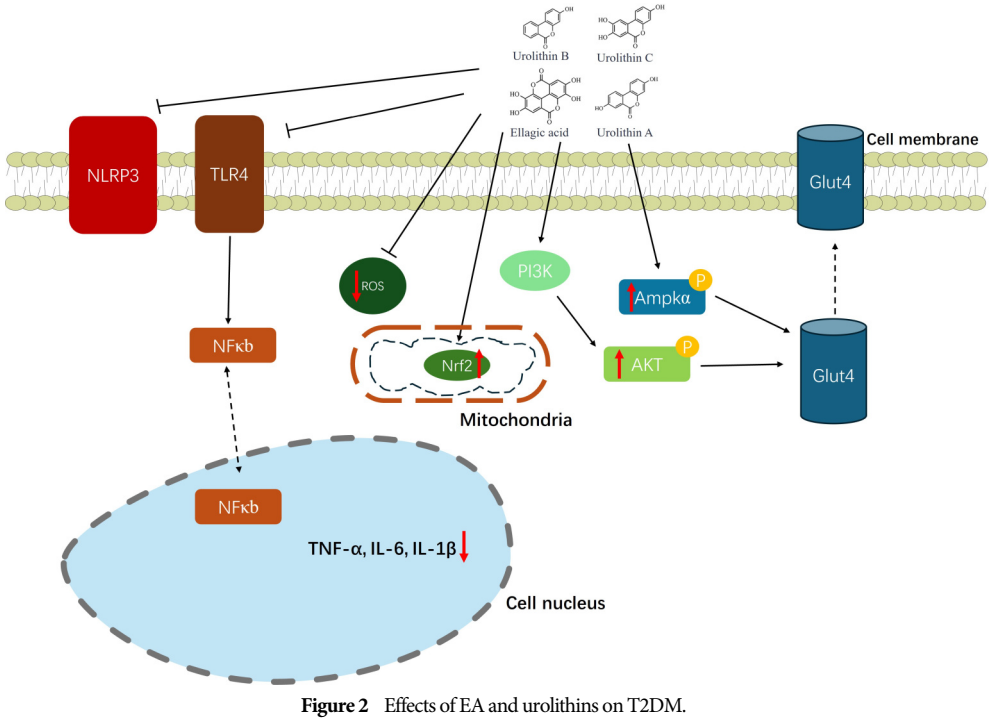

Figure 2 Effects of EA and urolithins on T2DM.

can lead to chronic inflammation, upregulating pro-inflammatory genes[95], a key factor in diabetes pathogenesis[96]. EA has been shown to significantly improve diabetic complications by inhibiting oxidative stress and inflammation[97]. EA also can mitigate effects on diabetic nephropathy by decreasing TLR4 and NF-κB P65 expression. Additionally, EA enhances general health status, reduces body weight, lowers blood glucose, and decreases serum inflammatory markers in diabetic mice[98]. Through the inhibition of renal NF-κB activation and the provision of anti-hyperglycemic effects, EA effectively alleviates renal dysfunction and oxidative stress in diabetic rats[99]. Urolithin A has been found to ameliorate diabetes by modulating the AMPK pathway and promoting pancreatic β-cell autophagy, inhibiting endoplasmic reticulum stress and inflammatory signaling within pancreatic β-cells[100].

4 The effects of ellagic acid on obesity

Obesity, often due to excessive energy intake, is increasingly prevalent. Current treatment strategies include dietary adjustments and drug therapy[101-103]. As reviewed in Wen *et al.*, obesity is intricately linked to several signaling pathways, including the mitogen-activated protein kinase (MAPK) signaling pathway, PI3K/AKT signaling pathway, TGF-β and AMPK signaling pathway, JAK/STAT signaling pathway, Wnt/β-catenin pathway, as well as endoplasmic reticulum (ER) stress and immune-related pathways[104]. EA and urolithins have been shown to prevent obesity through multiple mechanisms (Fig. 3).

4.1 Ellagic acid and urolithins inhibit fat synthesis and accumulation

The escalation of fat synthesis in adipose tissue is a significant factor in obesity development. Research has shown that EA can inhibit fat synthesis in adipocytes by affecting cell cycle proteins[105]. Woo *et al.* have reported that EA not only impacts adipocyte cell cycle proteins, but also reduces fat accumulation by lowering the expression adipogenesis markers such as peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα) in a dose-dependent manner[106]. EA also influences lipid accumulation within adipocytes, study suggesting that it can lessen liver lipid accumulation by upregulating SIRT1, p-AMPK, and PPAR-α in rats[107]. Furthermore, EA's Metabolites, UA and UB, produced by intestinal microbiota, have been observed to diminish lipid accumulation in the livers of obese rats fed a high-fat diet, potentially by enhancing antioxidant capacity and effecting fat absorption[108].

4.2 Ellagic acid and urolithins promote white adipose tissue browning and BAT thermogenesis

White adipose tissue (WAT) browning is essential for energy metabolism and obesity improvement[109]. The accumulation of mitochondria in WAT indicates browning, also known as beige fat[110]. Treatment with black raspberry, rich in tannic acid, activates of PR domain zinc finger protein 16 (PRDM16), uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), and T-box protein 1 (TBX1) in WAT, increasing rectal temperature and thermogenesis. Treating 3T3-L1 cells with electroacupuncture has shown a potential in facilitating the transformation of WAT to beige fat by increasing UCP-1, PGC-1a, and TBX-1 expression[111]. Additionally, Wang *et al.* have shown that electroacupuncture can improve dyslipidemia and hepatic steatosis in obese rats by downregulating the mRNA expression of Zfp423 and Aldh1a1 genes in WAT, while simultaneously upregulating thermogenic genes, thus promoting the WAT browning[112]. Further research has indicated that electroacupuncture primarily induces browning of WAT through the regulation of mitochondrial dynamics and activation SIRT3[113]. On the other hand, urolithin A has been found to enhance thermogenesis in BAT and promote WAT browning, leading to increased energy expenditure, and potential improvements in obesity. The key mechanism is the ability of urolithin A to boost thermogenesis by elevating triiodothyronine (T3) levels in WAT and BAT[114].

5 The effects of ellagic acid on atherosclerosis

Atherosclerosis (AS) is a chronic inflammatory vascular disease, recognized as the leading cause of mortality in cardiovascular disease patients globally[115]. The pathology of AS involves the lipid

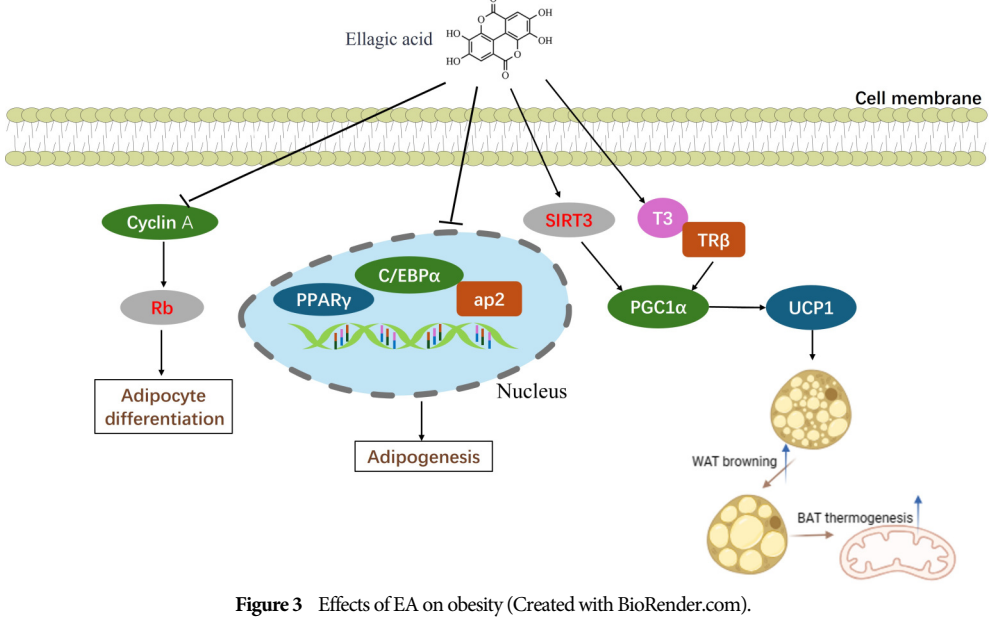

Figure 3 Effects of EA on obesity (Created with BioRender.com).

accumulation of in the arterial endothelium, which can trigger bleeding and thrombus formation within the blood vessels. Over time, this leads to fibrous tissue proliferation, calcification, and the gradual narrowing of the vessel lumen[116]. EA and urolithins possess multiple biological activities that are beneficial in the context of AS prevention and treatment. These activities include anti-inflammatory effects, anti-oxidant stress response, and the regulation of cholesterol accumulation (Fig. 4).

5.1 Ellagic acid and urolithins inhibit inflammation to improve AS

Inflammation is a key factor in AS development[117]. Research indicates that pomegranate juice, which is rich in tannic acid and anthocyanins, can lower levels of inflammatory markers such as tumor necrosis factor-alpha (TNF-α), plasminogen activator inhibitor-1 (PAI-1), interleukin-17A (IL-17A), interleukin-6 (IL-6), interleukin-1beta (IL-1β)). It also inhibits monocyte chemoattractant protein 1 (MCP-1) and reduce low-density lipoprotein cholesterol (LDL) levels by 39%, demonstrating its anti-atherosclerotic properties[118]. EA has been shown to significantly inhibit LOX1-induced endothelial dysfunction, thereby reducing the uptake of oxidized low-density lipoprotein (oxLDL) and the overproduction of superoxide by NADPH oxidase. Furthermore, EA enhances the antioxidant defense capacity of endothelial cells, aiding in the mitigation of AS formation[119]. Certain urolithin inhibitors and EA can decrease the adhesion between THP-1 monocytes and human umbilical vein endothelial cells (HUVECs), as well as the secretion of cell adhesion molecule sVCAM-1 and pro-inflammatory cytokine IL-6, thus slowing the progression of atherosclerosis[120]. UA also exhibits protective effects against endothelial dysfunction induced by oxLDL, which contributes to AS development[121].

5.2 Ellagic acid and urolithins inhibit cholesterol accumulation

Atherosclerosis (AS) is characterized by lipid accumulation, primarily low-density lipoprotein cholesterol (LDL-C). Reducing levels of low-density lipoprotein cholesterol effectively decrease the risk of developing AS[122]. EA has demonstrated the ability to significantly reduce cytotoxicity, apoptosis, and reactive oxygen species (ROS) production induced by oxLDL. This is achieved by modulating the PI3K/AKT and eNOS signaling pathways, which in turn inhibit inflammation and thrombus formation triggered by oxLDL[123]. Oral administration of emodin anthrone to apolipoprotein E knockout (apoE KO) mice has been shown to improve hypercholesterolemia and reduce the AS index, primarily by attributed decreasing LDL receptor transcription levels in the liver[124]. EA also prevents high cholesterol -induced atherosclerosis by inhibiting oxidative stress and cell apoptosis[125]. Ursolic acid (UA) mitigates diet-induced atherosclerosis by activating SRBI and Nrf2 signaling pathways[126] and modulating miR-33a and ERK/AMPKα/SREBP1 signaling pathway to enhance reverse

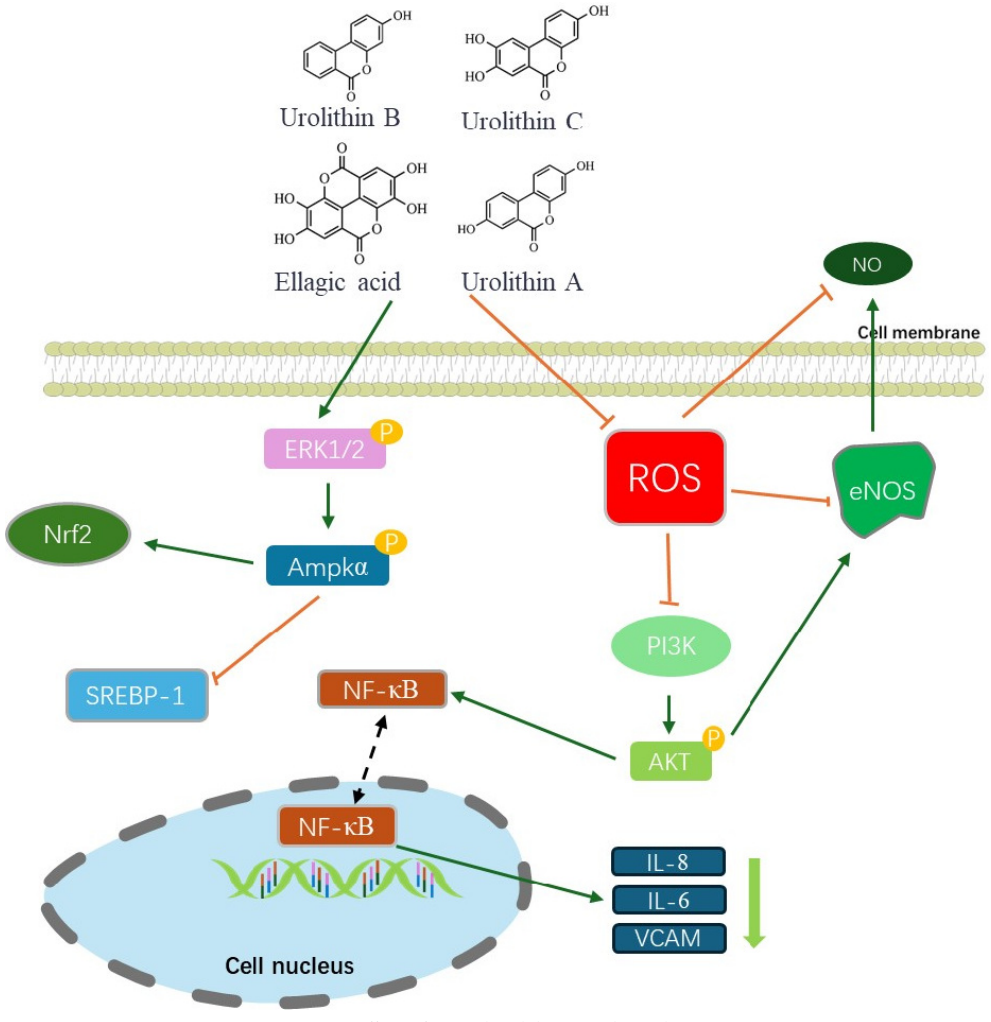

Figure 4 Effects of EA and urolithins on atherosclerosis.

cholesterol transport, disrupt cholesterol metabolism, and hinder the formation of atherosclerotic plaque[127].

5.3 Ellagic acid and urolithins inhibit oxidative stress

Oxidative stress is a major contributor to AS development, primarily resulting from endothelial dysfunction caused by an excess of ROS[128]. Natural compounds, such as EGCG and tannic acid can prevent atherosclerosis by reducing endothelial cell apoptosis induced by ROS[129]. EA can enhance atherosclerosis development caused by HOCL oxidant-induced injury to vascular endothelial cells by increasing aortic Nrf2 and HO-1 expression[130]. EA also inhibits the intracellular generation of ROS and the activation of the platelet-derived growth factor-BB (PDGF-BB) receptor, and downstream activation of extracellular signal-regulated kinase 1/2, effectively reducing the proliferation of vascular smooth muscle cells to prevent AS formation[131]. Urolithin A, Urolithin B, and Urolithin B-glucuronide have been shown to exhibit antioxidant properties, significantly inhibiting eNOS activation in endothelial cells and improving oxidative stress levels[132]. Treatment with UA and ox-LDL on human arterial endothelial cells enhances NO and eNOS production in a dose-dependent manner, primarily through the regulation of miR-27 and the ERK/PPARγ signaling pathways, alleviating atherosclerosis induced by endothelial dysfunction[121].

6 The effects of ellagic acid on metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multifaceted condition characterized by the abnormal accumulation of lipid in the liver. It is frequently associated with metabolic disorders such as obesity, diabetes, and dyslipidemia[133,134]. The pathogenesis of MASLD involves lipid accumulation, oxidative stress, inflammation and lipotoxicity[111], with liver inflammation being a primary driver of metabolic dysfunction-associated steatohepatitis (MASH) progression to fibrosis. Various natural products have been shown potential in ameliorating MASLD[135]. EA and urolithin exhibit anti-oxidant and anti-inflammatory activities, making them effective in improving MASLD conditions. EA has demonstrated benefits not only in treating T2DM and obesity, but also in MASLD treatment. This review provides a comprehensive overview of the mechanisms through which EA and urolithin alleviating MASLD (Fig. 5).

A study by Yin Qin *et al.* explored the mechanisms of *Rubus corchorifolius* L. fruit extract (RCE), rich in polyphenols including EA, in mitigating MASLD. The study revealed that RCE positively affected mitochondrial damage, oxidative stress, and blood lipid levels in the liver, influencing metabolic pathways related to glucose and lipid metabolism[136]. The water extract of *Phyllanthus emblica* (WEPE), containing EA, has been shown to improve liver steatosis by enhancing antioxidant enzymes activity[137]. EA and its derivatives can selectively inhibit liver pyruvate kinase (PKL) to effectively improve MASLD[138]. EA can also reduce liver inflammation by lowering ROS, TNF-α and IL-6 levels and enhancing the expression of CPT1α and CPT1β genes through the AMPK signaling pathway, thus ameliorating high-fat diet-induced MASLD[139]. UA has been shown to inhibit lipid metabolism and promote lipid autophagy via the AMPK/ULK1 signaling pathway, leading to an improvement in MASLD by reducing excessive lipid accumulation in the livers of fructose-fed mice[140]. Urolithin C, as identified by Battisti *et al.*, can also act as a PKL inhibitor to prevent MASLD development[141]. These findings collectively suggested that foods rich in EA have a beneficial impact on mitigating MASLD induced by high-fat and high-fructose diets.

7 The effects of ellagic acid on gout and Hyperuricemia

Gout is a chronic progressive disease primarily influenced by hyperuricemia[142], which is also a significant factor in various metabolic diseases[143] (Fig. 6). Hyperuricemia arises mainly from the imbalance between uric acid (UA) production and excretion. Uric acid crystals can trigger acute gouty arthritis by activating

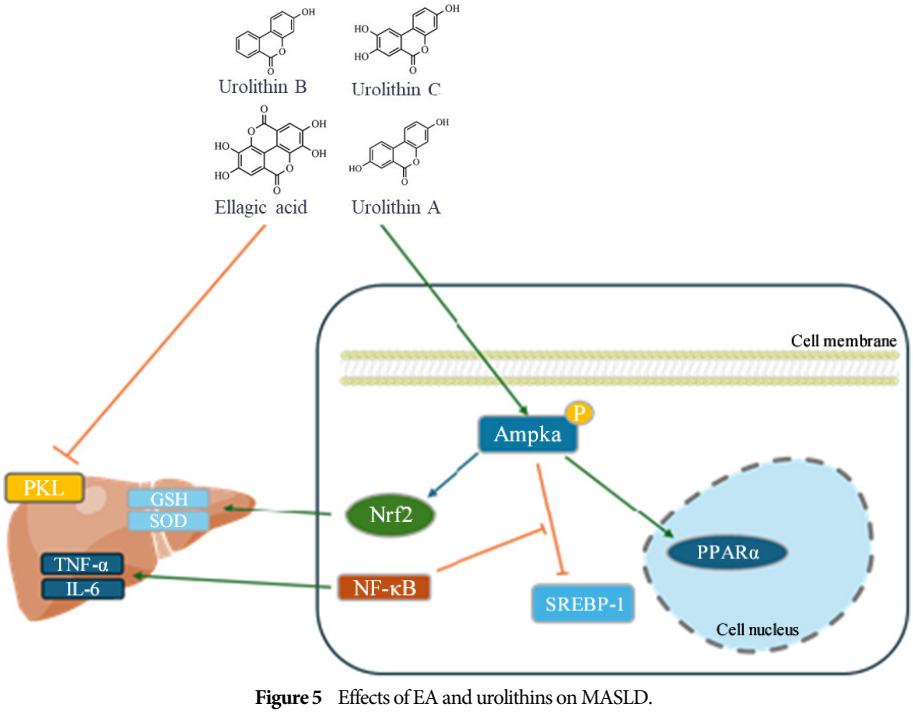

Figure 5 Effects of EA and urolithins on MASLD.

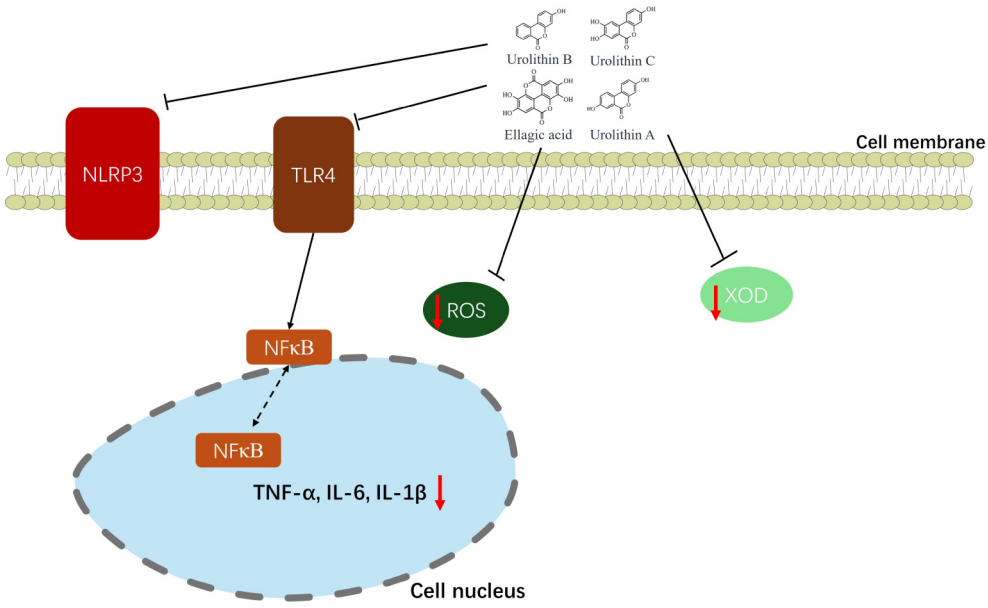

Figure 6 Effects of EA and urolithins on gout and hyperuricemia.

xanthine oxidase (XO) and the NOD-like receptor protein 3 (NLRP3) inflammasome. Inhibitors of XOD and NLRP3 are crucial in treating hyperuricemia and acute gout[144]. Pomegranate fruit extract, rich in EA, has been shown to lower uric acid levels *in vivo*[145]. EA, a natural polyphenolic compound, has demonstrated efficacy in improving hyperuricemia through its anti-inflammatory and anti-oxidant properties, acting as an inhibitor of XOD and NLRP3[37]. Computational analysis has shown that that EA can inhibit XO activity by entering its catalytic center[146]. EA can also reduce XO levels in the liver and inflammatory markers, improving fructose-induced hyperuricemia. Urolithin A has also been found to reduce uric acid production in a dose-dependent manner, acting as a potent XO inhibitor[147]. This inhibition of hepatic purine metabolism helps prevent and improve hyperuricemia and gout[148].

8 The effects of ellagic acid on Hypertension

Hypertension is linked to genetics, dietary patterns, and metabolic disorders like obesity, diabetes, and cardiovascular diseases[11,149] (Fig. 7). The mechanisms underlying hypertension are complex. The regulation of blood pressure involves the calcium signaling pathway, the NO (nitric oxide)-NOsGC (nitric oxide-sensitive guanylate cyclase)-cGMP pathway, and vascular remodeling. The calcium and NO-NOsGC-cGMP signaling pathways are reversible, whereas vascular remodeling is difficult to reverse[150]. Plant-based bioactive compounds like polyphenols, fatty acids, alkaloids, organic sulfur compounds, and terpenes are important in hypertension management[151]. Pomegranate juice, rich in tannins and ellagic acid, has vascular protective effects and can lleviate hypertension[152]. EA treatment has been shown to reduce alkaline phosphatase activity, calcium content, and cardiac hypertrophy in a hypertension rat model[153]. In oxidative stress-induced hypertension models, treatment with Nω-Nitro-L-arginine methyl ester hydrochloride (L-NAME), electroacupuncture was found to reduce hypertension by lowering the expression of NADPH oxidase subunit p47phox, thus preventing oxidative stress and enhancing nitric oxide (NO) bioavailability[154]. Deficiency of the 17β-estradiol hormone is associated with endothelium-dependent vascular dysfunction[155]. UA also significantly improves spontaneous hypertensive mesenteric vascular dysfunction in ovariectomized rats, primarily due to its antioxidant activity[156].

9 Conclusion and Outlook

Chronic metabolic diseases are a significant public health concern, impose significant economic burdens on both families and national healthcare systems. Natural compounds found in food and medicine have garnered increasing attention for their diverse health benefits and minimal side effects, leading to their increased acceptance as dietary components.

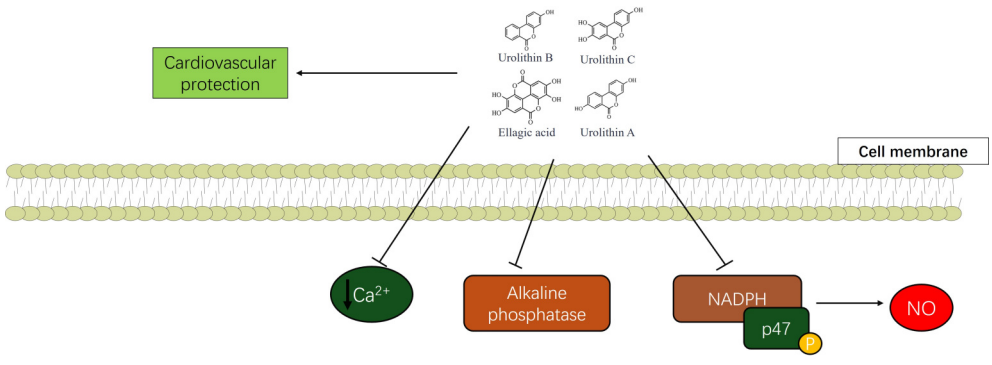

Figure 7 Effects of EA and urolithins on hypertension.

EA is a polyphenolic compound commonly found in pomegranate, blueberry, walnut, and tea. It has shown notable efficacy in managing chronic conditions such as T2DM, obesity, and AS. This review systematically examines EA's therapeutic effects and mechanisms on metabolic diseases, providing insights into its medicinal potential (Fig. 8, Table 2). Literature investigation suggests that EA and its metabolites potential lyin ameliorate chronic metabolic diseases through their multi-target, multi-pathway effects and regulation of intestinal flora. AMPK is identified as a primary target for EA, with actions mainly involving inflammatory and energy metabolism pathways. As a high molecular weight polyphenol, EA is metabolized into urolithins by intestinal flora, with different urolithins derivatives produced by various intestinal flora, indicating an influence on intestinal flora composition.

Clinical applications and safety of EA are understudied, with its low bioavailability being a major concern. While EA is converted to urolithins by gut microbiota, further research is needed to confirm if these metabolites share EA's biological activities. Determining the optimal dosage for desired effects is crucial for

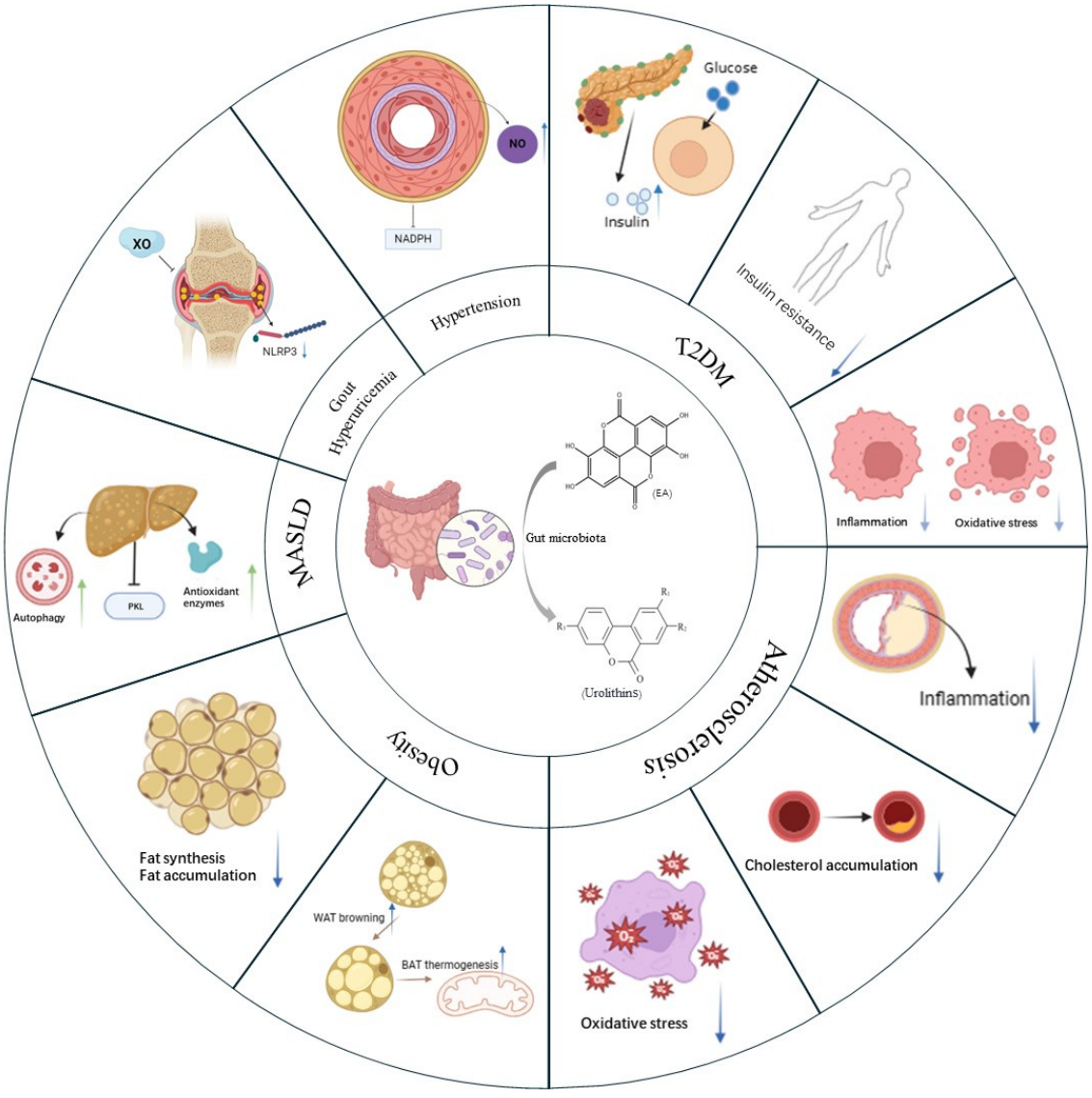

Figure 8 Schematic diagram of the ameliorating effect and pathway of ellagic acid and its metabolite urolithins on MDs (Created with BioRender.com).

Table 2 Pharmacology of EA and urolithins

Diseases	Activity/mechanism(s) of action		Cell lines/model	Dose	Application (route of amelioration)	Reference
T2DM	Promote glucose uptake and insulin secretion	Alter lipase, amylase, IL-6, PCNA and TNF- α expression and enhanced islet cell renewal, insulin, and immunoreactivities	Streptozotocin-induced diabetic rats	50 mg/kg	*In vivo* (Oral gavage)	[83]
		Increase insulin expression of β cells and improve oxidation stress	Streptozotocin-induced diabetic rats	50 mg/kg	*In vivo* (Oral gavage)	[84]
		Inhibit beta-cell apoptosis and stimulation of insulin production	HFD with streptozotocin-induced diabetic rats	10 mg/kg	*In vivo* (Intraperitoneal Injection)	[85]
		Enhance ERK1/2 activation	INS-1 cells	20/100 μmol/L	*In vitro*	[86]

(Continued)

Diseases	Activity/mechanism(s) of action		Cell lines/model	Dose	Application (route of amelioration)	Reference
Obesity	Improve insulin resistance	Promotes mitochondrial biogenesis and mitochondrial respiration, improving whole-body insulin sensitivity	HFD mice	20 μg/day	*In vivo* (Intraperitoneal Injection)	[87]
		Prevents pancreatic β-cell apoptosis by inducing activation of SQSTM1/p62 and LC3II autophagy	Mouse islet β-cells; Streptozotocin-induced diabetic mice	11.5 μg/mL; 50 mg/kg	*In vitro*; *In vivo* (Oral gavage)	[88]
		Activate PI3K/AKT signaling pathway and AMPK signaling pathway	L6 myotubes; KK-A^y/TaJcl mice	100 μmol/L; 100 mg/kg	*In vitro*; *In vivo* (Oral gavage)	[89]
		KEAP1-Nrf2 activation mediated by miR-223	HepG2 cells	15/30 μmol/L	*In vitro*	[29]
		Reductions in p47-phox and HIF-&alpha, upregulation of NRF2 and enhancement of the Akt signaling pathway	Goto Kakizaki rats	50 mg/kg	*In vivo* (Oral gavage)	[90]
		Decreased the levels of TNF-α, IL-6 and CRP, increased the levels of 11β-HSD2 and PPARα-TRB3-AKT2-p-FOXO1-GLUT2 signal	Gestational diabetes mellitus rats	50/150/ 300 mg/kg	*In vivo* (Oral gavage)	[35]
		Improve mitochondrial function	High fat/high sucrose diet mice	diet supplemented with 0.1%	*In vivo* (Oral administration)	[91]
	Inhibit inflammation and oxidative stress	Increased TAC and decreased MDA and TOS level	Streptozotocin-induced diabetic rats	25/50 mg/kg	*In vivo* (Oral gavage)	[97]
		Inhibit MGB1-TLR4-NF-κB pathway	Streptozotocin-induced diabetic mice	50/100/ 150 mg/kg	*In vivo* (Oral gavage)	[98]
		Lower renal pathology and suppress TGF-β and fibronectin expressions, reduce the serum levels of pro-inflammatory cytokines,IL-1β,IL-6 and TNF-α,induce activation of NF-κB and pro-inflammatory cytokine synthesis	Rat NRK 52E proximal tubular epithelial cells; HFD with streptozotocin-induced diabetic rats	5 μmol/L; 20/40/60/80/ 100 mg/kg	*In vitro*; *In vivo* (Oral gavage)	[99]
		Activates AMPK and autophagy to inhibit endoplasmic reticulum stress associated TXNIP/NLRP3/IL-1β signal pathway	MIN6 pancreatic β cells; HFD with streptozotocin-induced diabetic mice	50 μmol/L; 50 mg/kg	*In vitro*; *In vivo* (Oral gavage)	[100]
	Inhibit fat synthesis and accumulation	Reduction of Cyclin A protein expression and Rb phosphorylation, blocking of G1/S phase transition	3T3-L1 cells	10/15/ 20 μmol/L	*In vitro*	[105]
		Reduced PPARγ and C/EBPα, arresting cells at the G0/G1 phase	3T3-L1 cells	5/25/50 μmol/L	*In vitro*	[106]
		Elevated the levels of SIRT1, p-AMPK, and PPAR-α and reduced SREBP-1c level	Young control, old control rats		*In vivo*	[107]
		Downregulated the expression of LXRα and SREBP1c, upregulating PPARα expression, decreased the expression of PERK and IRE1α	HFD rats	2.5 mg/kg	*In vivo* (Intraperitoneal Injection)	[108]
	Promote WAT browning and BAT thermogenesis	Promote beige differentiation/activation	3T3-L1 cells	100 μmol/L	*In vitro*	[111]
		Suppress white adipocyte maintaining genes and promoting expression of key thermogenic genes	HFD rats	10/30 mg/kg	*In vivo*	[112]
		Induce beige remodeling of WAT by regulating the mitochondrial dynamics and SIRT3	3T3-L1/SVF cells; Cold-exposed mouse	25 μmol/L; 20 mg/kg	*In vitro*; *In vivo* (Oral administration)	[113]
		elevation of triiodothyronine (T3) levels in BAT	HFD mice	30 mg/kg	*In vivo* (Oral gavage)	[114]
Atherosclerosis	Inhibit inflammation	Increased adiponectin levels, decreased levels of inflammation markers, inhibited MCP-1	HFD apolipoprotein E-deficient mice		*In vivo*	[118]
		inhibiting NADPH oxidase-induced overproduction of superoxide, down-regulating iNOS	Human umbilical vein endothelial cells	5/10/15/ 20 μmol/L	*In vitro*	[119]
		Reduce the adhesion of monocytes and sVCAM-1 and IL-6	THP-1 monocytes to human umbilical vein endothelial cells	10 μmol/L	*In vitro*	[120]
		Alleviate endothelial dysfunction induced by ox-LDL partially through modulating miR-27 expression and ERK/PPAR-γ pathway	Human artery endothelial cells	0.5/2.5/ 5 μmol/L	In vitro	[121]
	Inhibit cholesterol accumulation	Anti-oxidant and modulate the PI3K/Akt/eNOS signaling pathway	Human umbilical vein endothelial cells	5/10/15/ 20 μmol/L	*In vitro*	[123]
		Improved RCT functionality and HDL function	High-cholesterol paigen diet induce hypercholesterolemia mice	10 mg/kg	*In vivo* (Oral gavage)	[124]

(Continued)

Diseases	Activity/mechanism(s) of action		Cell lines/model	Dose	Application (route of amelioration)	Reference
	Inhibit oxidative stress	Suppressed the aortic level of 8-(OH) dG and the expression of caspase-8, caspase-9 and Fas ligand	High fat and cholesterol diet rabbits	diet supplemented with 1%	*In vivo* (Oral administration)	[125]
		Upregulation of SR-BI expression and inhibition of p-ERK1/2 levels	high cholesterol diet supplemented with Vitamin D3 rats	3 mg/kg	In vivo (Oral administration)	[126]
		Regulating the miRNA-33 expression and interaction with the ERK/AMPKα/SREBP1 signaling pathway	RAW264.7 cells	50 μg/mL	*In vitro*	[127]
		Increased Nrf2 and HO-1 expression	HFD apolipoprotein E-deficient mice	30 mg/kg	*In vivo* (Oral gavage)	[130]
		Blocking proliferation of vascular smooth muscle cells	Rat aortic smooth muscle cells; Streptozotocin-induced diabetic rats	25 μmol/L; diet supplemented with 2%	*In vitro*; *In vivo* (Oral administration)	[131]
		activated eNOS expression	Human aortic endothelial cells	15 μmol/L	*In vitro*	[132]
NAFLD		Improved liver and mitochondrial damage, oxidative stress index, liver function markers and lipid levels	HFD mice		*In vivo*	[136]
		Enhance the antioxidant enzyme activities, elevating adiponectin, PPAR-α and lowering SREBP-1c	HFD rats		*In vivo*	[137]
		Inhibit pyruvate kinase（PKL）	Structure-activity analysis			[138, 141]
		Reduced inflammatory levels of ROS, TNF-a, and IL-6, and activated the AMPK signaling pathway to enhance the expression of genes such as CPT1a and CPT1b	Streptozotocin-induced diabetic rats	50 mg/kg	*In vivo* (Oral gavage)	[139]
		Suppressing lipid metabolic reprogramming and triggering lipophagy	HepG2 cells and primary hepatocytes; High-fructose-fed mice	10/20/ 40 μmol/L; 50/100 mg/kg	*In vitro*; *In vivo* (Oral administration)	[156]
Gout and hyperuricemia		Inhibit of NLRP3 and XOD			*In vitro*	[144]
		Inhibits the activity of XO	AML12 hepatocytes; Purine bodies-induced hyperuricemia mice	100 μmol/L; 100/300 mg/kg; 80/240 mg/kg	*In vitro*; *In vivo* (Oral gavage)	[146, 148]
		Activation of CTRP3 and inhibition of ACL activities	HFD rats	15 mg/kg	*In vivo* (Oral gavage)	[147]
Hypertension		Improving nitric oxide bioavailability, attenuated plasmatic alkaline phosphatase activity, calcium content	N_{ω}-Nitro-L-arginine methyl ester hydrochloride induced hypertension rats	10/30 mg/kg	*In vivo* (Oral gavage)	[153]
		Reduce NADPH oxidase subunit p47phox expression	N_{ω}-Nitro-L-arginine methyl ester hydrochloride induced hypertension rats	7.5/15 mg/kg	*In vivo* (Oral administration)	[154]
		Endothelial nitric oxide synthase activation, stimulating the Superoxide Dismutase 2-catalase pathway	Ovariectomized spontaneously hypertensive rats	10 mg/kg	*In vivo* (Oral administration)	[155]

future research. Extensive research and clinical trials are essential to understand EA's efficacy and safety in managing chronic metabolic diseases. Identifying potential therapeutic targets and interaction patterns will allow for a more precise evaluation of their therapeutic effects and pharmacokinetics, aiding in the development of new drugs and treatment strategies for chronic metabolic diseases.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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