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CONCISE REVIEW

Beneficial effects of ginger *Zingiber officinale Roscoe* on obesity and metabolic syndrome: a review

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In recent years, metabolic syndromes (MetSs), including diabetes mellitus, dyslipidemia, and cardiovascular diseases, have become a common health problem in both developed and developing countries. Accumulating data have suggested that traditional herbs might be able to provide a wide range of remedies in prevention and treatment of MetSs. Ginger *(Zingiber officinale Roscoe*, Zingiberaceae) has been documented to ameliorate hyperlipidemia, hyperglycemia, oxidative stress, and inflammation. These beneficial effects are mediated by transcription factors, such as peroxisome proliferator–activated receptors, adenosine monophosphate–activated protein kinase, and nuclear factor κB. This review focuses on recent findings regarding the beneficial effects of ginger on obesity and related complications in MetS and discusses its potential mechanisms of action. This review provides guidance for further applications of ginger for personalized nutrition and medicine.

Keywords: metabolic syndrome; *Zingiber officinale*; obesity; diabetes mellitus; mechanism

Introduction

Over the years, diverse definitions for metabolic syndrome (MetS) have been published by different health organizations. What is clear is that MetS is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors linked to an increased risk of abdominal obesity, hyperglycemia, dyslipidemia, inflammation, and hypertension that raise the risks of nonalcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and diabetes.[1] MetS is a growing health problem that has reached pandemic proportions, as it now affects a quarter of the world's population.[2] Increasing attention has been directed toward finding effective strategies to detect, treat, and control the comorbidities associated with MetS.

In recent years, there has been a growing interest in exploiting the potential of natural phytochemicals and plant-derived foods for restoring metabolic balance.[3] A variety of natural plants (e.g., vegetables, fruits, and herbs), active ingredients derived from plants (e.g., phytochemicals, fibers, and unsaturated fatty acids), and other natural dietary compounds have been used to help counteract obesity-related metabolic dysfunction.[4] Ginger *(Zingiber officinale Roscoe*, Zingiberaceae*)* is one of the most widely consumed spices and/or medicinal herbs worldwide. From its origin in Southeast Asia and its spread to Europe, ginger has a long history of use as an herbal medicine to treat a variety of ailments.[5] Ginger contains various phytochemicals and biologically active compounds, such as phenolics and flavonoids.[6] Among the identified components, gingerols and shogaols have been found to be the major bioactive compounds in ginger. 6-Gingerol is the major gingerol, and several gingerols of various chain lengths (n6–n10) are also present in ginger.[7] Shogaols, the dehydrated form of gingerols, are mainly contained in semidried and thermally treated ginger as a degradation product of the thermally labile

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gingerols.[8] They have shown numerous pharmacological benefits, including improvement of blood glucose tolerance,[9] enhancement of lipid profile,[10] and modulation of inflammatory factors.[11] This review focuses on the recent findings regarding the beneficial effects of ginger and its active compounds in the field of prevention and therapy of some MetSs, such as diabetes, NAFLDs, and CVDs, and discusses the underlying mechanisms of action.

Preventive effects of ginger on metabolic diseases

Obesity

Obesity is a serious health problem because of an imbalance between energy intake and expenditure that results in excessive energy stored as triglycerides in adipose tissue.[12] The prevalence of obesity is increasing at an alarming rate around the world. As World Health Organization (WHO) data show, nearly two billion people are overweight, and one-third of them are obese.[13] The use of natural materials has been considered an effective tool for obesity control. Among them, ginger has shown the most significant antiobesity effects in *in vitro* and *vivo* studies (Tables 1 and 2). It was observed that oral administration of ginger extract significantly reduced body weights and serum lipid levels in rats fed a high-fat diet (HFD).[14] Furthermore, it was found that ginger extract attenuated HFD-induced obesity by increasing skeletal muscle fat catabolism and energy expenditure.[15] In particular, 6-gingerol, one of the major active compounds of ginger, exhibited antiobesity effects by altering the activities and expressions of some lipid metabolism marker enzymes, such as fatty acid synthase (FAS), acetyl-coA carboxylase, HMG co-A reductase, lecithin choline acyl transferase, and lipoprotein lipase.[16] In addition, 6-gingerol suppressed the activity of amylase and pancreatic lipase, leading to a reduction of plasma and tissue lipids.[10,17] The antiobesity effects of ginger may be associated with its anti-inflammatory properties. The studies have shown that ginger extract and 6-gingerol can significantly downregulate mRNA levels of interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) in adipose tissue of male rats fed a HFD.[15,16]

Adipogenesis constitutes a complex process of cell differentiation by which preadipocytes become adipocytes. It was reported that 6-gingerol can effectively inhibit the differentiation of preadipocytes into adipocytes and prevent triglyceride deposition. It also prevented lipid accumulation and lowered the protein expression of adipogenesis-related transcription factors and the key lipogenic enzymes in 3T3-L1 cells.[18,19] 6-Shogaol, another major bioactive constituent in ginger, has significantly higher effects on inhibiting adipogenesis of 3T3-L1 preadipocytes and decreasing expression of various adipogenic/lipogenic marker proteins.[20] In addition, an analysis of cellular respiration revealed that cultured skeletal muscle myotubes pretreated with ginger extract increased the palmitate-induced oxygen consumption rate, leading to an increase in cellular fatty acid catabolism.[14]

Despite the *in vitro* and animal experiments described above, only a few clinical trials performed on ginger are available for MetSs. This lack of clinical studies may be attributed to numerous factors, including ethical issues, limited commercial support, and the complex chemical composition of ginger.[8] The effects of ginger supplementation on some obesity-associated indices and metabolic risk factors in overweight humans are listed in Table 3. For example, an early study showed that dietary intake of ginger could enhance thermogenesis and reduce feelings of hunger.[21] Moreover, ginger supplementation showed a beneficial effect on weight loss and some obesity-associated parameters in overweight and obese adults.[22,23]Therefore, further research is needed to explore the potential application of ginger for weight management.

Diabetes

Diabetes mellitus (DM) is a complex metabolic disease associated with impaired insulin secretion, developing insulin resistance, and β cell dysfunction that leads to abnormal glucose, protein, and lipid metabolism, inflammatory responses, and damage.[65] The majority of diabetes cases fall into two broad categories: type 1 DM (T1DM), caused by destruction of the pancreatic β cells resulting in lack of insulin secretion, and type 2 DM (T2DM), caused by insulin resistance and impaired insulin secretion leading to high blood insulin levels and hyperlipidemia. Of these two types, the latter is the more prevalent form and generally receives more attention. To date, a number of studies have demonstrated that ginger extract can exert beneficial effects on serum glucose and tissue glycogen content in alloxan-induced[39] and streptozotocin-induced

Table 1. ***In vitro*** **studies of** ***Zingiber officinale*** **and the active compounds in modulating metabolic responses**

Effect on metabolic syndrome	Model	Type of extract/constituents	Dose	Experimental outcome	References
Obesity	3T3-L1 cells	6-Gingerol	5, 10, or 15 μg/mL	Suppressed oil droplet accumulation Reduced oil droplet size Reduced protein levels of peroxisome proliferator-activated receptor (PPAR)γ, CCAAT/enhancer-binding protein (C/EBP)α, fatty acid synthase (FAS), and adipocyte-specific fatty acid–binding protein (aP2) Diminished the insulin-stimulated serine phosphorylation of Akt (Ser473) and GSK3β (Ser9)	18
	3T3-L1 cells	6-Shogaol	40 μM	Inhibited adipogenesis Decreased protein expression levels of PPAR-γ, C/EBPα, and FAS Increased glycerol release and decreased intracellular lipid accumulation	20
	3T3-L1 cells	6-Shogaol (6S) and 6-gingerol (6G)	10 μM	Inhibited TNF-α-mediated downregulation of adiponectin expression Increased PPAR-γ transcriptional activity Inhibited the phosphorylation of anti-phospho-c-Jun-NH2-terminal kinase (JNK) and the activation of the upstream kinase of JNK (6G)	24
	Human embryonic kidney 293	Ginger extract; 6-Gingerol and 6-shogaol	0.001%, 0.002% 1 μM, 2 μM	Increased PPARδ-dependent luciferase activity	14
	Human skeletal muscle myoblasts	Ginger extract	0.002%	Increased the mRNA levels of carnitine palmitoyl transferase 1a (CPT1a), CPT1b, and pyruvate dehydrogenase 4 (PDK4)	
	C2C12 myotubes	Ginger extract;	0.001%, 0.002%	Increased the oxygen consumption rate	
	3T3-L1 cells	6-Gingerol	5, 10, and 15 μg/mL	Inhibited the differentiation of 3T3-L1 cells into adipocytes and prevented lipid content accumulation Decreased the triglyceride level and glycerol-3-phosphate dehydrogenase (GPDH) activity Decreased mRNA expression levels of PPAR-γ, C/EBPα and their downstream lipogenic enzymes, such as FAS and acetyl-CoA carboxylase (ACC) Increased the mRNA and protein expression levels of β-catenin, cyclin D1 (CCND-1), LRP6, and DVL2 Enhanced the phosphorylation levels of glycogen synthase kinase 3 (GSK3β)	19
Diabetes	Pancreatic β cells and hepatocytes	6-Gingerol	50 and 75 μg/mL	Increased cell viability Inhibited intracellular reactive oxygen species (ROS) generation Increased the level of intracellular glucose transporter 4 (GLUT4)	25
	L6 skeletal muscle cell line	Ginger extract	0, 100, 200, 400, and 600 mg/mL	Increased glucose uptake Enhanced glucose transportation	26
	L6 skeletal muscle cells	6-Gingerol	0, 50, 100, and 150 μg/mL	Enhanced glucose uptake Increased AMPKα subunit phosphorylation	27
	L6 myoblasts	Ethyl acetate extract of ginger	0.5, 1, 5, 10, and 50 μg/mL	Enhanced glucose uptake Induced surface expression of GLUT4	28

Continued

Table 1. *Continued*

Effect on metabolic syndrome	Model	Type of extract/constituents	Dose	Experimental outcome	References
	L6 skeletal muscle cells	6-Gingerol	0, 50, 100, and 150 μg/mL	Enhanced glucose uptake Increased AMPKα subunit phosphorylation Increased the relative mitochondrial content	29
	Biochemical tests	Ethyl acetate extract of ginger	100, 150, 200, and 250 μg/mL; 500, 750, 1000, and 1250 μg/mL	Inhibited the activity of α-glucosidase and α-amylase	30
	C2C12 myoblasts L6 myoblasts	6-Gingerol	0, 0.5, 1, 3, 10, and 30 μM; 0, 50, 100, 200, 300, and 600 μM	Increased insulin sensitivity Enhanced glucose uptake Activated AMPKα2 and its downstream target as ACC Increased the phosphorylation of Akt-substrate 160 (AS160)	9
Inflammation	HuH-7 cells	6-Gingerol	50, 100, and 200 μM	Suppressed mRNA levels of cytokines interleukin-6 (IL-6), interleukin-8 (IL-8), and serum amyloid A1 (SAA1) Decreased intracellular superoxide levels Attenuated the inhibitory effect of IL-1β on 24-dehydrocholesterol reductase (DHCR24) levels Downregulated cyclooxygenase 2 (COX2) expression and nuclear factor κB (NF-κB) activity Suppressed ROS levels	31
	Raw 264.7 cells	12-Dehydro-gingerdione	50, 100, 150, and 200 μg/mL	Inhibited lipopolysaccharide (LPS)-stimulated production of nitric oxide (NO), IL-6, and prostaglandin E2 (PGE2) Inhibited the LPS-stimulated increase in inducible NO (iNOS) and COX-2 mRNA levels	32
Antioxidant	Human polymor-phonuclear neutrophils and RAW 264.7 cells	6-Gingerol, 8-gingerol, 10-gingerol, and 6-shogaol	0, 1, 2, 3, 4, 5, and 6 μM	6-Shogaol exhibited the most potent antioxidant and anti-inflammatory properties on free radical scavenging, nitrite release, and PGE_2 release	33
	Primary hepatic cells	Water extract of ginger	0,1 3, 10, 30, and 300 μg/mL	Reduced H_2O_2-induced apoptotic signals and the levels of intracellular ROS Increased the phosphorylation of c-Jun and JNK kinase Increased the expression of oxygenase-1 (HO-1) and heat shock protein 72 (HSP72)	34
Nonalcoholic steatohep-atitis	HepG2 cells	6-Gingerol	25, 50, or 100 μmol/l	Reduced oleic acid (OA)–induced lipid deposition Inhibited lipid accumulation Attenuated OA-induced increase in cholesterol and triglyceride content Attenuated the OA-induced production of inflammatory cytokines (monocyte chemoattractant protein-1 (MCP-1), TNF-α, IL-1β, and IL-6)	35
	HepG2 cells	6-Gingerol	100 μmol/l	Reduced free fatty acid (FFA) mixture–induced lipid deposition Inhibited lipid accumulation Attenuated the FFA-induced increase in triglyceride contents Attenuated the FFA mixture–induced production of MCP-1, TNF-α, and IL-6	36

Continued

Table 1. *Continued*

Effect on metabolic syndrome	Model	Type of extract/constituents	Dose	Experimental outcome	References
	HuH-7 cells	Ginger	50, and 100 μg/mL	Reduced NF-κB and IKK activity Reduced IκBα protein level Suppressed NF-κB target gene expression Reduced expression of NF-κB target genes IL-6, IL-8, and SAA1 Suppressed IL-1β-increased IL-6 protein expression	11
Atherosclerosis	Human umbilical vein endothelial cells (HUVECs)	6-Shogaol	1, 5, 10, and 30 μmol/l	Suppresses LDL oxidation and inhibits oxidized LDL (oxLDL)-induced ROS generation Reduces oxLDL-stimulated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity Protected HUVECs from oxidative stress-related cellular injuries Inhibited NF-κB activation and decreased expression of adhesion molecules	37

diabetic animal models[40–42,44–47] through enhancing the peripheral utilization of glucose, regulating the activities of glycolytic enzymes, and limiting gluconeogenic formation.[45] Ginger extract could increase the activities of glycolytic enzymes, which drives the metabolic degradation of glucose to form pyruvate.[45] Moreover, the protective effects of ginger on the development of diabetes have been investigated in a high-fat/high-carbohydrate (HFHC) diet–fed rat model, and the results showed that ginger extract significantly improved the insulin sensitivity using the homeostatic model assessment of insulin resistance.[29]

As oxidative stress plays a key role in insulin resistance and β cell dysfunction, it is considered the pathogenesis of DM and its complications. Recent studies indicated that ginger and its bioactive components exerted a therapeutic protective effect in diabetes by regulating oxidative stress markers and decreasing activities of antioxidant enzymes.[25,43,44,46,47] Furthermore, it was demonstrated that 6-gingerol could protect pancreatic β cells from oxidative stress by reducing the artificial D-glyceraldehyde–induced increase in the intracellular reactive oxygen species (ROS) level in RIN-5F cells.[48] On the other hand, it is generally accepted that inflammation is usually associated with the pathogenesis of T2DM. Ginger has shown significant anti-inflammatory properties in amelioration of fructose-induced adipose tissue insulin resistance, probably owing to its capacity to suppress adipose macrophage–related proinflammatory cytokines.[38] As a treatment, 6-gingerol could inhibit the expression of proinflammatory cytokines, such as TNF-α and IL-6, which demonstrated that ginger mat exert its hypoglycemic effects via controlling inflammation.[25,48] Apart from 6-gingerol, the other constituents of ginger, such as 12-dehydrogingerdione and 6-shogaol, also exhibit antioxidant and anti-inflammatory properties, which significantly inhibited lipopolysaccharide-stimulated production of nitric oxide (NO) and suppressed mRNA levels of cytokines (IL-6, IL-8) in RAW 264.7 cells.[32,33] Moreover, ginger extracts showed a significant inhibitory effect on carbohydrate-hydrolyzing enzymes, such as α-glucosidase and α-amylase, in *in vitro* studies. This may help to reduce the intestinal absorption of carbohydrates, enhance insulin sensitivity, and contribute to antihyperglycemic effects.[30] In addition, several cell-based experiments have also shown beneficial effects of ginger and its active ingredients on glucose regulation. In mouse myoblast and skeletal muscle cells, both ginger extract and 6-gingerol can enhance glucose uptake and promote mitochondrial biogenesis, resulting in alleviation of insulin resistance.[9,26,28,29] The results obtained in *in vivo* and *vitro* studies indicated that ginger extract and its major pungent phenolic compounds possessed the ability to modulate glucose metabolism effectively (Fig. 1).

In recent years, several clinical trials have demonstrated that ginger treatment can reduce levels of blood glucose and inflammation in

Table 2. Summary of animal studies on *Zingiber officinale* and the active compounds in metabolic syndromes

Effect on metabolic syndrome	Model	Dose and duration	Experimental outcome	References
Obesity	HFD-induced obese rats	6-Gingerol (25, 50, and 75 mg/kg) for 30 days	↓Glucose levels, bodyweight, leptin, insulin, amylase, and lipase ↓Plasma and tissue lipids	17
	Male C57BL/6J mice	Ginger extract (0.3% and 0.4%) for 18 weeks	↑The number of type I muscle fibers ↑Running endurance capacity and peroxisome proliferator–activated receptor δ (PPARδ)-targeted gene expression	14
	HFD-induced obese rats	6-Gingerol (75 mg/kg) for 30 days	↓Body weight, glucose, insulin ↓The activity and mRNA level of HMG-CoA reductase ↑The activities and mRNA levels of carnitine palmitoyl transferase-1 (CPT-1), lecithin choline acyl transferase (LCAT) and lipoprotein lipase (LPL) ↓The activities of fatty-acid synthase (FAS), PPARγ, and sterol regulatory element binding protein-1c (SREBP1) ↓The expression levels of inflammatory markers (TNF-α and IL-6)	16
	HFD-induced obese rats	Ethanolic extract of ginger (100, 200, and 400 mg/kg) for 6 weeks	↓Body weight, glucose, insulin, total cholesterol, LDL cholesterol, triglyceride, free fatty acids, and phospholipids	15
	HFD-induced obese rats	6-Gingerol (25, 50, and 75 mg/kg) for 30 days	↓Glucose, bodyweight, leptin, insulin, amylase, and lipase ↓Plasma and tissue lipids ↓The levels of total cholesterol (TC), free fatty acids (FFAs), triglycerides (TGs), phospholipids (PLs), LDL, and very-low-density lipoprotein (VLDL) in plasma and liver ↓The activities of amylase and pancreatic lipase	10
Diabetes	Fructose overconsumption–induced fatty liver and hypertriglyc-eridemia rats	Extract of ginger (50 mg/kg) for 5 weeks	↓Body weights, eWAT weight, the ratio of epididymal white adipose tissue (eWAT) weight to body weight, and adipocyte size ↓Plasma glucose, insulin concentrations, and the homeostasis model assessment of insulin resistance (HOMA-IR) index ↓Expression of two important macrophage markers (CD68, F4/80) ↓Expression of proinflammatory cytokines (TNF-α, IL-6) and MCP-1 and its receptor chemokine (C-C motif) receptor-2	38
	Alloxan-induced diabetes rats	Aqueous extract of ginger (500 mg/kg) for 6 weeks	↓Serum glucose level	39
	Streptozotocin (STZ)-induced diabetes rats	The juice of ginger (4 mg/kg) for 6 weeks	↑Serum insulin ↓Fasting glucose levels, serum cholesterol, serum triglyceride, and blood pressure	40
	STZ-induced diabetes rats	Ethanolic extract of ginger (200 mg/kg) orally for 20 days	↓Serum total cholesterol, triglycerides ↓The liver and pancreas thiobarbituric acid–reactive substances (TBARS) values ↑High-density lipoprotein (HDL)-cholesterol level	41
	STZ-induced diabetes rats	Aqueous extract of ginger (500 mg/kg) daily for 7 weeks	↓Serum glucose, cholesterol, and triacylglycerol levels	42

Continued

Table 2. *Continued*

Effect on metabolic syndrome	Model	Dose and duration	Experimental outcome	References
	STZ-induced diabetes rats	Ginger (1% and 2%) in diet supplementation for 30 days	↓Glucose level ↓Malondialdehyde (MDA) level ↑Activities of antioxidant biomarkers: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) and glutathione (GSH)	43
	iAs intoxicated rats	6-Gingerol (50 and 75 mg/kg) for 3 weeks	↓Blood glucose ↑Activities of antioxidant biomarkers: SOD, GPx, and GSH ↓The expression levels of TNF-α and IL6 ↑The expression of signaling molecules both at protein and mRNA levels: glucose transporter 4 (GLUT4), insulin receptor substrate 1 (IRS1), I insulin receptor substrate 2 (IRS2), protein kinase B (AKT), phosphatidylinositol 3 kinase(PI3K) ↑Plasma insulin level	25
	STZ-induced diabetes rats	Ginger (0.5%, 1%, and 5%) for a month	↓Glucose levels, triglycerides, and cholesterol ↓MDA and protein carbonyl levels ↑The activities of SOD, catalase, and glutathione peroxidase (GSHPx) ↑Comet ratios	44
	STZ-induced diabetes rats	Aqueous extracts of ginger (100, 300, 500 mg/kg) for 30 days	↓Plasma glucose levels, kidney weight, and glycogen content ↑The activities of hepatic glycolytic enzymes: glucokinase, phosphofructokinase, and pyruvate kinase	45
	STZ-induced diabetes rats	Free and bound polyphenols of ginger (125, 250, and 500 mg/kg) for 28 days	↓Fasting blood glucose ↓The activities of liver function enzymes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ↑Rhe level of glycogen ↑Rhe activities of antioxidant enzymes: CAT and SOD ↑The activities of carbohydrate-metabolizing enzymes: fructose-1,6-bisphosphatase and glucose-6-phosphatase	46
	STZ-induced diabetes rats	Ginger (60 mg/kg) for 3 weeks	↓The activities of SOD and CAT ↓The MDA concentration ↑Glutathione (GSH) content and GSH/oxidized glutathione (GSSG) ratio	47
	High-fat/high-carbohydrate diet–fed rat model	Ginger extract (200 mg/kg) for 10 weeks	↓Blood glucose and serum insulin ↑Insulin sensitivity ↑AMP-activated proteinkinase (AMPK)α phosphorylation and total AMPKα in skeletal muscle tissue	29
	Obese diabetic *db/db* mice	6-Gingerol (0.05 %) for 4 weeks	↓Fasting blood glucose and blood glucose levels ↑Glucose intolerance ↓Serum TG, TC, TBARS, and TNF-α levels ↓The gene expressions of phosphoenol pyruvate carboxy kinase (PEPCK), glucose-6-phosphatase (G6Pase), and glycogen synthase (GS)	48
Cardiovascular	Apolipoprotein E–deficient mice	Ethanol extract of ginger (25 and 250 μg) for 10 weeks.	↓Plasma triglycerides, cholesterol, VLDL, and LDL ↓LDL-associated lipid peroxides and LDL aggregation	49
	HFD-induced obese rats	Ethanol extract of ginger (400 mg/kg) for 6 weeks.	↓Hepatic triglyceride and cholesterol levels ↑The mRNA and protein level of LDL receptor ↓The protein expression of HMG-CoA reductase	50

Continued

Table 2. *Continued*

Effect on metabolic syndrome	Model	Dose and duration	Experimental outcome	References
	Wistar rats in a cholesterol-enriched diet	Ginger (500 mg/day) for 12 weeks	↓The mRNA expression of retinoid binding protein (RBP)	51
	Wistar strain albino rats in a cholesterol-enriched diet	Ginger (2% and 4%) for 3 days	↓Angiotensin-1-converting enzyme (ACE) activity ↓The levels of TC, TG, VLDL-C, and LDL-C ↓MDA content	52
	Golden Syrian hamsters	Gingerol- and shogaol-enriched ginger extract (0.5% and 1.0%) for 6 weeks	↓Plasma total cholesterol, liver cholesterol, and aorta atherosclerotic plaque ↑Excretion of both neutral and acidic sterols ↓The mRNA levels of Niemann–Pick C1–like 1 protein (NPC1L1), acyl CoA: cholesterol acyltransferase 2 (ACAT2), microsomal triacylglycerol transport protein (MTP), and ATP binding cassette transporter 5 (ABCG5) ↑The mRNA level of cholesterol-7α-hydroxylase (CYP7A1)	53
	L-NAME-induced hypertensive rats	Ginger (4%) for 24 days	↓ACE and arginase activities ↑Nitric oxide level	54
	L-NAME-induced hypertensive rats	Ginger (4%) for 24 days	↓ATP and AMP hydrolysis ↓Adenosine deaminase (ADA) and acetylcholinesterase (AChE) activities	55
Nonalcoholic fatty liver disease	Fructose-induced fatty liver and hypertriglyc-eridemia rats	Aalcoholic extract of ginger (50 mg/kg) for 5 weeks	↓Plasma total cholesterol, liver weight, plasma triglyceride, nonesterified fatty acid (NEFA), glucose concentrations, the ratio of liver weight to body weight and hepatic triglyceride content ↓Vacuolization and Oil Red O staining area ↓The mRNA levels of acetyl-CoA carboxylase (ACC)1, FAS, stearoyl-CoA desaturase (SCD)1, and G6Pase ↓Hepatic expressions of the carbohydrate response element-binding protein (ChREBP) and targeted lipogenic genes	56
	Methionine and choline-deficient diet induced steatohepatitis rats	6-Gingerol (25, 50, or 100 mg/kg) for 4 weeks	↓Liver weight, hepatic TC, and TG ↓ALT and AST activities ↓The protein and mRNA levels of MCP-1, TNF-α, and IL-6 ↓Hepatic level of cytosolic nuclear transcription factor (NF-κB) p65 protein ↓Hepatic diacylglycerol acyltransferase 2 (DGAT2) mRNA levels ↑Hepatic peroxisome PPARα mRNA levels	36
	Male golden hamsters on a high-fat diet	6-Gingerol (25, 50, or 100 mg/kg) for 8 weeks	↓Body weight, liver weight index, plasma glucose, HOMA-IR, plasma leptin, and insulin levels ↓Plasma levels of TG, TC, LDL-C, and FFA ↓Hepatic TC and TG levels ↓The number of macrovascular fat droplets and mild inflammatory foci ↓The protein and mRNA levels of MCP-1, TNF-α, IL-1β, and IL-6 ↓The protein levels of NF-κB and p65 and NF-κB–p65 binding activity ↓The mRNA levels of sterol-regulating element–binding protein-1c (SREBP-1c), liver X receptor-α (LXR-α), ACC, FAS, SCD-1, and DGAT-2 ↑Plasma adiponectin and HDL-cholesterol concentrations	35

Continued

Table 2. *Continued*

Effect on metabolic syndrome	Model	Dose and duration	Experimental outcome	References
	HFD-induced obese rats	Ginger essential oil (12.5, 62.5, and 125 mg/kg) and its major component citral (2.5 and 25 mg/kg) for 12 weeks	↓Serum free fatty acid, triglyceride, and total cholesterol levels ↓Hepatic lipid accumulation ↓The protein expressions of SREBP-1c, ACC, FAS, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), cytochrome P450 2E1 (CYP2E1)	57

diabetic patients (Table 3).[60,61,66] The consumption of ginger significantly improved insulin sensitivity and glucose homeostasis.[59,62] Additionally, ginger exhibited beneficial effects on blood pressure and endothelial function in T2DM patients.[64] These results mean that ginger could be useful in improving glucolipid metabolism and the treatment of diabetic complications.

Nonalcoholic fatty liver disease

NAFLD is a metabolic stress, and its prevalence is rapidly increasing owing to strong association with obesity, dyslipidemia, T2DM, and hypertension.[67] Several factors (hepatic lipid accumulation, oxidative stress, and inflammation) are involved in the pathologic metabolic mechanisms that ultimately lead to the accumulation of liver fat and NAFLD progression.[57] Ginger has been reported to have significant anti-NAFLD effects in both *in vivo* and *in vitro* studies. The ethanolic extract of ginger can ameliorate fructose-induced fatty liver and suppress hepatic *de novo* lipogenesis in rats.[56] Another experiment showed that 6-gingerol could protect against HFD-induced hepatic steatosis and related metabolic disorders by decreasing the induction of inflammatory cytokines.[35] In a methionine and choline-deficient (MCD) diet–induced steatohepatitis animal model, 6-gingerol was able to regulate the expression of key genes related to lipid metabolism and inflammation and showed an inhibitory effect on hepatic steatosis.[36]

In vitro studies demonstrated that preincubation with 6-gingerol significantly attenuated the accumulation of lipids and alleviated the overproduction of cellular fatty drops and inflammatory cytokines in HepG2 cells.[35,36] Furthermore, 6-gingerol could potentially protect against IL-1β–induced inflammation and oxidative stress in human hepatocyte (HuH-7) cells.[31] In primary hepatic cells, it was observed that ginger could significantly reduce intracellular ROS accumulation to prevent cell death and liver injury.[34]

Besides the laboratory results, a clinical trial also demonstrated that ginger supplementation resulted in a significant reduction in alanine aminotransferase, γ-glutamyl transferase, inflammatory cytokines, and the insulin resistance index and hepatic steatosis grade in comparison with placebo.[63] Overall, current data provide strong evidence that ginger and its active components possess beneficial effects that may contribute to the management of NAFLD.

Cardiovascular disease

CVDs appear as important causes of morbidity and mortality in both developed and developing countries. Aside from genetic causes, CVDs are usually associated with several risk factors, such as high levels of low-density lipoprotein (LDL) cholesterol, hypertension, diabetes, inflammation, atherosclerosis, and abdominal obesity. Several studies have suggested that consumption of ginger and ginger-derived bioactive agents are associated with decreased risk of CVDs.[49,52,53,58] Hyperlipidemia, which is characterized by increased plasma triglyceride concentration and lowered high-density lipoprotein cholesterol, is one of the major risk factors for the development of the progression of atherosclerosis and its associated CVDs. It was found that ginger extract significantly lowered plasma triglycerides and cholesterol in both an HFD-fed rat model[48] and a hypercholesterolemic rat model.[51,68] Oxidative modification of LDL is thought to be key to the pathogenesis of atherosclerosis. It was found that the antiatherogenic effect of ginger was associated with a significant reduction in plasma cholesterol levels and a significant reduction in the LDL basal oxidative state, as well as their susceptibility to oxidation and aggregation in apolipoprotein E–deficient (E^0) mice.[49] In addition,

Table 3. Clinical trials to assess the beneficial effects of *Zingiber officinale* in metabolic syndromes

Effect on metabolic syndrome	Study design	Subject	Dose and duration	Results (intervention vs. placebo/baseline)	References
Obesity	A randomized, double-blind, placebo-controlled clinical trial	80 eligible obese women (aged 18–45 years)	2 g ginger rhizomes powder for 12 weeks	↓Body weight, body mass index, waist and hip circumferences, appetite score	22
	A randomized, double-blind, placebo-controlled clinical trial	80 eligible obese women (aged 18–45 years)	2 g ginger rhizomes powder for 12 weeks	↑Quantitative insulin sensitivity check index (QUICKI) index ↓Body mass index (BMI), serum insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) index	23
	A 2-arm, randomized, crossover design	10 Overweight men (age 39.1 ± 3.3 years and BMI 27.2 ± 0.3 kg/m^2)	2 g ginger powder dissolved in a hot water beverage	↑Thermic effect of food ↑Fullness ↓Feelings of hunger, prospective food intake	21
Cardiovascular disease	A randomized, double-blind, placebo-controlled trial	36 peritoneal dialysis patients	1000 mg ginger daily for 10 weeks	↓Serum fasting glucose	58
Diabetes	A double-blinded placebo-controlled clinical trial	70 patients with type 2 diabetes mellitus (T2DM)	1600 mg ginger daily for 12 weeks	↓Fasting plasma glucose, glycated hemoglobin A1c (HbA1C), insulin, HOMA, triglyceride, total cholesterol, C-reactive protein (CRP), and PGE_2	59
	A randomized, double-blind, placebo-controlled clinical trial,	41 patients with T2DM	2 g/day of ginger powder supplement for 12 weeks	↑Apolipoprotein A-I ↓Fasting blood sugar, hemoglobin A1c, apolipoprotein B, apolipoprotein B/apolipoprotein A-I, and malondialdehyde	60
	A randomized, double-blind, placebo-controlled trial	88 patients with T2DM	1-g capsules containing ginger powder daily for 8 weeks.	↑QUICKI index ↓Fasting blood sugar, HbA1c	61
	A randomized double-blind placebo-controlled trial	64 Patients with T2DM	One tablet of ginger twice a day immediately after lunch and dinner for 8 weeks	↑QUICKI index ↓Insulin, low-density lipoprotein cholesterol, triglyceride, HOMA index	62
Nonalcoholic fatty liver disease	A randomized, double-blind, placebo-controlled clinical trial	44 Patients with nonalcoholic fatty liver disease (NAFLD)	2 g per day of a ginger supplement for 12 weeks	↓Alanine aminotransferase, γ-glutamyl transferase, inflammatory cytokines, insulin resistance index, and hepatic steatosis grade	63
Blood pressure	A parallel, randomized, single-blind placebo-controlled clinical trial	204 Patients with T2DM	3 g ginger with three glasses of black tea for 8 weeks	↓Intercellular adhesion molecule-1 concentrations, systolic blood pressure	64

6-shogaol could prevent the oxidized LDL–induced development of atherosclerosis and plaque rupture, probably via its antioxidant and anti-inflammatory properties.[37]

Angiotensin-1-converting enzyme (ACE) is a powerful vasodilator that plays critical roles in the regulation of vascular tone and cardiac functions.[52] An increase in ACE activity is believed to influence the development of hypertension. The antihypercholesterolemic properties of ginger were observed in a high cholesterol–fed rat model.[52] The activities of some key enzymes, such as ACE and arginase, were inhibited, and a concomitant increase in NO level was observed.[54] Simultaneously, the antihypertensive effect of ginger was also associated with the platelet hyperactivity[55] and potential neuroprotective effects.[69]

Lipid abnormalities are one of the major risk factors for CVD in peritoneal dialysis (PD) patients. In a clinical study examining PD patients, ginger treatment reduced serum triglyceride concentration.[58] On the basis of the above results, it is concluded

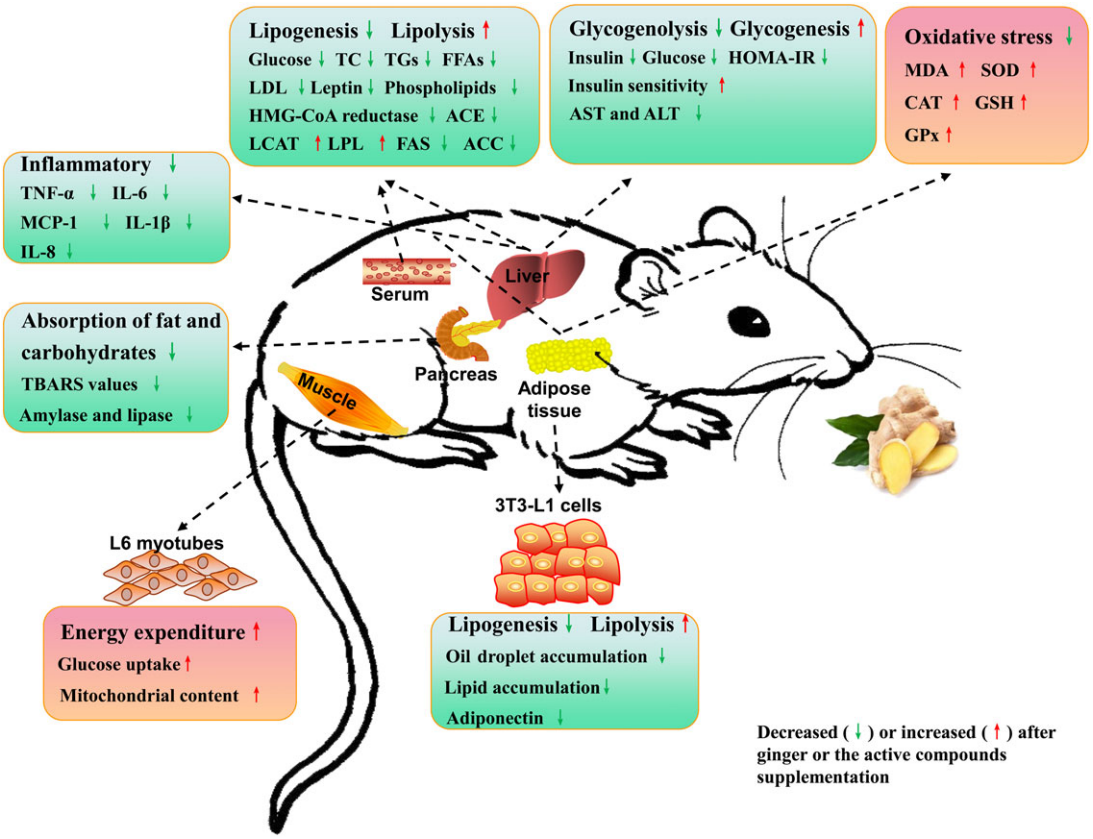

Figure 1. Schematic diagram depicting the beneficial effects of ginger and its active compounds on metabolic responses. Ginger or the active compounds prevented an increase in serum lipid and glucose concentrations by inhibiting the activity of enzymes in carbohydrate and lipid metabolism, increased lipolysis in liver and adipose tissue, decreased oxidative stress in white adipose tissue, increased capacity of energy metabolism in skeletal muscle, and decreased the expression of inflammation-related genes in adipose tissue and liver.

that the beneficial effects of ginger in controlling lipid disorders, lowering plasma cholesterol levels, preventing hypertension, and improving endothelial function contribute to the prevention of cardiovascular and metabolic disorders.

Signaling pathways modulating lipid and glucose metabolism by ginger

Recently, ginger has been shown to ameliorate obesity, diabetes, NAFLD, CVDs, and related metabolic disorders via different mechanisms, such as improvement of blood lipid profiles, alleviation of insulin resistance, normalization of blood glucose levels, and inhibition of oxidative stress and inflammation. The molecular mechanisms responsible for the observed hypolipidemic and hyperglycemic activities of ginger probably involve its capacity to inhibit mediators and transcription factors, such as peroxisome proliferator–activated receptors (PPARs), adenosine monophosphate (AMP)–activated protein kinase (AMPK), and nuclear factor κB (NF-κB; Fig. 2).

PPARs signaling pathway

The PPARs, transcription factors of the nuclear hormone receptor superfamily, are the main regulators of many genes involved in cellular lipid homeostasis, adipocyte differentiation, and insulin regulation.[70] There are three members of the PPAR family: α, γ, and δ. While PPAR-α is present in the liver and PPAR-δ is highly active in skeletal muscle, PPAR-γ is primarily expressed in adipose tissue. Recent studies indicated that PPARs are the major mediators of the antiobesity and antidiabetic effects of ginger and its constituent compounds. In adipocytes, PPAR-γ

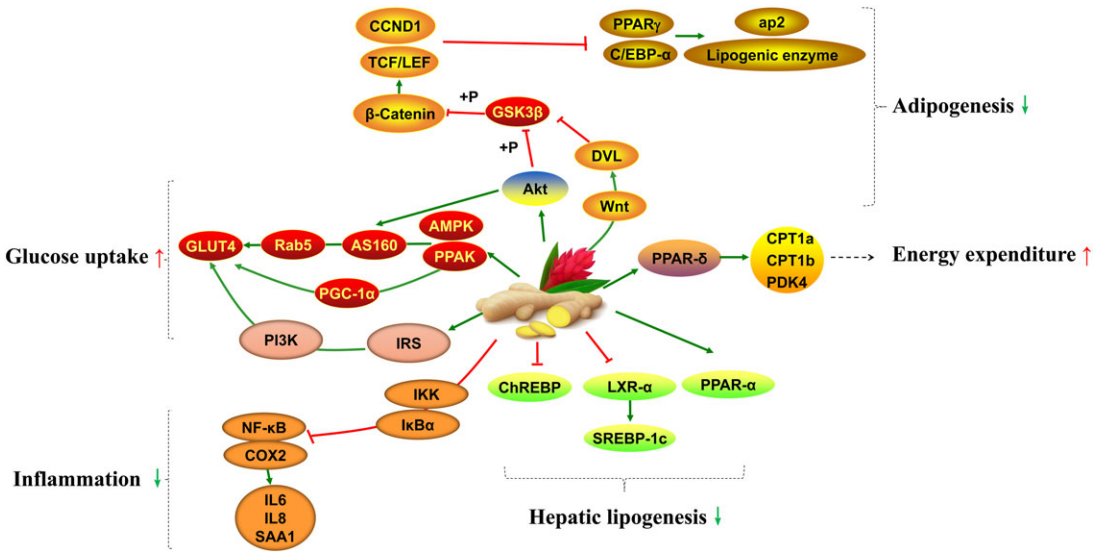

Figure 2. Ginger and its active compounds improve lipid and glucose metabolism through multiple mechanisms, including regulation of the AMPK, PPARs, and NF-κB signaling pathways.

and CCAAT/enhancer-binding protein α (C/EBP-α) are the key transcription regulator genes involved in adipogenesis. Studies in 3T3-L1 cells showed that 6-gingerol effectively suppressed adipogenesis through significant downregulation of PPAR-γ and C/EBP-α and inhibited their subsequent transactivation of adipocyte-specific genes, such as adipocyte-specific fatty acid binding protein (aP2), and lipogenic enzymes like FAS, which are relevant to lipid accumulation and lipid metabolism. Meanwhile, 6-gingerol could inhibit adipocyte differentiation by attenuating the Akt/GSK-3β pathway[18] and activating the Wnt/β-catenin signaling pathway.[19] 6-Shogaol reduced the expression of PPAR-γ-associated genes and reduced adipogenesis in the same cell line.[20] PPAR-γ is always activated by SREBP-1c, which is a crucial lipogenic transcription factor. SREBP-1c plays a key role in lipid metabolism in adipose tissue by regulating the expression of enzymes involved in fatty acid synthesis. Oral treatment with 6-gingerol significantly downregulated the adipogenesis gene expression levels of PPAR-γ and SREBP-1c and modulated the expression of lipid marker enzymes and inflammatory markers in HFD-induced obese rats.[16] Carbohydrate response element–binding protein (ChREBP) plays a critical role in converting excess carbohydrates into triglycerides; inhibition of ChREBP can improve hepatic steatosis, hypertriglyceridemia, and insulin resistance.[71] It was found that ginger supplementation could ameliorate fructose-induced fatty liver and hypertriglyceridemia in rats by modulation of the hepatic ChREBP-mediated pathway instead of the PPAR-γ pathway.[56] These results were attributed to the tissue-specific regulation of the lipogenic protein/genes by ginger treatment.

PPAR-δ is a major transcriptional regulator of energy metabolism in skeletal muscle. The activation of PPAR-δ has been shown to induce fatty acid oxidation and can be regarded as a promising strategy to ameliorate obesity. It was demonstrated that dietary supplementation with ginger extract could attenuate diet-induced obesity in mice by increasing energy expenditure via PPAR-δ signaling in mice. The underlying mechanism *in vitro* suggests that 6-shogaol and 6-gingerol in ginger may serve as PPAR-δ agonists with subsequent effects on energy homeostasis in skeletal muscle.[14]

PPAR-α is mainly characterized in the liver, where it controls lipid homeostasis by regulating the expression of genes involved in fatty acid transport and oxidation, hence lowering plasma levels of triglycerides.[72] In a methionine- and choline-deficient diet–induced hepatosteatosis animal model, 6-gingerol presented a repressive effect on hepatic steatosis, which was associated with the induction of PPAR-α.[73] In short, the results of recent studies appear to support the view that the

regulation of PPARs by ginger is one of the main pathways linked to therapeutic areas related to lipid and glucose metabolism and inflammation, such as T2DM, obesity, and NAFLD.

AMPK signaling pathway

AMPK is an enzyme that plays an important role in cellular and whole-body energy homeostasis. AMPK is activated upon phosphorylation at threonine 172 (Thr172) of its α-subunit.[9] The activation of AMPKα is accompanied by the upregulation of peroxisome proliferator–activated receptor γ coactivator 1-α(PGC-1α), which plays a key role in regulating mitochondrial biogenesis in tissues with active oxidative metabolism. Recently, in an HFHC diet–fed rat model of MetS, ginger extract treatment significantly improved insulin sensitivity by enhancing AMPKα phosphorylation and total AMPKα in skeletal muscle tissue. The further *in vitro* mechanistic study showed that 6-gingerol could increase AMPKα activation and PGC-1α gene expression and promoted mitochondrial biogenesis in L6 myotubes.[29] These results suggested that the beneficial effects of ginger on modulating glucose metabolism are probably associated with the molecules mediated by energy-sensing, such as AMPK.

The activation of AMPK also increases glucose uptake by promoting glucose transporter (GLUT4) to the cell membrane. GLUT4 translocation involves the binding of insulin to insulin receptor and the subsequent activation of phosphatidylinositol-3 kinase (PI3K) and Akt.[48] It was found that ginger extract and 6-gingerol enhanced glucose uptake with associated activation of AMPKα-subunit in cultured L6 skeletal muscle cells.[27] Findings also implied that the ethyl acetate extract of ginger and 6-gingerol stimulated glucose uptake through promotion of GLUT4 translocation via AMPK activation in L6 myotubes[26,46] and hepatocyte cells.[25] An *in vivo* study recently confirmed that 6-gingerol has significant potential to enhance the activation of AMPKα and PGC-1α in the regulation of lipid profiles in diet-induced obesity. 6-Gingerol plays an important role in glucose metabolism via the AMPKα2-mediated AS160–Rab5 pathway and through insulin-mediated glucose regulation.[9]

NF-κB signaling pathway

Overnutrition-induced chronic inflammation is a key contributor to the pathogenesis of insulin resistance and MetS. NF-κB is the master regulator of the inflammatory response. When cells are exposed to proinflammatory stimuli, NF-κB is activated and migrates to the cell nucleus, where it directs transcription of target genes, including genes encoding cytokines, chemokines, and the enzyme cyclooxygenase 2 (COX2).[18] COX2 is responsible for production of prostaglandins in response to inflammation and promotes the production of proinflammatory cytokines.[31] Different studies have shown that ginger suppress inflammation through inhibition of the classical NF-κB pathway in various cell types and tissues.[24,33,74] It was shown that ginger treatment could decrease the expression of cytokine genes (TNF-α and IL-6) in the liver of HFD-fed rats, which was associated with suppression of NF-κB activation. A further *in vitro* study demonstrated that ginger could suppress NF-κB activation by attenuating signaling through the IKK/IκBα/NF-κB classical pathway.[11]

Gingerols, as well as other active compounds, are major foci of research related to the anti-inflammatory effects of ginger. It was found that 6-gingerol protects against hepatic inflammation, which underlies the pathogenesis of chronic diseases, such as insulin resistance and type 2 DM, through inhibition of the ROS-activated NF-κB/COX2 pathway.[31] 6-Gingerol also suppressed the upregulation of nuclear NF-κB DNA-binding activity in the livers of MCD diet–fed mice, suggesting that the anti-inflammatory effect of 6-gingerol on nonalcoholic steatohepatitis is mediated, in part, through the NF-κB signaling pathway.[36] Moreover, 6-gingerol could attenuate HFD-induced hepatic inflammation and insulin resistance by decreasing the induction of inflammatory cytokines via an NF-κB-dependent pathway.[35] Taken together, the results above revealed that ginger, as an anti-inflammatory agent, played an essential role in protecting against hepatic inflammation through the activation of NF-κB, which underlies the pathogenesis of chronic diseases, such as type 2 DM and nonalcoholic steatohepatitis.

Conclusions

Epidemiological and clinical studies from recent years have built a consensus that ginger and its major constituents exert beneficial effects against obesity, diabetes, CVDs, and related disorders, more commonly referred to as MetS. These effects are

mediated through regulation of lipid metabolism; suppression of carbohydrate digestion; modulation of insulin secretion and response; inhibition of oxidative stress; enhancement of anti-inflammatory activities; and antihyperlipidemic, hypotensive, and antiatherosclerotic mechanisms (Fig. 1). The regulation of mediators and transcription factors, such as PPARs, AMPK, and NF-κB, contribute to the therapeutic effects of ginger (Fig. 2). Except for animal models and *in vitro* cell studies, many clinical studies have been conducted on humans to evaluate the beneficial effects of ginger (Tables 1–3). However, further studies are advocated to evaluate the effects of ginger and its main components in human subjects in the prevention and/or treatment of metabolic disorders.

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Competing interests

The authors declare no competing interests.

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