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REVIEW

Rosemary (*Rosmarinus officinalis*) as a potential therapeutic plant in metabolic syndrome: a review

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Abstract Metabolic syndrome is defined by a constellation of complex coexisting cardiometabolic risk factors such as hyperglycemia, dyslipidemia, inflammation, abdominal obesity, coagulopathies, and hypertension that raise the risk of diabetes mellitus and cardiovascular disease. Recently, there has been an increasing interest in the use of herbs and natural compounds in prevention and treatment of diseases and a large number of published articles have focused on this issue. *Rosmarinus officinalis* L. or rosemary (Lamiaceae) is a rich source of phenolic phytochemicals having significant anti-oxidant, anti-inflammatory, hypoglycemic, hypolipidemic, hypotensive, anti-atherosclerotic, anti-thrombotic, hepatoprotective, and hypocholesterolemic effects. The purpose of this review is to highlight the interesting pharmacological effects of rosemary, and its active compounds, and the related mechanisms in the management of metabolic syndrome that are documented in in vitro and in vivo studies.

Keywords Metabolic syndrome · *Rosmarinus officinalis* · Cardiovascular disease · Obesity · Diabetes

Introduction

Metabolic syndrome (syndrome X) is defined as a complex metabolic disorder with disturbance of glucose metabolism (insulin resistance, high blood glucose, and impaired glucose tolerance), central obesity and being overweight, abnormalities in serum lipid levels, hypertension, and atherosclerosis (Alberti et al. 2006; Miranda et al. 2005). It is considered as a major public health problem and the cause of morbidity and mortality due to high risks for developing cardiovascular diseases (Isomaa et al. 2001) and diabetes mellitus (Haffner et al. 1992). According to the National Cholesterol Education Program (NCEP) criteria, diagnosis of the metabolic syndrome is confirmed in person who meets at least three of the following: abdominal obesity: waist circumference >102 cm in men and >89 cm in women (in case of body mass index (BMI) >30 kg/m^2, central obesity can be assumed instead of measuring waist circumference), raised plasma triacylglycerol (TG) ≥150 mg/dL, reduced high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men or <50 mg/dL in women, raised blood pressure ≥130/85 mm Hg, and fasting plasma glucose of 110 to 125 mg/dL (Alberti et al. 2005; Miranda et al. 2005).

Medicinal plants have been in the center of attention for the following: their potential effect in improving and maintaining human health, low side effects, and low costs for thousands of years. They are commonly used to treat various disorders such as dyslipidemia and hypertension and to restore metabolic balance (Huang et al. 2005; Ramadan et al. 2013). So, identifying herbs and their active compounds with these effects can be a good choice in the treatment of metabolic syndrome (Hosseini and Hosseinzadeh 2015; Hosseinzadeh and Nassiri-Asl 2014; Razavi and Hosseinzadeh 2014; Sahebkar 2013). *Rosmarinus officinalis* Linn. (rosemary) belonging to the family Lamiaceae is an evergreen aromatic plant with 1-m height, upright stems, whitish-blue flowers, and dark green leaves distributed in the Mediterranean region. Rosemary extract, especially the leave extract, was shown to be one of the most popular herbal products that has been consumed as a flavoring and anti-oxidant agent in food conservation and

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cosmetics (Cui et al. 2012; Perez-Fons et al. 2010). In many countries, rosemary is frequently used as a medicinal plant in the traditional and modern medicines to treat diabetes complications and hypertension (Amel 2013; Javanmardi et al. 2003; Martynyuk et al. 2014). In folk medicine, it is widely used as a remedy for several purposes like reducing pain, antispasmodic in renal colic and dysmenorrhea, anti-rheumatic, carminative, cholagogue, diuretic, expectorant, anti-convulsant, stimulating hair growth (hair tonics, hair lotion), and many other effects (al-Sereiti MR et al. 1999). Hypoglycemic (Ramadan et al. 2013), anti-atherogenic (Ullevig et al. 2011), anti-hypertensive (Kwon et al. 2006), hypocholesterolemic (Afonso et al. 2013), anti-oxidant and anti-inflammatory (Rocha et al. 2015), hepatoprotective (Fahim et al. 1999), anti-depressant (Sasaki et al. 2013), anti-proliferative (Tai et al. 2012), and anti-bacterial (Wang et al. 2012b) activities; diminishing morphine withdrawal syndrome (Hosseinzadeh and Nourbakhsh 2003; Hosseinzadeh et al. 2006); healing diabetic wounds (Abu-Al-Basal 2010; Umasankar et al. 2012); and the treatment of cognitive disorder (Hosseinzadeh et al. 2004) are approved as diverse pharmacological activities for rosemary in modern scientific research projects. It has also been reported that the bioactive compounds of rosemary have either direct or indirect epigenetic targets in cancer chemoprevention and chemotherapy and hold great potential in the prevention and the therapy of a wide variety of diseases by altering various epigenetic modifications (Meeran et al. 2010). Analysis of chemical composition of different rosemary extracts shows that the most important pharmacologically active constituents are phenolic diterpenes, triterpenes, and phenolic acids such as carnosic acid (CA), carnosol, rosmanol, ursolic acid, betulinic acid, and rosmarinic acid (RA) (al-Sereiti MR et al. 1999; Borras-Linares et al. 2014; Okamura et al. 1994; Tu et al. 2013). The chemical structures of these compounds of rosemary are presented in Fig. 1. Among the isolated phenolic compounds, CA and RA have been shown to possess predominant pharmacological effects of rosemary including anti-oxidant, anti-inflammatory, anti-viral, and anti-bacterial actions and to interact with multiple molecular targets that are involved in the pathogenesis of metabolic syndrome (Birtic et al. 2015; Jayanthy and Subramanian 2014; Lipina and Hundal 2014; Sedighi et al. 2015). The aims of the present review are to summarize the potential efficacy of rosemary and its active compounds in metabolic syndrome and to identify the underlying mechanisms of action.

Effects on diabetes and on the lipid profile

Suppression of gluconeogenesis

High blood glucose concentration in type II diabetes is the final result of imbalance among intestinal absorption, gluconeogenesis in the liver, glucose consumption, and uptake by the peripheral tissues. There are several enzymes that control gluconeogenesis in the liver including cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C) and glucose-6-phosphatase (G6Pase). Cyclic adenosine monophosphate (CAMP) response element binding protein (CREB: a transcription factor) which is activated via the adenylate cyclase/cAMP/protein kinase A (AC/cAMP/PKA) signaling pathway

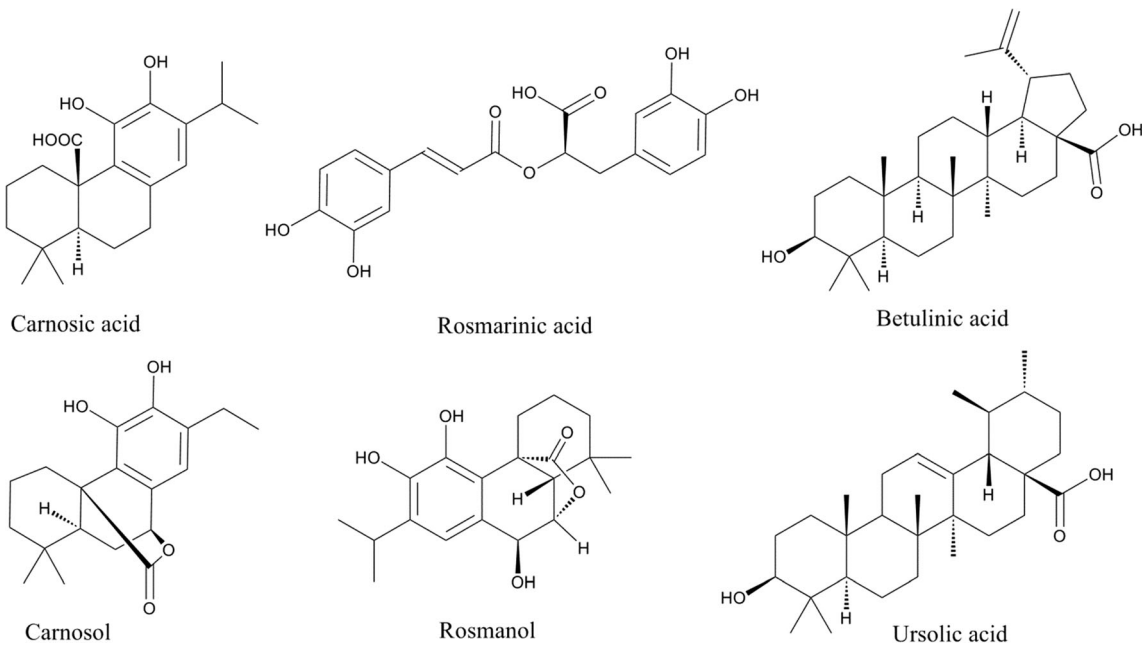

Fig. 1 Chemical structures of rosemary constituents

binds to the promoters of the PEPCK-C, G6Pase, and peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC1α) genes (a transcription coactivator which induces PEPCK-C and G6Pase) and enhances their transcription (Herzig et al. 2001). So, suppression of these enzymes or related genes results in the reduction of fasting blood glucose and are important goals for managing type II diabetes. According to these facts, results of Yun et al. (2013) study showed that 100 μg/mL methanolic extract of rosemary especially 7-*O*-methylrosmanol and royleanonic acid constituents in HepG2 cells suppressed the cAMP responsiveness of gluconeogenic genes, PEPCK-C and G6Pase promoters. Carnosol showed suppressive activity toward cAMP/CREB-induced gene expression under the G6Pase promoter control. So, inhibition of the cAMP/PKA/CREB pathway may involve in the mechanism of action of rosemary-induced reduction of fasting blood glucose (Yun et al. 2013). In a model of type 2 diabetes, RA (100 mg/kg) decreased blood glucose, urine sugar, and glycosylated hemoglobin (HbA1C), which is an important predictor of diabetic complications and long-term glycemic control. These effects were exhibited through the modulation of carbohydrate-metabolizing enzymes such as hexokinase, pyruvate kinase (glycolytic enzymes), and G6Pase and fructose 1,6-bisphosphatase (gluconeogenic enzymes) and glycogen metabolism (Jayanthy and Subramanian 2014). Hormone-sensitive lipase (HSL) is a kind of neutral lipase which catalyzes the hydrolysis of triglycerides leading to a flux of free fatty acids (FFAs) from the adipocytes. Since the activity of this enzyme is normally inhibited by insulin, in type 2 diabetes (insulin resistance) suppression of the HSL activity is diminished resulting in excessive FFAs levels in plasma. Plasma FFA levels are involved in the modulation of carbohydrate metabolism in several tissues, including liver and muscle (Voshol et al. 2003). Elevated FFA levels stimulate overproduction of glucose in the liver and contribute to the inhibition of glucose uptake and utilization by muscles (Bergman and Ader 2000). Bustanji et al. (2010) undertook an investigation to identify how rosemary could ameliorate the blood glucose and lipid profile simultaneously. In in vitro assay, they revealed that methanol rosemary extract dose dependently (with the component gallic acid: IC_{50} 14.5 μg/mL) inhibited the activity of this enzyme (Bustanji et al. 2010) (Fig. 2).

Inhibition of the breakdown of carbohydrates

An important carbohydrate in daily dietary is starch which is converted to monosaccharides by α-glucosidase (AGc) and α-amylase in the small intestines. Oral administration of rosemary-distilled extract to normal and diabetic mice was effective in reduction of plasma glucose levels. The anti-diabetic effect of rosemary observed in this study was deduced from the activity of the active compounds in inhibiting the action of AGc (maltase and sucrase) in the diabetic group (Koga et al. 2006). In biochemical tests, the aqueous and methanol extracts of rosemary inhibited AGc and α-amylase activities (Cazzola et al. 2011). In another survey, α-amylase inhibitory effects of RA were also seen on porcine pancreatic amylase (McCue and Shetty 2004). The aqueous extract of clonal herbs of Lamiaceae species especially rosemary and the active phenolic compounds including caffeic acid and RA (water extracts contained more phenolic compound than ethanol extracts) had also a great AGc inhibitory activity (68 %), but they did not have inhibitory effects on α-amylase activity (Kwon et al. 2006).

Regulation of PPAR-γ

PPAR-γ, which is a nuclear receptor protein, controls the glucose transport and metabolism and the transcription of the proteins and enzymes responsible for glucose and fatty acid cellular uptake (Scazzocchio et al. 2011). PPAR-γ agonists like thiazolidinediones (glitazones), a class of hypoglycemics, have shown to increase glucose catabolism and decrease hepatic glucose output. In skeletal muscle, PPAR-γ increases glucose uptake to lower blood glucose levels, and in the liver, G-protein downregulation may mediate PPAR-γ-elicited insulin sensitization (Jay and Ren 2007). In Rau et al. (2006) research, 80 % using a reporter gene assay aqueous ethanol extract of rosemary was effective in PPAR-γ activation. The analysis of active constituents revealed that both phenolic diterpene compounds carnosol and CA were responsible for these effects, and as a result, it can be a part of the mechanism of anti-hyperglycemic effects of rosemary like glitazone, a type of glucose-lowering drugs (Rau et al. 2006). Based on the anti-oxidant and ameliorating effects of dichloromethane-methanol rosemary extract on complications associated with type-2 diabetes mellitus and obesity, Tu et al. 2013, described the mechanism of metabolic regulation of the extract in HepG2 cells. The rosemary extract showed hypoglycemic and hypolipidemic effects by activation of signaling pathways including AMP-activated protein kinase (AMPK) (which induce glycolysis) and PPAR-γ and up-regulation of low-density lipoprotein cholesterol (LDL-C) receptor (responsible for endocytosis of LDL-C from circulation to liver hepatocytes), sirtuin 1 (increases fatty acid oxidation), and PGC1α (activates PPAR-γ) (Tu et al. 2013) (Fig. 2). Findings of another survey implied that CA in 3T3-L1 adipocytes increased the PPAR-γ messenger RNA (mRNA) expression, suppressed activation of nuclear factor-κB (NF-κB) (which is activated by tumor necrosis factor-α (TNF-α) and inhibits the activity of PPAR-γ in adipocytes), and improved glucose uptake through promotion of glucose transporter type 4 (GLUT4) translocation in adipocytes (Tsai et al. 2014).

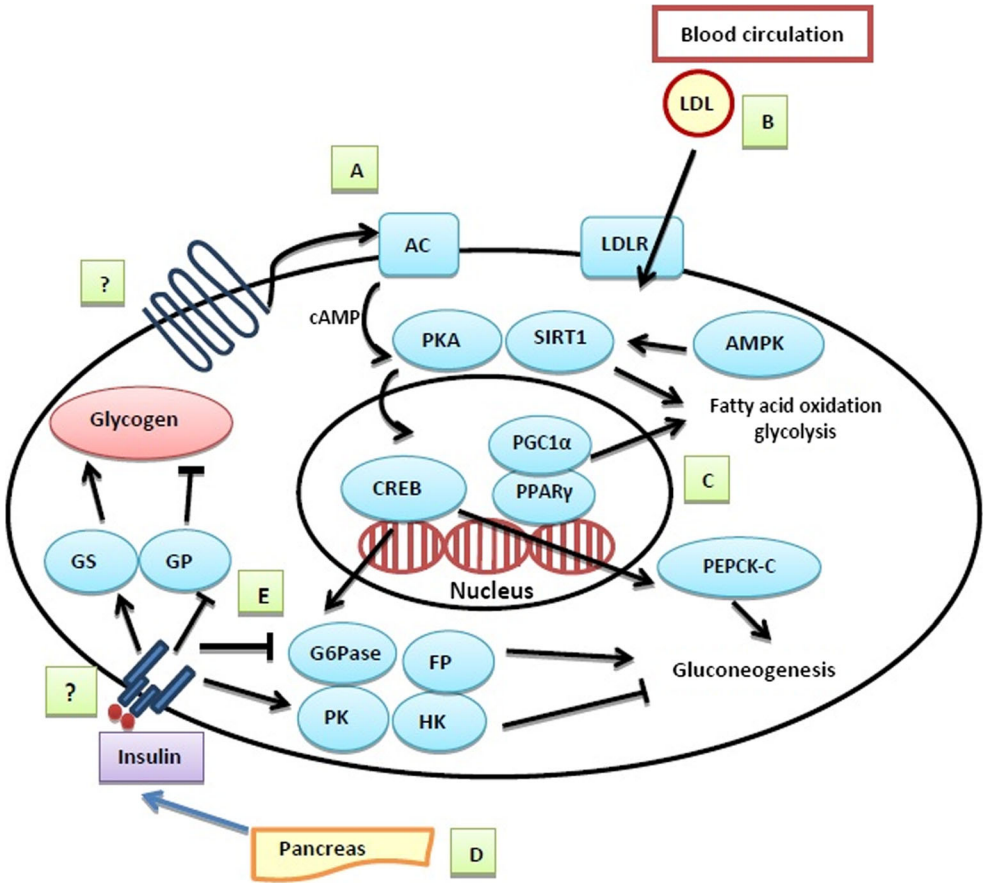

Fig. 2 Rosemary and related compounds improve lipid and glucose metabolism through multiple mechanisms: *A* suppressing the cAMP responsiveness of gluconeogenic genes, PEPCK-C, and G6Pase; *B* up-regulation of LDLR; *C* activation of the AMPK and PPAR signaling pathways, up-regulation of sirtuin 1, and PGC1α; *D* increasing insulin secretion; and *E* modulation of carbohydrate-metabolizing enzymes and glycogen metabolisms. There is no information about the receptors involved in these effects. *AC* adenylate cyclase, *AMPK* AMP-activated protein kinase, *CREB* cAMP response element binding protein, *FP* fructose 1,6-bisphosphatase, *G6Pase* glucose-6-phosphatase, *GP* glycogen phosphorylase, *GS* glycogen synthase, *HK* hexokinase (glycolysis), *LDLR* low-density lipoprotein receptor, *PEPCK-C* cytosolic phosphoenol pyruvate carboxykinase, *PGC* PPAR-γ coactivator, *PK* pyruvate kinase (glycolysis), *PKA* protein kinase A, *SIRT1* sirtuin 1, *PPAR* peroxisome proliferator-activated receptor

Reduction of inflammatory cytokines

Low-grade chronic inflammation in adipose tissue is associated with obesity and insulin resistance. Inflammatory cytokines, such as TNF-α, interleukin 6 (IL-6), and monocyte chemotactic protein-1 (MCP-1), secreted by adipose tissue, inhibit the expression of GLUT4, mediating glucose uptake in adipocytes, and cause insulin resistance (Tsai et al. 2014; Xie et al. 2010). The results of the study done by Tsai et al. (2014) indicated that CA reduced the TNF-α-mediated inflammation and improved insulin resistance in 3T3-L1 adipocytes. The mechanism has been suggested to be inhibition of mRNA expression of the inflammatory genes (IL-6 and MCP-1) and protein levels of multiple agents of mitogen-activated protein kinase (MAPK) signaling pathway (extracellular signal-regulated kinase [ERK] and c-Jun NH2-terminal kinase [JNK]), mammalian target of rapamycin (mTOR), and forkhead transcription factor 1(FOXO1 binds to PPAR-γ and inhibits its function) (Tsai et al. 2014). Ursolic acid (UA), b-hydroxy-12-urs-12-en-28-oic acid, a pentacyclic triterpenoid carboxylic acid with anti-oxidant, anti-inflammatory, anti-tumor, anti-atherosclerotic, and anti-hypertensive activities, is another bioactive compound of rosemary. The inhibition of T cell and B cell proliferation, ERK, JNK, MAPK kinase, and c-raf phosphorylation, which control T cell survival; suppression of regulators of antigen-induced immune response including NF-κB, nuclear factor of activated T cell (NF-AT), and activator protein-1(AT-1); and reduction of the IL-1b, TNF-α, and IL-6 secretion are responsible for anti-inflammatory actions of UA (Checker et al. 2012).

Anti-oxidative stress

Hyperglycemia induces oxidative stress through generation of free radicals that results in development of diabetic complications such as atherosclerosis, hyperlipidemia,

hypertension, and tissue and cell (like pancreatic β-cells) damages (Bakirel et al. 2008). As expression of anti-oxidant enzymes is low in pancreatic β-cells, they are particularly susceptible to the deleterious effects of reactive oxygen species (ROS) which induce apoptosis and suppress insulin biosynthesis (El-Alfy et al. 2005; Vijayakumar et al. 2006). So, the anti-oxidant agents can protect the functional β-cells from further deterioration or they can induce the regeneration of β-cells by alleviating the oxidative damage. Oral administration of high doses of ethanol rosemary extract (especially 200 mg/kg) reduced blood glucose, in normoglycemic and glucose-hyperglycemic rabbits. Evaluation of in vivo anti-oxidant activity revealed that the rosemary extract reduced serum malondialdehyde (MDA) (as a marker of lipid peroxidation) and elevated activities of serum superoxide dismutase (SOD) and catalase (CAT) (an anti-oxidant enzymes) (Bakirel et al. 2008). Ameliorating effect of endurance exercise with aqueous rosemary extract on blood anti-oxidant enzyme activities and lipid peroxidation was also demonstrated in Nazem et al. (2015) research. Anti-hyperlipidemic and anti-oxidant effects of two kinds of rosemary extracts including aqueous (major compound: RA) and nonesterified phenolic fraction (NEPF) (major compound: CA) were evaluated in hypercholesterolemic rats. Both kinds of extracts increased anti-oxidant enzymes activity in liver and kidney. The NEPF showed no significant effect on the hyperlipidemia, but the aqueous rosemary extract improved the lipid profile (70 mg/kg) (Afonso et al. 2013).

Anti-hyperlipidemic effects

Hyperlipidemia is known to be a cause of lipid peroxidation and atherosclerosis. The lipid-lowering and anti-oxidant activities of aqueous rosemary extract (RA was the most important active constituent), essential oil, and crude plant powder (mixture of hydrophilic and lipophilic compounds are similar to the aqueous extract and essential oils, respectively) were studied in high-fat-diet-fed SD rats (hyperlipidemia rat model). The effects of these three forms were different on hyperlipidemic rats. While essential oil in all doses resulted in higher cholesterol levels, the aqueous extract and the plant powder with greater extent decreased the serum cholesterol levels. The lowering effect on TG levels was obvious with the essential oil and more significant with the powder. The aqueous extract, essential oil, and crude plant powder reduced MDA levels, increased serum HDL-C levels and SOD activity, and improved anti-oxidant capacity (Wu et al. 2011). In another attempt, Al Sheyab et al. (2012) found that administration of 100 mg/kg aqueous rosemary extract to the mice on a high fat diet reduced the plasma levels of total cholesterol, TG, and LDL-C and increased the HDL-C levels.

Improvement of insulin action and secretion

Type 2 diabetes mellitus is characterized by high blood glucose and insulin resistance. Lipina and Hundal 2014 reported that CA at 20-μM concentration like insulin stimulated glucose clearance by rat skeletal L6 myotube through protein phosphatase methylesterase-1/ protein phosphatase 2A/ protein kinase B or Akt (PME-1/PP2A/PKB) signaling axis. It also increased the translocation of the GLUT4 to plasma membrane. Mechanistically, CA increased demethylation (inactivation) of the PP2A catalytic subunit through PME-1, so reduced the suppressive effects of PP2A on PKB which mediates insulin-induced glucose uptake in skeletal muscle independent of AMPK. Moreover, this study indicated that the effect of CA on glucose uptake was not mediated by PPAR-γ signaling pathway and anti-oxidant activities in L6 myotube (Lipina and Hundal 2014). Naimi et al. (2015) showed that methanol rosemary extract stimulated L6 myotube glucose uptake through increasing AMPK and acetyl-CoA carboxylase (ACC) phosphorylation but did not affect GLUT4 or GLUT1 translocation or insulin receptor substrate 1/phosphoinositide 3-kinase (PI3K)/Akt signaling cascade which is involved in the insulin-stimulated glucose uptake (Naimi et al. 2015). In another study, the effects of greenhouse-grown or commercially purchased herbs on dipeptidyl peptidase IV and protein tyrosine phosphatase 1B were evaluated. Inhibition of these two enzymes results in the improvement of insulin secretion and insulin signaling cascade, respectively. Among all of the herbs, rosemary extract was one of the most potent inhibitors of the mentioned enzymes (Bower et al. 2014). B-Hydroxy-lup-20(29)-en-28-oic acid (betulinic acid (BA)) is a pentacyclic triterpenoid found in hydroalcoholic extract of aerial parts of rosemary. Different doses of BA (especially 10 mg/kg) in male Wistar rats mimicked insulin action and increased insulin secretion, glucose uptake, and glycogen content in muscle via PI3K and MAPK pathway which stimulates GLUT4 synthesis and translocation (Castro et al. 2014).

Obesity

Modulation of lipid synthesis and lipolysis and inhibition of adipocyte differentiation

Obesity is a major public health problem which is characterized by disequilibrium between lipogenic and lipolytic processes which cause storage of excessive fat in the form of TG in white adipose tissue and predispose person to diabetes, coronary heart disease, and hypertension (Langin 2006). Diacylglycerol acyltransferase (DGAT2 and DGAT1), proved to be one of the drug targets in pharmacological studies, is a major enzyme responsible for TG synthesis. Abietane-type

diterpenes and, especially carnosol (40 μm), which is one of the main compounds of the methanol rosemary extract, could suppress DGAT1 activity moderately in in vitro assay and exhibited inhibitory effects on intracellular TG synthesis in human hepatocyte HepG2 cells (Cui et al. 2012). In male obese leptin-deficient C57BL/6J-ob/ob mice model, CA showed anti-obesity activity and reduced hepatic lipid accumulation, food intake, and body weight gain. These metabolic effects were related to decreasing hepatic lipogenesis gene expression (liver fatty acid-binding protein, stearoyl-CoA desaturase 1 (SCD1), fatty acid synthase), regulator of calcineurin 2–3 mRNA expression, which regulates food intake and weight gain, and increasing fatty acid oxidation molecules (carnitine palmitoyltransferase 1, uncoupling protein 2) (Park and Sung 2015a). Treatment with 500 mg/kg of a standard aqueous rosemary extract containing 20 % CA in C57BL/6J mice on a high-fat diet significantly reduced weight gain and cholesterol levels through increasing fecal fat and energy excretion, the inhibition of the pancreatic lipase activity, and the activation of PPAR-γ (30 μg/mL) but did not affect the food or energy intake. The pharmacological dose of the extract used in this study was based on the normal dietary exposure of CA estimated in adults and preschool children (0 · 04 and 0 · 11 mg/kg, respectively) by the European Food Safety Authority Panel on Food Additives (Ibarra et al. 2011). Consumption of a diet containing rosemary ethanol extract rich in CA (40 %) modulated serum lipids, increased fecal weight, and reduced weight gain in obese female Zucker rats. These effects were accompanied with the inhibition of lipase activity in the stomach and reduction of fat absorption, modification of microbiota composition, and decrease in β-glucosidase activity in the cecum of both groups as shown by Romo Vaquero et al. (2012). In intestinal microbiota, β-glucosidase contributes to the fermentation of non-digested polysaccharides to short-chain fatty acids (Romo-Vaquero et al. 2014b; Romo Vaquero et al. 2012). So, the inhibition of the activity of this enzyme reduces dietary energy extraction from short-chain fatty acids which turns into host carbohydrates and lipids. The differentiation of the adipocytes and increase in their size are other causes of obesity and considered as therapeutic targets for the treatment of obesity. Acetone rosemary extract and CA in murine 3T3-L1 cells inhibited preadipocyte differentiation, exerted anti-adipogenic effects, and blocked mitotic clonal expansion and expression of PPAR-γ and CCAAT/enhancer-binding protein α (C/EBPα), which are critical for acquiring the adipocyte phenotype (Gaya et al. 2013). In Park and Sung 2015b study, CA in 3T3-L1 adipocytes suppressed adipogenesis and lipid accumulation. Downregulation of adipogenesis-related genes (PPAR-γ, C/EBPα, SCD1, and SREBP1) and decreasing glycerol 3-phosphate dehydrogenase activity, a key enzyme involved in TG synthesis, are the reported mechanisms for anti-adipogenic effects of CA (Park and Sung 2015b). The endogenous activators of all members of the PPAR family are a variety of fatty acids, which suggests that the PPARs are highly involved in lipid metabolism. Moreover, it has been shown that ligands for this receptor (like thiazolidinediones) have emerged as potent insulin sensitizers used in the treatment of type 2 diabetes. Increased levels of circulating FFAs and lipid accumulation in non-adipose tissue have been implicated in the development of insulin resistance. This situation is improved by PPAR-γ ligands, which promote fatty acid storage in fat depots and regulate the expression of adipocyte-secreted hormones that impact on glucose homeostasis. Although the result is the improvement of insulin sensitivity, undesired side effects such as weight gain through the increased adipogenesis and fat storage limit the utility of this therapy (Larsen et al. 2003; Rangwala and Lazar 2004). So, more studies need to be done on rosemary to dissociate the anti-diabetic and the adverse effects. It may be possible through finding or synthesizing new derivatives that selectively target the PPAR-γ in the desired tissue. The regulatory effects of a commercial rosemary extract on specific genes and also microRNAs that play a role in adipogenesis and the pathogenesis of obesity were evaluated in Stefanon et al. (2015) research. The induction of phase 2 enzymes related to glutathione metabolism and increased levels of total reduced glutathione (GSH) through activation of transcription factor Nrf2 (nuclear factor (erythroid-derived 2)-like 2 is a regulator of phase2 enzyme expression) are other mechanisms for inhibition of 3T3-L1 adipocyte differentiation by CA and carnosol (Takahashi et al. 2009).

Anti-inflammatory effects

Obesity is associated with the activation of the innate immune system that alters metabolic homeostasis over time. Analysis of gene expression networks in adipose tissue identified a signature gene expression pattern enriched for macrophage activation gene that predicted risk for the features of metabolic syndrome. In addition, elevated production of inflammatory cytokines, decreased protective factors (e.g., adiponectin), and communication between inflammatory and metabolic cells appear to contribute to the link between inflammation and metabolic dysfunction (Lumeng CN and Saltiel 2011). In obese individuals, production of many inflammatory cytokines including TNF-α, IL-1β, and leptin is increased by adipocytes (adipokines). In contrast, the levels of anti-inflammatory adipokines (adiponectin) are reduced. These imbalances induce inflammatory processes and signaling pathways (AMPK, PPARs) and negatively affect different organs (liver, brain, adipose tissue, and muscle) (Romo-Vaquero et al. 2014a). Reduced serum inflammatory cytokine levels, MCP-1, TNF-α, and IL-6, which contribute to insulin resistance and diabetes, are another observed mechanism for anti-inflammatory effects of CA in obesity (Park

and Sung 2015a). Consuming a diet containing rosemary extract enriched in CA (40 %) in lean and obese female Zucker rats resulted in increased adiponectin levels (has anti-inflammatory effects, improves insulin resistance, reduces serum TG levels and weight) and induction of PGC1α gene expression (improves fatty acid oxidation and insulin-stimulated glucose transport) (lean rats). Modulation of the transcript levels of phase I and II metabolizing enzyme gene expression such as cytochromes P450 and glutathione transferases (in both groups) and decrease in adipokines (lean group) and adenosine monophosphate activated protein kinase (pAMPK) (obese group) levels are other mechanisms underlying the anti-inflammatory effects of CA (Romo-Vaquero et al. 2014a). The activation of Toll-like receptors (TLRs), which results in increased IL-6 and MCP-1 levels via ERK signaling pathway and NF-κB (which is activated through myeloid differentiation factor 88: MyD88 and TNF receptor-associated factor 6: TRAF6) in adipocytes, is recognized in chronic inflammation induced by obesity. CA dose dependently decreased inflammatory cytokines (TNF-α, IL-6, and MCP-1); TLR4 mRNA expression; and MyD88, TRAF6, p-ERK, and NF-κB (10 and 20 μM) protein levels in lipopolysaccharide-induced inflammation in 3T3-L1 adipocyte (Park and Mun 2014). In other experience in ob/ob mice, Wang et al. 2011 demonstrated that CA (0.05 % *w/w*) induced weight loss in 3 weeks and reduced serum lipids, as well as liver TG content, and size of visceral fat regions. According to Wang et al. 2012a, these effects were mediated by reduced inflammatory cytokine levels such as IL-1β, IL-12, IL-17, interferon (IFN)-γ, macrophage inflammatory protein-1β, MCP-1, and hepatic levels of PPAR-γ (which is a regulator of TG homeostasis and contributes to hepatic steatosis). Moreover, CA activated signaling molecules such as AMPK, ACC, and MAPK (ERK 1/2) and upstream regulators epithelium growth factor receptor which inhibit preadipocyte proliferation and differentiation (Wang et al. 2012a). It has also been demonstrated that obese adipose tissue is characterized by the enhanced infiltration of macrophages that produce various inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and thereby contribute to inflammation. Rosemary-derived CA and carnosol strongly suppressed *Gaussia* luciferase secretion induced by macrophages and up-regulated adiponectin secretion and the nitric oxide production and inducible nitric oxide synthase (iNOS) gene expression by inhibiting NF-κB activation (Lo, et al. 2002; Nagasaki et al. 2012). The various anti-obesity mechanisms of rosemary and the active compounds are presented in Fig. 3.

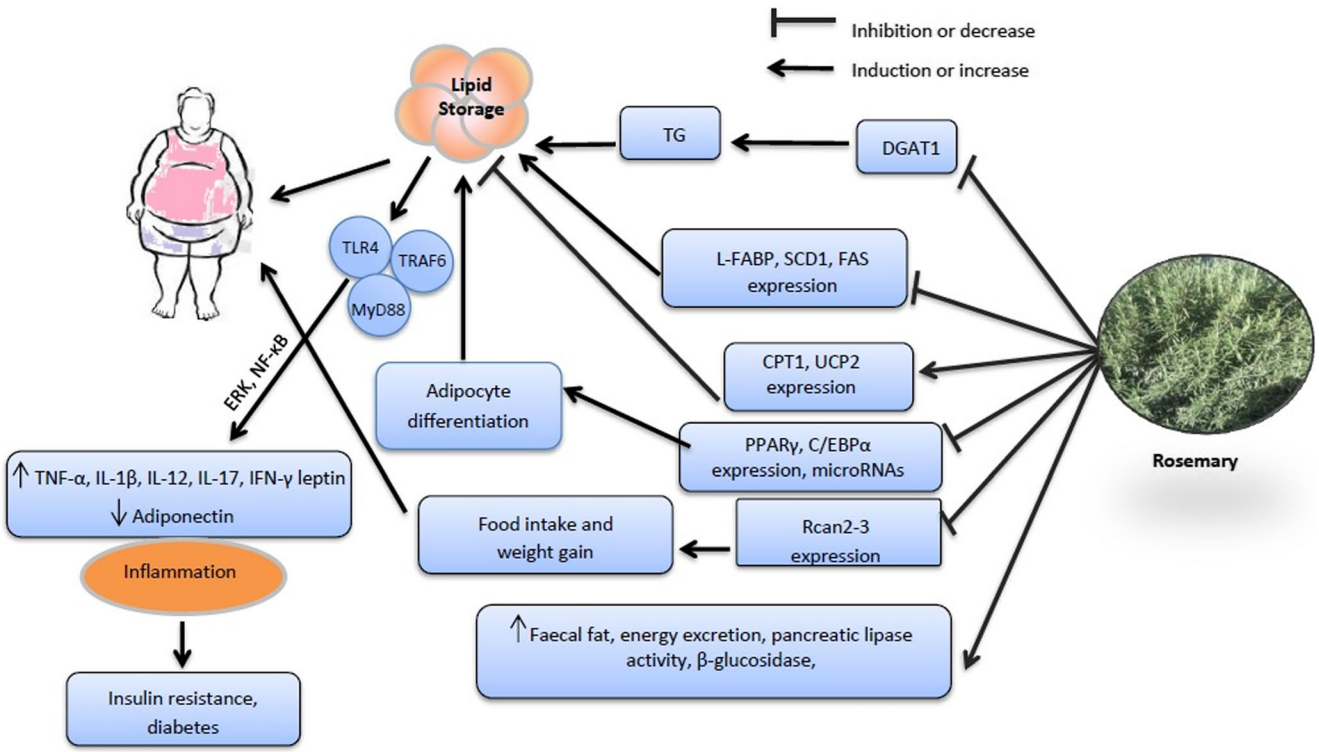

Fig. 3 Different anti-obesity mechanisms of rosemary and related compounds. *CPT1* carnitine palmitoyltransferase 1, *DGAT1* diacylglycerol acyltransferase 1, *FAS* fatty acid synthase, *IL* interleukin, *INF-γ* interferon-γ, *L-FABP* liver fatty acid-binding protein, *MyD88* myeloid differentiation factor 88, *PPAR* peroxisome proliferator-activated receptor γ, *Rcan2–3* regulator of calcineurin 2–3, *SCD1* stearoyl-CoA desaturase 1, *TG* triglyceride, *TLR4* Toll-like receptors 4, *TNF-α* tumor necrosis factor-α, *TRAF6* TNF receptor-associated factor 6, *UCP2*: uncoupling protein 2

Cardiovascular effects

Anti-hypertensive and cardioprotective effects

Angiotensin I-converting enzyme (ACE-I) is a key enzyme in controlling blood pressure by producing vasoconstrictor agents, which increase the blood pressure. According to the results of in vitro studies, rosemary (25 %) in combination with cranberry (75 %) (Apostolidis et al. 2006) and the aqueous extracts of rosemary LA (one of clonal lines of rosemary) among other clonal herbs of Lamiaceae (Kwon et al. 2006) inhibited ACE-I activity. Based on the beneficial effects of omega-3 fatty acids in reducing plasma lipids, atherogenic LDL-C, and hypertension, researchers investigated the effects of a diet containing Omega-3 plus lecithin, curcumin, and rosemary extracts on the lipid disturbance, high blood pressure, and hyperinsulinemia associated with cardiovascular disease (CVD). After dietary supplementation in a double-blind placebo-controlled trial in CVD patients, a significant decrease was observed in blood pressure especially the systolic blood pressure without producing significant changes in blood glucose (Yam et al. 2002). It was also demonstrated that rosemary extract decreased the levels of blood glucose and enzyme activities related to cardiac injury and corrected the lipid profile (Alnahdi 2012). Rosmarinic acid (10 mg/kg) supplementation in fructose-fed hypertensive rats (model of insulin resistance) also reduced blood pressure and prevented cardiac injury and hypertrophy. Decrease in endothelin-1 (a vasoconstrictor) level and ACE-I activity, downregulation of the expression of NADPH oxidase p22phox subunit, increase in NO (which has vasorelaxant effect) levels, and improvement of cardiac anti-oxidant defense were the observed mechanisms for cardioprotective effects of RA (Karthik et al. 2011).

Anti-atherogenic effects

Inhibition of

Advanced glycation end products (AGEs), which trigger cytokine secretion and oxidation reactions, are produced through

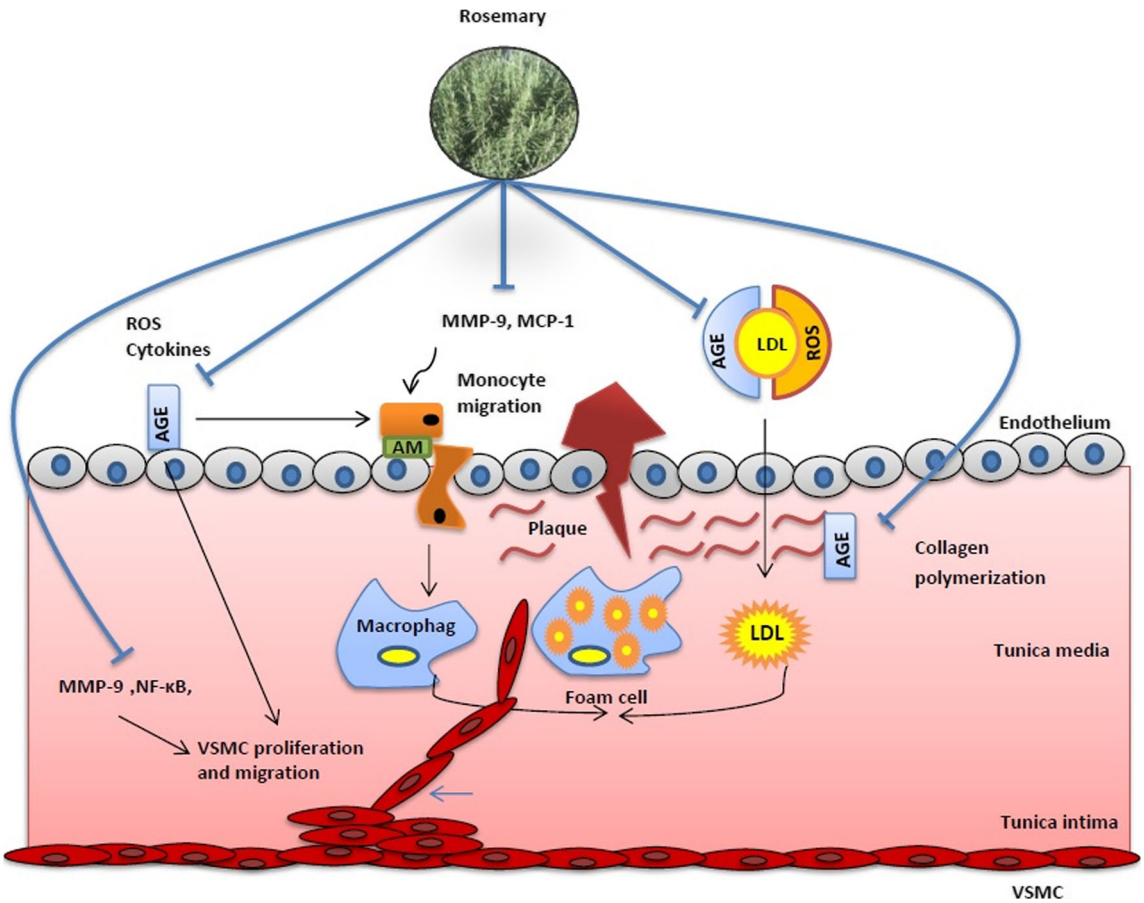

Fig. 4 Inhibitory effects of rosemary on atherosclerosis plaque progression. Rosemary or the active compounds inhibit LDL-C glycation and oxidation and AGE formation in collagen, have radical scavenging activities, reduce MMP-9, MCP-1, and NF-κB activities and macrophage infiltration into the lesion, and suppress VSMC migration. *AGE* advanced glycation end products, *AM* adhesion molecules (vascular cell adhesion molecule-1 and intracellular adhesion molecule-1), *LDL-C* low-density lipoprotein cholesterol, *MCP-1* monocyte chemotactic protein-1, *MMP-9* matrix metallopeptidase 9

non-enzymatic glycation of proteins by sugar and cause vessel damage. The glycation of LDL-C, one of the pro-atherogenic factors, which enhances its oxidation and accumulation in vessel walls; polymerization of collagen that inhibits the proteolytic attacking enzyme and results in atrophy of vascular basal membranes; and the induction of thrombosis by the glycation of anti-thrombin III and plasminogen are the mechanisms by which AGEs induce platelet and endothelial cell dysfunction and vascular damage (Gugliucci 2000; Gugliucci and Menini 2002). The anti-glycation-related features of the aqueous and acetone extract of rosemary have been evaluated in biochemical tests. Both extracts of rosemary were capable of inhibiting LDL-C glycation and AGE formation in collagen. The active ingredients RA, carnosol, CA, 12-methoxycarnosic acid, and methyl carnosate also showed radical scavenging effects and potentiated the activity of the anti-thrombin III which can inhibit coagulation by lysing thrombin and other blood coagulation factors (Hsieh et al. 2007). In another study, rosemary extract (50 mg/kg) rich in high levels of phenolic compound indicated significant anti-diabetic effects and the decrease in the percentage of glycated hemoglobin (Silva et al. 2011).

Anti-chemotaxic action

Another early event in the development of atherosclerotic plaque is the recruitment and persistent accumulation of monocyte-derived macrophages in the subendothelial layer of the vessel. The release of chemokine (MCP-1) from vessels and adhesion molecules (vascular cell adhesion molecule-1 and intracellular adhesion molecule-1) and matrix metalloproteinase (MMP) expression by endothelial cells trigger these events. Then, the cells transform into lipid-laden foam cells and are characterized as early lesions of atherosclerosis (Chae et al. 2012; Ullevig et al. 2011). Ullevig et al. 2011 evaluated the potential anti-atherogenic effect of UA in high-fat-diet-fed LDL receptor-deficient mice, which develop accelerated atherosclerosis, and in in vitro model of human THP-1 monocytic cells. The result showed that dietary supplementation with UA decreased the mortality of diabetic mice (90 %), blood glucose, and the formation of atherosclerotic lesions in aortic arch. These anti-atherogenic effects of UA were attributed to reduced macrophage infiltration into the lesions and possibly anti-oxidative stress activity. In this study, 24 mg/kg/day = 1.7 g/day for a 70-kg person was estimated as the approximate efficient dose of UA for anti-atherosclerotic activity (Ullevig et al. 2011).

Inhibition of lipid oxidation

Glycation and oxidation of LDL-C and HDL-C are important in pathophysiology of atherosclerosis in diabetes. Results of Jin and Cho (2011) study revealed that aqueous extract of rosemary (less than cinnamon and clove) inhibited glycation of apolipoprotein A-I (major protein constituent of HDL-C) and LDL-C oxidation and had anti-oxidant and good radical scavenging activities (Jin and Cho 2011). Similar to the previous study, the aqueous rosemary extract rich in phenolic compounds (carnosol, RA, genkwanin, rosmadial, CA) and the methanol extract had high anti-oxidant, radical scavenging, anti-glycant, and anti-lipid peroxidation effects in biochemical tests (Cazzola et al. 2011). The inhibitory activities of CA, carnosol, RA, rosmanol, carnosol, and epirosmanol on LDL-C oxidation were also observed in human aortic endothelial cells and biochemical tests (Pearson et al. 1997; Zeng et al. 2001). So, rosemary can be a good choice for the prevention and treatment of diabetes, CVDs, and their complications.

Inhibition of vascular smooth muscle cells' migration

Arterial endothelial dysfunction is a key marker in the pathogenesis and complication of atherosclerosis. In a clinical research done in healthy young volunteers, rosemary extract rich in carnosol, CA, and RA increased flow-mediated dilatation of the brachial artery and decreased endothelial dysfunction and plasminogen activator inhibitor-1 level (Sinkovic et al. 2011). Another key event that contributes to the progression of atherosclerosis is the proliferation and migration of vascular smooth muscle cells (VSMCs) from the tunica media into the intima and is facilitated through NF-κB-induced expression of MMP in VSMCs. Yu et al. (2008) reported that CA inhibited the TNF-α-induced migration of human aortic smooth muscle cells, MMP-9 activity, and expression through downregulation of NF-κB (Yu et al. 2008). In another investigation, CA, methanol extract (CA content 9.4 %), and *n*-hexane fraction (CA content 8.4 %) of rosemary reduced MMP-9 and MCP-1 activities and suppressed TNF-α-induced rat VSMC migration (Chae et al. 2012). Schematic of anti-atherogenic effects of rosemary and active compounds is presented in Fig. 4.

Some predictable adverse effect reactions

Although many studies have confirmed the positive health effects of rosemary, little research has been done to evaluate the possible risk to human health. Rosemary volatile oil at dose of 25 mg/kg administered to hyperglycemic normal and diabetic rabbits increased the plasma glucose and decreased insulin levels (al-Hader et al. 1994). In another research, the volatile oil was able to increase blood pressure in patients diagnosed with primary hypotension (Fernandez et al. 2014). Therefore, this product of rosemary should be used with caution in patients with hypertension and diabetes. In the study of Lee et al. (2007), CA showed anti-platelet activity through inhibition of cytosolic calcium mobilization in experimental model of rabbit platelet aggregation induced by arachidonic acid, U46619, collagen, and thrombin. Despite the

Table 1 In vivo and clinical studies of *Rosmarinus officinalis* and the active compounds in modulating metabolic responses

Subjects	Exposure/type of extract (part of plant)/ constituents	Time of exposure/dose	Endpoints	Reference
Diabetes and lipid profile				
Four days a week for 8 weeks moderate-intensity treadmill exercise + STZ-induced diabetic (TDR) male Wistar albino rats	Oral (gastric cannula), aqueous extract (leaves)	8 weeks, 200 mg/kg	Decreased BG, erythrocyte MDA Increased SI related to high BG, erythrocyte SOD, GPx, CAT Body weights were not significantly different between the TDR and sedentary control groups	Nazem et al. (2015)
Male Wistar rats	Oral (gavage), BA	Single does, 0.1, 1, 10 mg/kg	Decreased BG. Increased SI related to high BG	Castro et al. (2014)
High-fat diet + low doses of STZ-induced type 2 diabetic in male albino Wistar rats	Oral, RA	30 days, 100, 150, 200 mg/kg	Decreased BG, HbA_{1C}, food and water intake, urine sugar, AST, ALT, ALP, LDH, G6Pase, fructose 1,6-bisphosphatase, glycogen phosphorylase. Improved elevated values at all points of oral glucose tolerance test, and insulin resistance Increased BW, SI, hexokinase, pyruvate kinase and glucose-6-phosphate dehydrogenase, glycogen synthase, glycogen levels	Jayanthy and Subramanian (2014)
STZ-induced diabetic male albino rats	Oral (gastric cannula), aqueous extract (leaves)	21 days, 200 mg/kg	Decreased BG, ALT, AST, ALP. Increased SI related to high BG, C-peptide levels	Ramadan et al. (2013)
High-fat-diet-fed male Wistar rats	Oral (gavage), aqueous xextract (leaves), non-esterified phenolic fraction (NEPF)	4 weeks, 70, 140 mg/kg (aqueous extract), 7 and 14 mg/kg (NEPF)	Decreased TC, non-HDL-C (aqueous), MDA (both) Increased liver: CAT (both), GPx (aqueous), kidney: CAT, SOD (NEPF)	Afonso et al. (2013)
STZ-induced adult male albino Wistar rats	Oral (gastric cannula), aqueous extract (leaves)	21 days, 200 mg/kg	Decreased BG. Increased BW, SI, C-peptide	Ayaz (2012)
High-fat diet female BALB/c mice	Oral (gavage), aqueous extract (leaves)	36 days,100 mg/kg rosemary extract (10 % *w/v*) for the last 15 days	Decreased TC, LDL-C, TG. Increased HDL-C	Al Sheyab et al. (2012)
STZ-induced diabetic adult male albino rats	Oral (gastric cannula), aqueous extract (leaves)	21 days, 200 mg/kg	Decreased BG, TG, TC. Increased BW, amylase, SOD, CAT, GPx, albumin, ceruloplasmin, and ferritin, ascorbic, α-tocopherol, β-carotene, reduced glutathione, uric acid, bilirubin	Emam (2012)
SD rats, half male and half female fed high-fat feedstuff for 30 days	Oral (gavage), essential oil, aqueous extract (stems and leaves), crude plant powder	60 days, essential oil: 50, 250, 500 μL/kg, Aqueous extract: 400, 2000, and 4000 mg/kg, powder:10, 50, 100 mg/kg	Decreased TC, serum MDA (aqueous extract, and crude plant powder), TG (essential oil, crude plant powder). Increased serum SOD activities (all), HDL-C (aqueous extract, essential oil)	Wu et al. (2011)
Normoglycemic and hyperglycemic and alloxan monohydrate-induced diabetic adult New Zealand rabbits of either sex	Oral (gavage), ethanol extract (whole parts)	Acute and subacute (7 days)study, 50, 100, 200 mg/kg	Decreased BG, serum MDA. Increased SI related to high BG in alloxan monohydrate-induced diabetes, serum SOD and CAT	Bakirel et al. (2008)
Obesity				

Table 1 (continued)

Subjects	Exposure/type of extract (part of plant)/ constituents	Time of exposure/dose	Endpoints	Reference
High-fat-diet-fed male C57BL/6J mice	Oral (diet), A: CA-enriched extract (containing 80 % CA), B: commercial extract (containing 45 % CA)	16 weeks, 0.14 or 0.28 % (*w/w*) A, 0.5 % (*w/w*) B	Decreased BW gain, total fat mass gains, liver weight, liver TG and free fatty acid levels, BG, SI (obesity-induced hyperinsulinemia), plasma ALT, AST, plasma and liver MDA, advanced glycation end products (AGEs), and the liver expression of receptor for AGE (RAGE), lipid accumulation in hepatocytes Increased fecal lipid excretion to inhibit lipid absorption and increased the liver GSH/GSSG ratio	Zhao et al. (2015)
Male C57BL/6J wild-type and C57BL/6J-ob/ob leptin-deficient mice	Oral (diet), CA	4 weeks and 0.02 % (*w/w*)	Decreased BW, LW, 2-DG, daily food intake, serum TG and TC, hepatic TG, TNF-α, IL-6, MCP-1, BG, SI (obesity-induced hyperinsulinemia), C18:1/C18:0 ratio in adipose tissue, hepatic lipogenesis gene expression (L-FABP, SCD1, FAS), Rcan2–3 mRNA expression Increased fatty acid oxidation molecule expression (CPT1, UCP2), HDL-C	Park and Sung (2015a)
Lean (Le, fa/+) and obese (Ob, fa/fa) female Zucker rats	Oral (diet) ethanol extract that contains 40 % CA (leaves)	64 days, 0.5 % (*w/w*)	Decreased blood TNF-α, IL-1β, leptin (Le), adipose p-AMPK (Ob) Increased adiponectin (Le), induced hepatic PGC1α (Le) mRNA expression, induction of various phase I and phase II metabolizing genes (liver of Le)	Romo-Vaquero et al. (2014a)
Lean (Le, fa/+) and obese (Ob, fa/fa) female Zucker rats	Oral (diet), ethanol extract that contains 40 % CA (leaves)	64 days, 0.5 % (*w/w*)	Decreased BW (Le, Ob), *Lactobacillus*/*Leuconostoc*/*Pediococccus* group (Le, Ob), *Clostridium leptum* (Le), cecum β-glucosidase activity (Le, Ob), main SCFA in the feces (Le) Supplementation with the RE significantly enlarged the size and weight of the cecum (Le, Ob), increased the *Blautia coccoides* and *Bacteroides*/*Prevotella* groups (Le, Ob), *Bifidobacterium* (Le), fecal fiber excretion (Le, Ob), the main SCFA in the feces (Ob)	Romo-Vaquero et al. (2014b)
Lean (Le, fa/+) and obese (Ob, fa/fa) female Zucker rats	Oral (diet) ethanol extract that contains 40 % CA (leaves)	64 days (0.5 % *w/w*)	Decreased BW (Le, Ob), serum TG, cholesterol, LDL-C, HDL-C, SI (Le), inhibited stomach lipase activity. Increased fecal weight without affecting the food intake	Romo Vaquero et al. (2012)
Male ob/ob mice	Oral (diet) CA	5 weeks, 0.05 % (*w/w*)	Decreased total hepatic lipid content, PPAR-γ, as IL-1β, IL-12, IL-17, IFN-γ, MIP-1β, and MCP-1. Activated AMPK, ACC, increased P-MAPK (ERK1/2), P-EGFR	Wang et al. (2012a)

Table 1 (continued)

Subjects	Exposure/type of extract (part of plant)/ constituents	Time of exposure/dose	Endpoints	Reference
Male ob/ob mice	Oral (diet) CA	5 weeks, 0.05 % (*w*/*w*)	Decreased BW, LW, WAT, TG, TC, ALT, BG, hepatic TG	Wang et al. (2011)
High-fat-diet-fed male C57BL/6J mice	Oral (diet), aqueous extract that contains 20 % CA (leaves)	16 weeks, 500 mg/kg	Decreased BG, TC, BW. Increased total fecal lipid content and total fecal energy excretion	Ibarra et al. (2011)
Cardioprotective effects				
STZ-induced adult male albino rats	Oral (gastric cannula), aqueous extract (leaves)	21 days, 200 mg/kg	Decreased BG, TG, TC, LDL-C. Corrected the activities of cardiac enzymes (AST, CPK, LDH). Increased BW	Alnahdi (2012)
STZ-induced diabetic male albino Wistar rats	Oral, aqueous extract	30 days, 25, 50, 100 mg/kg	Decreased glycated hemoglobin. Increased GPx and CAT in the liver; SOD in the brain	Silva et al. (2011)
High-fat diet + STZ-induced diabetic female LDL receptor-deficient C57BL/6Jmice	Oral (diet), UA	11 weeks, 0.2 % diet (300 mg/kg)	Decreased BG, inhibited monocyte dysfunction, and accelerated atherosclerosis induced by diabetes, monocyte recruitment into MCP-1-loaded Matrigel plugs	Ullevig et al. (2011)
Fructose-fed male albino Wistar rats	Oral, RA	45 days, 10 mg/kg	Decreased BG, SI related to high BG, heart weight, cardiac hypertrophy, systolic BP, CPK-MB, cTnT, LDH, AST, ACE activity, TC, TG, free fatty acids (plasma and heart tissue), LDL-C, VLDL, AOPP, TBARS, ET-1, ACE-I activity, and p22phox NADPH oxidase subunit expression in the heart. Improved insulin sensitivity, NO levels, and expression of eNOS, kallikrein activity. Increased HDL-C, CAT, SOD, GPx, GSH/GSSG (plasma and heart)	Karthik et al. (2011)
Nineteen healthy young volunteers, 7 men and 12 women, were studied; the mean age 34.3 ± 7.7 years	Oral, rosemary extract	21 days (77.7 mg) consisting of active substances carnosol (0.97 mg), CA (8.60 mg), RA (10.30 mg)	Decreased the rate of endothelial dysfunction, mean plasminogen activator inhibitor type 1 Increased median levels of flow-mediated dilatation	Sinkovic et al. (2011)

ACC acetyl-CoA carboxylase, *ACE* angiotensin-converting enzyme, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BG* blood glucose, *BP* blood pressure, *C18:1/C18:0* oleate/stearate, *CA* carnosic acid, *CAT* catalase, *CPK* creatine phosphokinase, *cTnT* cardiac troponin T, *CPT1* carnitine palmitoyltransferase 1, *BW* body weight, *EGFR* epithelium growth factor receptor, *eNOS* endothelial nitric oxide synthase, *ERK* extracellular signal-regulated kinase, *ET* endothelin, *FABP4* fatty acid binding protein 4, *FAS* fatty acid synthase, *GPx* glutathione peroxidase, *GSH/GSSG* reduced glutathione to oxidized glutathione ratio, *HDL-C* high-density lipoprotein cholesterol, *IL* interleukin, *IFN* interferon, *LDH* lactate dehydrogenase, *LDL-C* low-density lipoprotein, *LW* liver weight, *MAPK* mitogen-activated protein kinase, *MCP* monocyte chemotactic protein, *MDA* malondialdehyde, *ob/ob* obese leptin-deficient, *MIP* macrophage inflammatory protein, *PGC1α* PPAR-γ coactivator-1α, *p-AMPK* phosphorylated AMP activated protein kinase, *RA* rosmarinic acid, *Rcan2–3* regulator of calcineurin 2–3, *SCD1* stearoyl-CoA desaturase 1, *SCFA* short chain fatty acids, *SI* serum insulin, *SOD* superoxide dismutase, *STZ* streptozotocin, *TBARS* thiobarbituric acid-reactive substances, *TC* total cholesterol, *TG* triacylglycerol, *TNF-α* tumor necrosis factor-α, *UA* ursolic acid, *UCP2* uncoupling protein 2, *VLDL* very low-density lipoprotein, *WAT* white adipose tissue

Table 2 In vitro studies of *Rosmarinus officinalis* and the active compounds[SC1] in modulating metabolic responses

Subjects	Type of extract (part of plant)/ constituents	Dose	Endpoints	Reference
Diabetes and lipid profile				
L6 myotube cell culture	Methanol extract (leaves)	5, 10, 20 μg/mL	Increased 2-DG uptake, p-AMPK, P-ACC	Naimi et al. (2015)
L6 myotube cell culture	CA	20 μM	Stimulated glucose clearance by rat skeletal L6 myotube through PME-1/PP2A/PKB signaling axis Decreased PP2A activity Increased 2-DG uptake, p-PKB	Lipina and Hundal (2014)
3T3-L1 adipocytes	CA	1, 5, 10, and 20 μM C + A	Decreased IL-6, MCP-1 mRNA expression, p-ERK, p-JNK, NF-κB, p-mTOR, FOXO1 protein levels Increase 2-DG uptake, PPAR-γ mRNA expression	Tsai et al. (2014)
HepG2 cell culture	Methanol extract (whole parts) and phenolic diterpenes	100 μg/mL (extract), 100 μM (isolated compounds)	Suppressed gluconeogenesis via inhibition of the cAMP/PKA/CREB pathway	Yun et al. (2013)
HepG2 cell culture	Dichloromethane-methanol extract (Whole parts)	2, 10, and 50 μg/mL	Decreased G6Pase, glycogen content Increased glucose consumption, p-AMPK, p-ACC, LDL receptor, sirtuin 1, PGC1α mRNA expression, glycolysis	Tu et al. (2013)
Biochemical tests	Aqueous extract (whole parts)	100 μL aqueous or methanol extract, corresponding to 1 mg dry spice	High radical scavenging activity, inhibited the oxidation of deoxyribose, lipid peroxidation, AGc, α-amylase activities	Cazzola et al. (2011)
Colorimetric assay	Methanol extract (whole parts), RA, chlorogenic acid caffeic acid, and gallic acid	6.3–200 μg/mL	Inhibited hormone-sensitive lipase and pancreatic lipase	Bustanji et al. (2010)
Obesity				
3T3-L1 adipocytes	CA	0.1, 1, 10 μM	Decreased intracellular lipid accumulation, TG content, PPAR-γ, C/EBPα, and SREBP1mRNA expression, glycerol 3-phosphate dehydrogenase activity, C16:1/C16:0 and C18:1/C18:0 ratios, SCD1 mRNA and protein expression levels	Park and Sung (2015b)
Primary omental preadipocytes from Caucasian normal (non-diabetic and non-smoker) women. The age was 48.67 ± 9.07 years, and mean BMI was 42.70 ± 6.95 kg/m^2	Commercial rosemary extract (leaves) and contained ≥20 % phenolic diterpenes and ≥10 % CA	30 μg/mL Treatments were performed in three different stages of the cell life cycle: (1) on preadipocytes for eight days (P8) in (2) on preadipocytes for 10 days (P10) and 20 days (P20) during differentiation in (3) on mature fully	Decreased lipid accumulation, TG content in P10 and P20, expression of cell cycle genes cyclin-dependent kinase 4 (CDK4), cyclin D1 (CCND1), cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A) Apoptotic activity of the extract on P8 and P20 cells was observed Increased the content of free glycerol in P20 and A7. Up-regulated genes with anti-adipogenic effects, as GATA binding protein 3 (GATA3)	Stefanon et al. (2015)

Table 2 (continued)

Subjects	Type of extract (part of plant)/ constituents	Dose	Endpoints	Reference
		differentiated adipocytes for seven days (A7) in	and wingless-type MMTV integration site family, member 3A (WNT3A) Downregulated microRNAs like miR-17, and miR-143 and up-regulated let-7f-1	
3T3-L1 adipocytes	CA	5–20 μM	Decreased in LPS-induced expression of TNF-α, IL-6, MCP-1, TLR4 mRNA, MyD88, TRAF6, p-ERK, NF-κB protein levels	Park and Mun (2014)
3T3-L1 adipocytes	Acetone rosemary extract (leaves), CA	0.3–20 μg/Ml (CA) 20–30 μg/mL (extract)	Decreased lipid accumulation, inhibited cell differentiation, mitotic clonal expansion, blocked PPAR-γ, C/EBPα, FABP4 expression, altered the ratio of the different C/EBPβ forms, induced the loss of C/EBPβ proper subnuclear distribution	Gaya et al. (2013)
HepG2 cell culture, the microsomal fractions from rat livers (male Sprague–Dawley rats)	Methanol extract (aerial parts) compounds (carnosol)	20, 40 μM (TG synthesis)	Inhibited TG synthesis, most of the isolates inhibited the DGAT1 activity	Cui et al. (2012)
COS-7 cells (African Green Monkey SV40-transformed kidney fibroblast cell line (PPAR-γ activity), biochemical test	Aqueous extract that contains 20 % CA (leaves)	100 μg/mL (lipase activity), 0.3–30 μg/mL (PPAR-γ)	Inhibited pancreatic lipase activity, activated PPAR-γ	Ibarra et al. (2011)
3T3-L1 adipocytes	CA, carnosol	24 h (0.01–10 μM) 10 μM	Decreased lipid accumulation, inhibited cell differentiation. Increased nuclear level of Nrf2 protein, GSH level, induced phase2 enzyme genes	Takahashi et al. (2009)
Cardiovascular				
RAW 264.7 cells, rat VSMCs	Methanol extract (leaves), *n*-hexane fraction, CA, carnosol	1, 2.5, 5, and 10 μg/mL (extract and fraction), 1, 2.5, 5, and 10 μM (CA, carnosol)	Decreased LPS-induced MMP-9 secretion and expression, MCP1 expression in RAW 264.7 cells, TNF-α-induced MMP-9 secretion and expression, migration of VSMCs	Chae et al. (2012)
Biochemical tests	Aqueous extract (from commercially available herb)	10 μg/mL	Decreased glycation of HDL-C, anti-oxidant, and radical scavenging activity	Jin and Cho (2011)
Human THP-1 monocytic cells	UA	0.3 – 10 μM	Inhibited MCP-1-induced monocyte chemotaxis accelerated by oxidative stress (H_2O_2)	Ullevig et al. (2011)
Biochemical tests	Aqueous extract (leaves), acetone extract (leaves)	1.3 μg/mL (LDL-C glycation), 0.5 mg/mL (TBARS), 0.1 mg/mL (AGE in collagen, radical scavenging activity),	Inhibited LDL-C and collagen glycation, suppressed TBARS and AGE formation, showed high radical scavenging and anti-thrombin III activity	Hsieh et al. (2007)

Table 2 (continued)

Subjects	Type of extract (part of plant)/ constituents	Dose	Endpoints	Reference
		0.05 mg/mL (anti-thrombin III activity)		
Angiotensin-converting enzyme inhibition assay	Aqueous extract (whole parts)	100, 200, and 500 μg/mL (25 % rosemary combination with 75 % cranberry)	ACE-I inhibition	Apostolidis et al. (2006)
Biochemical tests	Aqueous extract (whole parts), 12 % ethanol extracts (whole parts), caffeic acid, RA	5 g in 100 mL extracts, 200, 500, and 1000 μg/mL phenolics ACE-I (1000 μg/mL total phenolics)	Inhibited AGc (aqueous extract) and ACE-I	Kwon et al. (2006)
Biochemical tests	Carnosol, rosmanol, and epirosmanol	7–10 μmol/L	Inhibited TBARS formation in Cu^{2+}-mediated LDL-C oxidation, oxidized apolipoprotein B in LDL-C, decreased super oxide onion	Zeng et al. (2001)
Human aortic endothelial cells	Commercial rosemary extract, CA, carnosol, RA	0.3–2.5 μM	Inhibited LDL-C oxidation	Pearson et al. (1997)

ACC acetyl-CoA carboxylase , *ACE-I* angiotensin I-converting enzyme, *AGc* α-glucosidase, cAMP response element binding protein, AGE advanced glycation end products, C161/C160 palmitoleate/palmitate, C181/C180 oleate/stearate, CA carnosic acid, C/EBPs CCAAT-enhancer-binding proteins, *CREB* cAMP response element binding protein, *DGAT* diacylglycerol acyltransferase, *FABP4* fatty acid binding protein 4, *FOXO1* forkhead transcription factor 1, *GSH* reduced glutathione, *G6Pase* glucose-6-phosphatase, *HASMC* human aortic smooth muscle cells, *HDL-C* high-density lipoprotein cholesterol, *INF* interferon, *IL* interleukin, *LDL-C* low-density lipoprotein cholesterol, *LPS* lipopolysaccharide, *MCP-1* monocyte chemotactic protein-1, *MMP* matrix metallopeptidase, *MyD88* myeloid differentiation factor 88, *NF-κB* nuclear factor-κB, *Nrf2* nuclear factor (erythroid-derived 2)-like 2, *p-ACC* phosphorylated acetyl-CoA carboxylase, *p-AMPK* phosphorylated AMP activated protein kinase, *p-ERK* phosphorylated extracellular signal-regulated kinase, *p-JNK* phosphorylated c-Jun NH2-terminal kinase, *p-mTOR* phosphorylated the mammalian target of rapamycin, *p-PKB* phosphorylated protein kinase B, *PGC1α* PPAR-γ coactivator-1α, *PKA* protein kinase A, *PME-1* protein phosphatase methylesterase-1, *PPAR* peroxisome proliferator-activated receptor, *PP2A* protein phosphatase 2A, *RA* rosmarinic acid, *SCD1* stearoyl-CoA desaturase 1, *SREBP1* sterol regulatory element-binding protein1, *TBARS* thiobarbituric acid-reactive substances, *TG* triacylglycerol, *TLR4* Toll-like receptor 4, *TNF-α* tumor necrosis factor alpha, *TRAF6* TNF receptor-associated factor 6, *UA* ursolic acid, *VSMCs* vascular smooth muscle cells, *2-DG* 2-deoxy-D-glucose

anti-platelet activity of CA, two other active compounds of rosemary, UA and oleanolic acid, were able to potentiate platelet aggregation induced by thrombin or adenosine diphosphate (Kim et al. 2014). The hepatotoxicity and inhibitory effects of CA on cytochrome P450 (CYP) activities were indicated in primary human hepatocytes and microsomes. The hepatic toxic effects were increased in a dose-dependent manner (EC_{50} value of 94.8 ± 36.7 μM). The activity of important hepatic CYP like 2C9 and 3A4 was not inhibited. But, the CYP2B6 and CYP3A4 mRNA and enzyme activity were induced (Dickmann et al. 2012). So, the toxicity and drug interactions of rosemary and the pharmacologically active compounds should be considered in their therapeutic use.

Unifying data and conclusion

Metabolic syndrome is the combination of disturbances of glucose and insulin metabolism, central obesity, mild dyslipidemia, and hypertension that directly increase the risk of CVD and type 2 diabetes mellitus. Reports have established that rosemary extracts and the major phenolic constituents exert beneficial effects against diabetes, obesity, CVD, and metabolic syndrome as a whole syndrome through improvement of insulin secretion and response; inhibition of AGE production; suppression of gluconeogenesis; carbohydrate digestion; lipid synthesis; induction of lipolysis; anti-oxidant and anti-inflammatory activities; and anti-hyperlipidemic, hypotensive, and anti-atherosclerotic effects. These glorious effects are consistently related to modulation of enzymes, different critical signal transduction pathways, transcription factors, and key gene expressions. In spite of much evidence from animal and in vitro assays, more clinical studies are needed to confirm the effectiveness and safety of the phenolic compounds of rosemary in humans. Tables 1 and 2 present the most relevant in vivo and in vitro studies relating to the effects and proposed underlying the mechanisms of rosemary and its constituents in many metabolic responses.

Conflict of interest The authors declare that they have no conflicts of interest.

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