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Review Article

Resveratrol as a potential protective compound against metabolic inflammation

Hossein Ghahremani [1], Arash Bahramzadeh [2], Kosar Bolandnazar [3], Solaleh Emamgholipor [2], Hossein Hosseini [4], Reza Meshkani [2*]

[1] *Department of Clinical Biochemistry, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[2] *Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Department of Biological Sciences and Technology, Islamic Azad University of Mashhad, Mashhad, Iran*
[4] *Department of Clinical Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

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[*] **Corresponding Author:**

Reza Meshkani,
Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Email: rmeshkani@tums.ac.ir

ABSTRACT

Although the exact mechanism linking obesity to type 2 diabetes (T2D) remains unknown, accumulating evidence suggests that low-grade chronic metabolic inflammation or 'meta-inflammation' plays a pivotal role. Adipose tissue is the primary site of meta-inflammation, and overproduction of pro-inflammatory cytokines in this tissue affects other organs such as the liver, skeletal muscle, pancreas, and brain. This leads to the development of insulin resistance and metabolic irregularities in these tissues. Therefore, strategies targeting meta-inflammation could be effective in treating T2D and related metabolic traits. Resveratrol, a polyphenol, is suggested to possess anti-inflammatory and immunomodulatory activities. The anti-inflammatory effect of resveratrol is mediated through several mechanisms including the suppression of nuclear factor kB (NF-kB), down-regulation of extracellular signal-regulated kinase (ERK)/p38 mitogen-activated protein kinase (MAPK) signaling, suppression of toll-like receptor (TLR)-mediated pathway; inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, reduction of reactive oxygen species (ROS) generation, suppression of immune cell infiltration into tissues; and inhibition of pro-inflammatory cytokines production. This review will examine the evidence on the role of resveratrol in modulating inflammation in various organs affected by obesity such as liver, skeletal muscle, kidney, heart and brain

Keywords: Resveratrol, metabolic inflammation, type 2 diabetes, macrophage, Adipose tissue

Abbreviations: AP1: activator protein 1; ATMs: adipose tissue macrophages; AMPK: AMP-activated protein kinase; CVD: cardiovascular disease; CNS: central nervous system; CCR: chemokine (C-C motif) receptor ; CKD: chronic kidney disease; COX: cyclooxygenase ; ERK: extracellular signal-regulated kinase; FFA: free fatty acid; HFD: high fat diet; hs-CRP: high sensitive C reactive protein; JNK: Jun N-terminal kinase; ICAM-1: intercellular adhesion molecule-1; IFN-γ: interferon γ; IL: interleukin; IKKβ: inhibitor of κB kinase; I/R: ischemic/reperfusion; LPS: lipopolysacharide; MIP-1α : macrophage inflammatory protein 1α; MCP-1: macrophage chemoattractant protein-1; MAPK: mitogen-activated protein kinase; NKT: natural killer T cells; NO: nitric oxide; iNOS: nitric oxide synthase; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NF-kB: nuclear factor kB; Nrf-2: nuclear factor erythroid 2-related factor 2; NLRP3: NLR family pyrin domain containing 3; PARP: poly (ADP-ribose) polymerase; ROS: reactive oxygen species; SIRT1: sirtuin 1; SVF: stroma-vascular fraction; SOCS3: suppressor of cytokine signaling-3; TLR: toll-like receptor; T2D: type 2 diabetes; TNF-α: tumor necrosis factor α; TGFβ: transforming growth factor β; VCAM-1: vascular cell adhesion molecule-1; WAT: white adipose tissue

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Introduction

According to a report by the World Health Organization (WHO), overweight and obesity are major risk factors for several chronic diseases, including type 2 diabetes (T2D), cardiovascular diseases (CVD), and cancer (1). A systematic analysis for the Global Burden of Disease Study revealed that the prevalence of overweight and obesity in adolescents reached 36.9% in men and 38% in women in 2013 (2).

Obesity is known to be associated with low-grade chronic inflammation (3). This inflammation induced by obesity is closely linked to insulin resistance, T2D, atherosclerosis, and non-alcoholic fatty liver disease (NAFLD) (4). This low-grade inflammation, known as meta-inflammation, is characterized by increased levels of circulating pro-inflammatory cytokines and acute phase proteins, as well as enhanced recruitment of immune cells, especially macrophages, to adipose tissue. The cytokines and chemokines produced by macrophages cause local and systemic inflammation, which in turn leads to pancreatic β-cell dysfunction and peripheral insulin resistance (5).

In recent years, the use of natural plant products for the prevention/treatment of various chronic inflammatory diseases has attracted increased attention (6-9). Among many bioactive molecules derived from plants, polyphenols are of particular interest due to their potential anti-inflammatory effects (10). Over the last few decades, increasing evidence has focused on the field of metabolic inflammation to illustrate the beneficial effect of anti-inflammatory agents in the treatment of T2D and its complications. Resveratrol, due to its protective roles in inflammatory responses, is of particular interest for ameliorating meta-inflammation associated diseases. This review will summarize the effects of resveratrol on ameliorating meta-inflammation in different metabolic tissues.

Metabolic inflammation

By definition, metabolic inflammation or meta-inflammation is considered a chronic low-grade inflammation, triggered by a set of metabolic and inflammatory cells in response to an overload of nutrients or other intrinsic cues (11, 12). This definition differs from classical inflammation, which is the acute reaction of the immune system to cope with injuries and infection and is characterized by redness, swelling, fever, pain, heat, and edema (11, 13).

Adipose tissue is recognized as the central tissue in meta-inflammation, and overproduction of cytokines in this tissue might affect several other organs such as the liver, skeletal muscle, pancreas, and brain (11, 14). Apart from the secretion of inflammatory cytokines, adipocytes in obese subjects contribute to activating inflammatory processes through recruiting inflammatory cells such as macrophages and lymphocytes. Meta-inflammation can be activated by multiple factors such as inflammatory cytokines, excess free fatty acids (FFAs), reactive oxygen species (ROS), hypoxia and endoplasmic reticulum (ER) stress, inflammasome activation and alteration in gut microbiota (11). Notably, meta-inflammation is considered the central hallmark of all metabolic consequences of obesity such as insulin resistance, T2D and atherosclerosis (5).

Adipose tissue is considered the main source of inflammatory cytokines in T2D. Structurally, adipose tissue is composed of white adipose tissue (WAT), and brown adipose tissue. WAT is suggested to be the main central part of adipose tissue involved in meta-inflammation. WAT is further divided into subcutaneous and visceral fat tissues, with distinct physiology and function in pathologic processes. Abdominal WAT seems to play a major role in meta-inflammation (15). The mature adipose cells and stroma-vascular fraction (SVF) constitute two central parts of WAT (16). SVF itself is composed of extracellular matrix with dispersed fibroblasts, preadipocytes, endothelial, and immune cells such as macrophages, $CD3^+$ T cells ($CD4^+$ or $CD8^+$), mast cells, eosinophils and B cells. Adipocytes are the major cell population in the adipose tissue; however, the SVF is functionally important for this tissue (17). It is generally accepted that excessive fat accumulation can alter both the number and function of immune cells. Specifically, fat accumulation increases the number and activity of macrophages, mast cells, neutrophils, T- and B lymphocytes but reduces eosinophils and several subclasses of T lymphocytes including Treg, T helper 2 (Th2) and natural killer T (NKT) cells. This imbalance plays a significant role in the development of obesity-related local and systemic inflammation.

The increased infiltration of immune cells is considered the main characteristic of adipose tissue inflammation (18, 19). Evidence from rodent and human studies reveals that macrophages constitute more than 40% of the total adipose tissue content of obese subjects, compared to almost 10% in lean counterparts (20). Based on cytokine profile and surface markers, adipose tissue macrophages (ATMs) are categorized into two main subsets: M1 and M2. In lean conditions, adipocytes produce several cytokines, such as interleukin (IL)-13, that induce activation of M2 macrophages. Alternatively activated macrophages (M2) secrete anti-inflammatory factors, such as IL-10 and transforming growth factor β (TGF-β) (18, 20). Classically activated macrophages (M1) secrete pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and IL-6. Obesity can cause a switch from the M2 to M1 phenotype, characterized by a decrease in the production of anti-inflammatory cytokines and an increase in the production of pro-inflammatory cytokines. Adipocyte hypertrophy induced by over-nutrition promotes hypoxia-mediated death of adipocytes. Crown-like structures are formed as a result

of macrophage accumulation in hypoxic regions around the dead adipocytes (18). These events coincide with the release of several pro-inflammatory cytokines and chemokines, resulting in a vicious cycle amplifying ATM content and propagating the chronic inflammatory state. Indeed, pro-inflammatory cytokines and macrophage-secreted factors themselves exert paracrine effects to activate inflammatory pathways within insulin target cells. This leads to activation of Jun N-terminal kinase (JNK), inhibitor of κB kinase β (IKKβ), and other serine kinases that subsequently activate transcription factor targets, including activator protein 1 (AP1) and nuclear factor-κB (NF-κB). Serine kinases also phosphorylate insulin receptor substrate proteins, insulin receptors, and possibly other insulin signaling molecules, thereby interrupting the normal function of insulin and leading to insulin resistance (20).

In addition to macrophages, other leukocyte populations can infiltrate adipose tissue. Obesity is characterized by a remarkable elevation of $CD8^+$ T cells and a decrease in both $CD4^+$ helper and regulatory T cells (Treg) in visceral adipose tissue. $CD8^+$ T cells are involved in the differentiation, recruitment, and activation of macrophages during obesity. However, $CD4^+$ T helper and Treg cells play a fundamental role in determining the outcome of inflammatory responses. It is well known that TH1 cells are pro-inflammatory cells and enhance macrophage secretion of inflammatory cytokines, while TH2 and Treg cells induce an anti-inflammatory M2 macrophage phenotype. NKT cells have been observed in obese adipose tissue and recognize lipid antigens. Depletion of NKT cells decreases insulin resistance and adipose tissue inflammation following high-fat diet (HFD) feeding, while activation of these cells exacerbates metabolic effects of diet-induced obesity (21).

Mast cells accumulate in obese adipose tissue earlier than macrophages and produce and secrete various mediators, such as histamine, serotonin, heparin, serine protease, eicosanoids, and cytokines. Among these mediators, IL-6 and interferon γ (IFN-γ) have a notable impact on inflammation associated with obesity (18, 21). These cytokines increase protease expression in adipose tissue, which in turn leads to angiogenesis by degrading anti-angiogenic molecules and further infiltration of leukocytes into the adipose tissue (21).

Dendritic cells are specialized antigen-presenting leukocytes involved in macrophage activation and accumulation (M1) at the site of inflammation (18). Dendritic cells express a number of surface markers such as CD11c, which are similar to the markers used to characterize the M1 subpopulation of adipose tissue macrophages in mice (18). CD11c is a member of the β2-integrins and has been used as an activation marker for monocytes/macrophages (22-23).

Neutrophils are the first immune cells recruited to inflamed tissues and can enhance the consequent infiltration of inflammatory monocytes by secreting monocyte chemoattractant protein-1 (MCP-1) and other chemokines. The IL-4 and IL-13 induce the M2-polarisation of macrophages in WAT (24). The levels of eosinophils, one of the main sources of IL-4 and IL-13 in adipose tissue, are reduced during obesity. Eosinophils improve glucose homeostasis by sustaining the levels of anti-inflammatory M2 macrophages in the WAT, possibly through an IL-4 and IL-13 signaling-dependent manner (18).

As stated earlier, meta-inflammation has been suggested as the underlying mediator of obesity-induced T2D. Therefore, it is reasonable to conclude that strategies targeting meta-inflammation could be interesting options for treatment and prevention of metabolic disorders. In vitro and in vivo evidence has suggested that resveratrol could be a promising therapeutic agent against metabolic inflammation. In the following sections, this review will discuss in more detail the effects of resveratrol on metabolic inflammation in different tissues.

Resveratrol

In recent years, understanding the "French Paradox" has drawn increasing attention to investigate whether polyphenolic antioxidants such as resveratrol may be useful beyond the cardiovascular system. The French paradox refers to the paradoxical association of a diet high in saturated fat and cholesterol with low CVD mortality, which was initially attributed to consumption of red wine and its constituent resveratrol (25).

Resveratrol, chemically known as 3,5,4'-trihydroxystilbene, is a naturally occurring non-flavonoid polyphenolic antioxidant compound produced in a large variety of plant species such as mulberries, peanuts, and grapes (26-28). Resveratrol was first isolated from the roots of white hellebore (Veratrum grandiflorum O. Loes) in 1940, and later, in 1963, from the roots of Polygonum Cuspidatum (29). Its name has been derived from its source; a resorcinol derivative coming from a Veratrum species (30). Phenylalanine is a precursor of resveratrol biosynthesis that, following several reactions, is converted to 4-coumaroyl-CoA. Finally, the enzyme stilbene synthase converts one molecule of p-coumaroyl-CoA and three molecules of malonyl-CoA into resveratrol. There is evidence that biosynthesis of resveratrol is induced in plants in response to physical and chemical stresses (31). Resveratrol is a photosensitive molecule susceptible to isomerization via UV radiation. This polyphenol exists naturally as both cis- and trans-isomers; however, the trans-isomer is believed to be the most abundant and biologically active form (32).

There is increasing evidence that resveratrol prevents or attenuates progression of a variety of disorders, as well as improves stress resistance and extends the lifespans of various organisms from yeast to vertebrates (29). Since the discovery of caloric restriction-like effects of

resveratrol, it was shown that resveratrol might provide beneficial effects against CVD, metabolic diseases, and cancer. Based on in vitro and in vivo studies, the beneficial effect of resveratrol is mediated through its anti-aging, anti-carcinogenic, anti-inflammatory, and anti-oxidant activities (33).

Resveratrol and diabetes

There is increasing evidence showing the beneficial effects of resveratrol on alleviating insulin resistance and T2D (32). Clinical trials in T2D patients point to the anti-diabetic effects of resveratrol (26, 34). More recently, a meta-analysis of 11 randomized controlled trials demonstrated that resveratrol consumption significantly improves insulin sensitivity and glycemic control in patients with diabetes (35). Moreover, data from rodent studies have indicated the effects of resveratrol on improving insulin sensitivity, decreasing hyperglycemia, enhancing insulin secretion, and enhancing antioxidant capacity in pancreatic β-cells (36). In addition, a decrease in HbA1c concentrations in an animal model of diabetes (streptozotocin-nicotinamide-induced diabetic rats) after resveratrol administration reveals the anti-diabetic potential of this natural polyphenol (37).

Several mechanisms, including a decrease in oxidative stress, reduction of inflammation, down-regulation of protein-tyrosine phosphatase 1B, prevention of pancreatic β cell loss, and decrease in lipid accumulation in muscle and liver tissues, have been suggested to explain the anti-diabetic effects of resveratrol (33, 37). Moreover, resveratrol enhances the lipolytic response to epinephrine and reduces the insulin ability to counteract lipolysis in adipose tissue. Resveratrol also reduces hyperglycemia in diabetic rats (32). The underlying mechanisms for resveratrol benefits in glucose homeostasis are induction of sirtuin 1 (SIRT1) activity, stimulation of glucose uptake by increased expression and membrane trafficking of GLUT4, activation of glucose uptake in the absence of insulin, elevation of glycogen synthase activity and decrease of glycogen phosphorylase activity in the liver (32, 37). However, other mechanisms including the activation of 5'-AMP-activated protein kinase (AMPK) play an important role in induction of fatty acid oxidation (32).

Resveratrol as an anti-inflammatory agent

There is accumulating evidence that resveratrol, as an anti-inflammatory agent, inhibits the expression and secretion of pro-inflammatory mediators such as TNF-α, IL-6, IL-1, IL-12, and IFN-γ. Recently, a meta-analysis of 17 randomized controlled trials revealed that resveratrol consumption significantly reduces serum and plasma levels of TNF-α and high sensitive C reactive protein (hs-CRP) (38). Additionally, the inhibitory role of resveratrol in eicosanoid synthesis and activation of several enzymes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-1 (COX-1), or COX-2 has also been reported (39, 40). It has been shown that the anti-inflammatory property of resveratrol is mediated through the down-regulation of transcription factors NF-kB or AP-1 (27).

Resveratrol and inflammation in adipose tissue

As mentioned above, adipose tissue is a central organ in meta-inflammation. In this section, the effects of resveratrol on the inflammatory processes in adipose tissue are described. Several studies have provided data that resveratrol functions as an anti-inflammatory agent in adipose tissue and exerts its pivotal effects on reversing the deleterious actions of obesity on inflammation in T2D. The anti-inflammatory effect of resveratrol on adipose tissue has been studied in both immune cells and adipocytes.

Studies have reported the effect of resveratrol on macrophage infiltration into adipose tissue. It has been suggested that this polyphenol markedly attenuates visceral WAT inflammation and insulin resistance in a mouse model of sleep apnea. In detail, sleep fragmentation augments tissue inflammation and insulin resistance through recruiting macrophages to visceral WAT, reducing M2 polarity cell counts, suppressing the proportion of circulating Treg cells, and increasing the population of M1 polarity in mice. Interestingly, resveratrol treatment reversed all these alterations (41). In another study, Jeon et al. demonstrated that resveratrol reduced macrophage migration to adipose tissue in mice fed a HFD (42). In addition, intermittent hypoxia caused an increase in the total number of macrophages in visceral WAT which consists of an increase in the pro-inflammatory M1 macrophage and reduction in M2 macrophages. These changes were markedly abrogated in resveratrol administration state (43). Nøhr et al. reported that resveratrol supplementation alleviated lipopolysaccharide (LPS)-induced inflammation in mice which was associated with a reduced expression of TNF-α and IL-1β in epididymal fat. Resveratrol was not able to reduce macrophage infiltration, but it switched their phenotype into a more anti-inflammatory state (M2 macrophage) in the epididymal adipose tissue (44). Moreover, Lv Zm et al. evaluated macrophage infiltration in fat depots by measuring crown-like structure (CLS) density, which consisted of dead adipocytes and infiltrating macrophages. Histological analysis showed that a high-calorie and high-cholesterol diet increased adipocyte size and the density of CLSs in mice and resveratrol supplementation prevented these alterations (45). Resveratrol also reduced pro-inflammatory cytokines via suppressing macrophage infiltration and inhibiting NF-κB activity in adipose tissue of genetically obese rats (46).

There is accumulating evidence regarding the effects of resveratrol on adipocytes. In human adipose tissue explants, resveratrol reversed IL-1β-induced inhibition of adiponectin production (47). Moreover,

resveratrol suppressed ROS production and forskolin-induced lipolysis in human differentiated adipocytes (48). There is also a report that oral administration of resveratrol ameliorated adipose tissue dysfunction in fructose-fed rats through inhibiting NF-kB p65 phosphorylation, abrogating the expression of the pro-inflammatory adipocytokines, and elevating adiponectin and peroxisome proliferator-activated receptor (PPAR) expressions in perivascular adipose tissue in an AMPK/SIRT1-interdependent manner (49). Chronic administration of resveratrol improved insulin sensitivity and inflammatory responses in visceral WAT of diet-induced obese monkeys and 3T3-L1 adipocytes possibly through upregulating SIRT1 expression, decreasing adipocyte size, and suppressing NF-kB activation. Remarkably, serum from resveratrol-treated monkeys suppressed NF-κB activation as well as expression of IL-6 and IL-1β in 3T3-L1 adipocytes (50). In addition, SIRT1 activation by resveratrol diminished the expression of CD40 in 3T3-L1 adipocytes-treated with TNF-α partially via modulating NF-κB-dependent pathway (51). Further experiments have also shown that resveratrol suppresses obesity-associated inflammatory through downregulation of plasminogen activator inhibitor 1 (PAI-1) gene expression in vitro model of inflamed adipose tissue possibly through suppressing NF-κB activity. It was also demonstrated that signaling via phosphatidyl inositol 3 kinase (PI3K), SIRT1, AMPK, ROS, and nuclear factor erythroid 2-related factor 2 (Nrf-2) were not involved in mediating the inducing effects of resveratrol on PAI-1 production (52). In addition, it is evident that hypoxia and fibrosis are early triggers of the adipose dysfunction in obesity. Resveratrol effectively ameliorated fibrosis and inflammation in adipose tissue which was associated with HIF-1α degradation in a SIRT1-dependent manner (53). Importantly, resveratrol suppressed up-regulation of the inflammatory cytokines such as TNF-α, IFN-α and IFN-β, and their upstream signaling molecules, including toll-like receptor 2 (TLR2), TLR4, MyD88, Tirap, TRAF6, IRF5, TRIF, p-IRF3, and NF-kB in epididymal adipose tissues of obese mice (54). Moreover, resveratrol inhibited TNF-α-induced IL-6, PAI-1, MCP-1 (55, 56) and IL-8 levels in adipocytes. This effect was mainly due to the NF-κB inhibitory potential of resveratrol (24, 57, 58). Specifically, this polyphenol can repress NF-kB binding activity directly or indirectly through the activation of SIRT1 (58). Other potential mechanisms for the anti-inflammatory activity of resveratrol includes suppression of the activation of extracellular signal-regulated kinase (ERK), c-June N-terminal kinase (JNK), c-Jun, and also activation of PPARγ activity (59). Resveratrol also up-regulated the expression of adiponectin, PPAR-α, PPAR-γ, SIRT1 and AMPK in epididymal fat depots of HFD-induced obese mice (60). The expression of adipose triglyceride lipase (ATGL) and its downstream PPAR*α*-mediated lipid signaling pathway was reduced in both an animal model of aging and aged 3T3-L1 adipocytes, which coincided with upregulation of TNF-*α* and IL-6 production. Notably, resveratrol attenuated the production of pro-inflammatory cytokines in an ATGL/PPARα-dependent manner (61). Resveratrol also inhibited visceral adipogenesis through suppression of the galanin-mediated signaling molecules such as E2F1, and p-ERK and key adipogenic genes such as fatty acid synthase (FAS) and lipoprotein lipase in HFD-induced obesity. Furthermore, it attenuated cytokine production in adipose tissue by repressing TLR2 and TLR4-mediated inflammation (54). Resveratrol also maintained mitochondrial integrity by inhibiting Drp1 activity and prevented NLR family pyrin domain containing 3 (NLRP3) inflammasome activation by suppressing endoplasmic reticulum (ER) stress. These events were associated with reduced cell apoptosis in the adipose tissue of diabetic mice (62).

Resveratrol and inflammation in liver

Chronic inflammation is the hallmark of insulin resistance in the liver (63, 64). There is compelling evidence to support a central role for systemic and hepatic inflammation in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Preventing hepatic meta-inflammation through diet, exercise, lifestyle modifications, and pharmacological intervention might be helpful in the treatment of NAFLD and insulin resistance (65). In this regard, chronic supplementation of resveratrol in NAFLD patients significantly decreased inflammatory markers (hs-CRP, IL-6, and NF-κB) and cytokeratin-18 (as a biomarker of hepatocellular apoptosis) (66). In another study, resveratrol significantly increased adiponectin levels and reduced the levels of TNF-α, and fibroblast growth factor 21 (FGF-21) in patients with NAFLD (67).

Macrophages are widely distributed in the liver and they are a promising target for resveratrol intervention. Macrophages in the liver are classified into two subsets: (CD68+) Kupffer cells which are engaged in phagocytic activity and (CD11b+) Kupffer cells with cytokine producing capacity (TNF-α, IL-12), that are involved in inflammation and antitumor immunity. Resveratrol was shown to increase the number of phagocytic (CD68+) Kupffer cells and subsequently facilitated uptake of the lipid droplets by these cells. Moreover, resveratrol reduced the capacity of CD11b+ Kupffer cells to produce TNF-α (68). Resveratrol also conferred resistance to hepatocyte steatosis and apoptosis in an animal model of NAFLD which coincided with a significant increase in M2 Kupffer cells polarization (69). Resveratrol administration suppressed Kupffer cells recruitment and down-regulated the expression of pro-inflammatory cytokines such as TNF-α and IL-6 in bile duct ligation and CCL4-induced liver injuries models (70, 71). Furthermore, resveratrol dramatically

inhibited inflammation in a low-dose LPS-induced model of NASH (72). In contrast to above findings, Jeong et al. by measuring macrophage infiltration marker (F4/80), M1 macrophage marker (CD11c) and M2 macrophage marker (CD163), reported that resveratrol treatment could not improve obesity-induced macrophage infiltration and phenotypic switching from M1 to M2 state in the liver of HFD mice (73).

At the molecular level, several targets have been proposed for the anti-inflammatory effects of resveratrol. It was found that resveratrol could relieve HFD-induced inflammation through upregulation of hepatic expression of both SIRT1 and SIRT6. Furthermore, the beneficial effects of resveratrol on glycemic control and NAFLD were accompanied by alterations in NLRP3 inflammasome. Notably, resveratrol administration could reverse increased expression of NLRP3 components including ASC, CASP-1, NALP-1 and NALP-3 in old mice liver (65). Resveratrol prevented HFD-induced hepatic steatosis and ER stress by regulation of the expression of PPAR-δ, ATP citrate lyase, suppressor of cytokine signaling-3 (SOCS3), TNF-α, and IL-1β (74). Furthermore, administration of resveratrol remarkably inhibited inflammatory responses by suppressing NF-κB p65 expression and reducing the IL-1β cytokine level in the hepatic tissues of streptozotocin-induced type 1 diabetic rats (75). It has also been suggested that the inhibitory effect of resveratrol on activity of the NF-kB may be mediated by the restoration of its inhibitor; Ik-Ba (76). COX2, a marker of pro-inflammatory innate immune activity, was also upregulated in aged liver and reversed by resveratrol in old mice liver (77). There is ample evidence about the close link between oxidative stress and inflammation in the pathogenesis of liver injury. In this regard, resveratrol significantly reduced the hepatic expression of 4-hydroxynonenal; a marker of oxidative stress in mice with cholesteric liver injury (70).

Resveratrol and inflammation in pancreas

Impaired insulin secretion due to either β-cell dysfunction and/or β-cell loss is now recognized in the pathogenesis and progression of T2D (78). T2D is associated with increased islet-associated immune cells. Indeed, an increased number of islet-associated macrophages was observed early in HFD mice, the *db/db* mouse, and in type 2 diabetic patients during disease progression. Both the exposure of cultured islets to a type 2 diabetic milieu and islet isolation from HFD fed mice were associated with increased levels of islet-derived inflammatory factors including IL-6, IL-8, granulocyte colony-stimulating factor, and macrophage inflammatory protein 1α (MIP-1α) (79).

There is evidence regarding resveratrol effects on inflammatory cytokines and inflammatory signaling pathways in pancreatic tissue. It was reported that resveratrol decreased infiltration of neutrophil cells into the pancreas in severe acute pancreatitis (SAP) (80). Oral administration of dihydro-resveratrol also decreased production of TNF-α and activity of NF-kB in the pancreas of cerulein-treated rats (81). Furthermore, resveratrol administration significantly suppressed chemokine (C-C motif) receptor (CCR) 6 production in immune cells and down-regulated CCR6 expression in Th17 and CD11b+F4/80hi macrophages in a non-obese mouse model of type 1 diabetes. Resveratrol also reduced IFN-γ expression and its suppressive functions in T helper (Th)17 polarization. These effects were associated with inhibition of macrophage migration from peripheral lymphoid organs to the pancreas in the NOD mouse model of type 1 diabetes (82).

Resveratrol and inflammation in skeletal muscle

Skeletal muscle is another major site of insulin resistance in obesity and T2D. Skeletal muscle is the primary site of glucose disposal and accounts for almost 80% of insulin-stimulated glucose uptake in the body and, therefore, muscle insulin resistance has a profound effect on glucose intolerance and hyperglycemia in obesity and T2D (5, 83). Studies have suggested that lipid accumulation inside muscle cells, activation of the inflammatory signals in myocytes following exposure to stimuli such as LPS and FFAs, and recruitment of macrophages are some proposed mechanisms underlying skeletal muscle insulin resistance (5, 13). A high level of inflammatory markers such as TNF-α, IL-6, and IL-18 and increased infiltration of macrophages has been reported from skeletal muscle tissue of obese and insulin-resistant subjects (84).

The beneficial anti-inflammatory effects of resveratrol in skeletal muscle cells have been reported in several studies. In support of this notion, microarray analysis on vastus lateralis muscle biopsies revealed that 30 days of resveratrol supplementation in healthy obese subjects reduced the gene expression of genes involved in inflammation (85). Furthermore, resveratrol treatment decreased induction of iNOS, and nitric oxide (NO) production in skeletal muscle of LPS-challenged mice. In vitro studies revealed that the inhibitory effect of resveratrol on both iNOS protein induction and NO production in cytokine/LPS-treated L6 myocytes is partly mediated through a mechanism involving the activation of AMPK (86). Findings also demonstrated that resveratrol has an anti-inflammatory function in skeletal muscle C2C12 cells. Resveratrol pretreatment robustly attenuated palmitate-induced TNF-α and IL-6 expression in C2C12 cells. Molecular analyses revealed that the beneficial effects of resveratrol were accompanied by inhibiting ROS production and decreasing the activity of the MAPKs and NF-kB signaling pathways (87). In contrast to above reports, other studies have shown no effect of resveratrol on skeletal muscle inflammation. It was suggested that resveratrol did not affect the mRNA and protein levels of TNF-α and iNOS in skeletal muscle

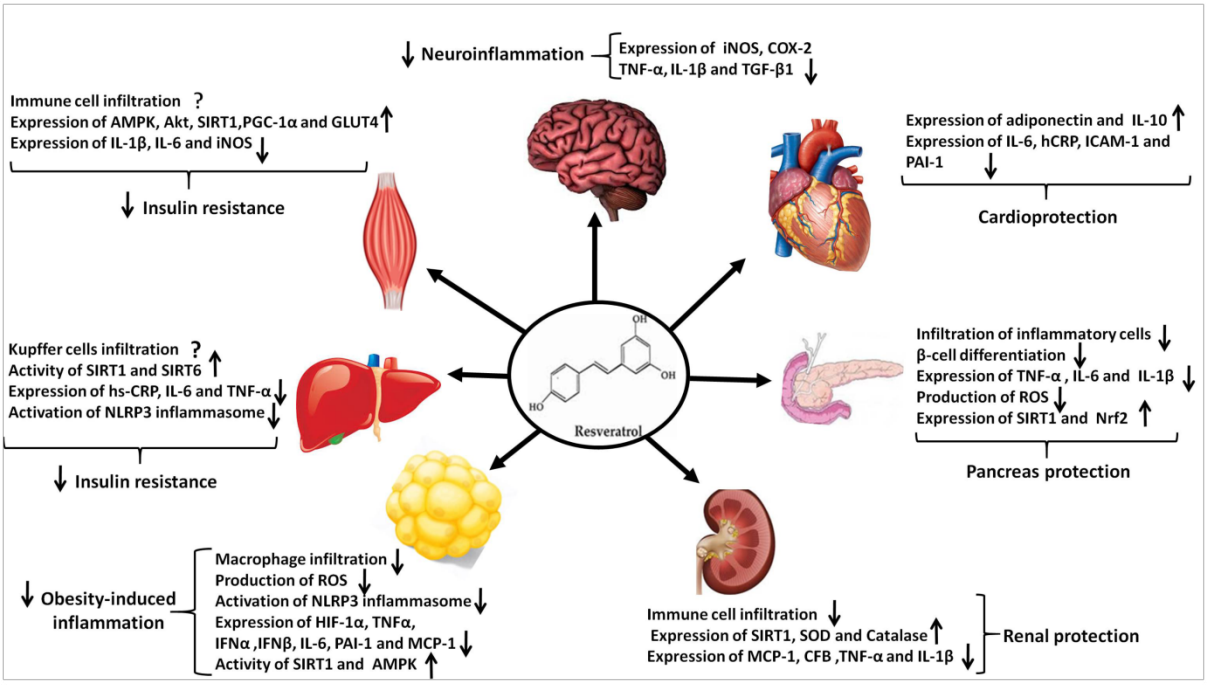

Figure 1. Possible effects of resveratrol on modulating inflammation in various organs affected by obesity. At the molecular level, several mechanisms have been proposed for resveratrol effects in ameliorating meta-inflammation. These mechanisms include suppression of infiltration of immune cells into tissues, inhibition of pro-inflammatory cytokines production, inhibition of NLRP3 inflammasome activation, oxidative stress suppression and SIRT1 activation. The modulation of these processes by resveratrol is associated with alleviating the meta-inflammation-induced tissue damage in liver, pancreas, skeletal muscle, kidney, heart and brain

AMPK: AMP-activated protein kinase; CFB: complement factor B; COX-2: Cyclooxygenase-2; GLUT4: Glucose transporter type 4; HIF-1α: Hypoxia-inducible factor 1-alpha; hs-CRP: A high-sensitivity c--reactive protein; ICAM-1: Intercellular Adhesion Molecule 1; IFNα: Interferon-alpha; IFNβ: Interferon-beta; IL-10: Interleukin 10;IL-1β: Interleukin 1beta;IL-6: Interleukin 6; iNOS: Inducible nitric oxide synthase; MCP-1: Monocyte chemoattractant protein-1; NLRP3: NLR Family Pyrin Domain Containing 3; Nrf-2: Nuclear factor (erythroid-derived 2)-like 2; PAI-1: Plasminogen activator inhibitor-1; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROS: Reactive oxygen species;
TGF-β1: Transforming growth factor beta 1; TNF-α: Tumor necrosis factor alpha

of aged human subjects. Furthermore, 8 weeks of daily intake of resveratrol in aged human subjects did not affect the abundance of the IκB-α and IκB-β or the JNK, p65, p38, and IKK phosphorylation (88). In addition, resveratrol supplementation did not alter the expression of TNF-α, IL-6, and MCP-1 in skeletal muscle of HFD-induced obese mice (89). In another report, resveratrol had no effect on CD14 (a marker of macrophage infiltration), TNF-α, and IL1-β expression in skeletal muscle of LPS-treated mice (44). Altogether, the results from above studies suggest that further studies are still needed to provide greater insight into the effects of resveratrol on the inflammatory responses in skeletal muscle cells.

Resveratrol and inflammation in kidney

It is well-accepted that obesity-induced inflammation plays a significant role in the initiation or development of chronic kidney diseases (CKD) and glomerulopathy (90, 91). Indeed, insulin resistance and inflammation are common features in CKD patients (92). Several in vivo and in vitro studies have indicated that infiltration of inflammatory cells (93-97) and elevation of inflammatory cytokines (98-102), play a significant role in the pathogenesis of renal injuries.

Resveratrol, through different signaling alterations, exhibits renoprotective effects in various animal models. In rat renal mesangial cells, resveratrol prevented high glucose-induced cell proliferation and fibronectin expression through inhibiting both NF-κB/NADPH oxidase pathway and ROS production (103). Palsamy et al. demonstrated the beneficial effect of resveratrol on nephropathy in a model of streptozotocin-nicotinamide-induced diabetic rats. Oral administration of resveratrol to diabetic rats significantly normalized the levels of TNF-α, IL-1β, IL-6, NO and NF-κB p65 subunit in renal tissues (104). In another study, it was revealed that resveratrol treatment inhibited renal lipotoxicity, oxidative stress and inflammation by enhancing the AMPK-SIRT1-PGC1α signaling pathway in db/db mice (105). The administration of resveratrol significantly ameliorated LPS-induced acute kidney injury (AKI) in

mice by reducing infiltrating cells and also inflammatory cytokine levels in kidney tissue (45). Interestingly, the suppressive effects of resveratrol on infiltration of macrophages and neutrophils have been reported in animal models of cystic kidneys, ischemic/reperfusion (I/R)-induced renal injury and sepsis-induced renal injury (108-110). Treatment of the AKI model with resveratrol also induced apoptosis in macrophages through downregulation of iNOS, Bcl-2, and Bcl-xL and decreased inflammation by suppressing TLR-4 activation and cytokine release (111). Moreover, resveratrol attenuated polycystic kidney disease (PKD) progression by inhibitory role in production of MCP-1, and TNF-α possibly via a pathway dependent on NF-kB (108).

In vitro and animal studies demonstrate a beneficial anti-inflammatory role for resveratrol in different chronic kidney diseases. There is no direct clinical evidence showing the protective and anti-inflammatory effects of resveratrol in CKD patients, however, a few studies imply its beneficial effects on human subjects. In this regard, dietary supplementation with red grape juice exerted anti-oxidative and anti-inflammatory efficacies in hemodialysis patients (112, 113). However, further investigations are required to reveal the potential beneficial effects of resveratrol in human kidney injuries.

Resveratrol and inflammation in heart

The increased incidence of CVD will lead to an expected worldwide number of CVD-related deaths of more than 23.6 million by 2030 (114, 115). Resveratrol has shown beneficial and protective effects against most degenerative and CVD, including I/R injury, atherosclerosis, hypertension, and heart failure.

There is accumulating evidence to support the central role of inflammation in the process of atherosclerosis. Notably, inflammation is involved in all stages of atherosclerosis including initiation, progression and plaque formation (116). Both in vivo and in vitro anti-inflammatory effects of resveratrol in atherosclerosis and the underlying mechanism have been suggested. Consistent with this, resveratrol treatment has been shown to inhibit IL-6 and IL-8 production in human coronary artery smooth muscle cells (117), inhibit IL-6 release by stimulated macrophages (118), and reduce serum levels of IL-1β, IL-6, and TNF-α in an atherosclerotic rabbit model (119). Resveratrol effects on NF-κB, an important transcription factor regulating various mediators or inflammation including cytokines, adhesion molecules, and growth factors was reported (120). Resveratrol has been shown to reduce the expression of adhesion molecules intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) via inhibiting the NF-κB pathway (121). Similarly, resveratrol suppressed hyperglycemia-induced ICAM-1 expression in endothelial cells through inhibiting the p38 mitogen-activated protein kinase (MAPK) pathway (122). In cultured endothelial cells, the beneficial effects of resveratrol on inflammatory angiogenesis have been attributed to inhibition of COX-2 and matrix metalloproteinase-9 (MMP-9) (123). Resveratrol also counteracted oxysterol-induced inflammation and NF-κB activation in human macrophages, suggesting the potential effects of resveratrol in preventing or treating atherosclerosis (124). Furthermore, resveratrol has been shown to reverse the pro-inflammatory phenotype in vascular smooth muscle cell of aged non-human primates, suggesting a vasoprotective effect of resveratrol in animal models of aging (125). Resveratrol effects on inflammation could be mediated by modulating the expression of miRNAs that can be anti-inflammatory (e.g., miR-663) or pro-inflammatory (e.g., miR-155) (126).

Inflammation is also a key player in myocardial ischemia. TNF-α can trigger the inflammatory reaction caused by myocardial I/R. Vascular endothelial cell injury, and inflammatory cells, such as neutrophils activated by cytokines, and adhesion molecules are also involved in the inflammatory responses (127). In a recent study, rats with myocardial I/R injury were administered with resveratrol at the onset of reperfusion. The results indicated the propagation of the cascade of inflammatory responses through activating NLRP3 inflammasome and secreting the inflammatory cytokines IL-1β and IL-18. The authors showed that resveratrol may exert protective effects against I/R injury by inhibiting the expression and activation of the NLRP3 inflammasome (128). Moreover, resveratrol suppressed the inflammatory reaction in rat heart with myocardial I/R by inhibiting TLR4/NF-κB signaling, activating the Nrf2/ARE pathway, increasing NO production and inhibiting both neutrophil infiltration and TNF α expression (129).

Heart failure is a clinical syndrome that arises from a variety of pathophysiologies including hypertension, myocardial infarction, and congenital cardiomyopathies (130). Data from animal studies have reported that the administration of resveratrol prevents and/or slows the progression of heart failure in animal models of heart failure induced by myocardial infarction, pressure overload, and myocarditis (29). Gupta et al. demonstrated that resveratrol treatment significantly attenuated adverse cardiac remodeling in pressure overload-induced heart failure in C57/BL6 mice. In this study, oxidative stress, left ventricular macrophages and mast cells infiltration was significantly increased after 4 weeks of transverse aortic constriction compared to sham-operated mice. Treatment with resveratrol significantly abolished this inflammatory response when compared to transverse aortic constriction alone. This response has been shown to be mediated, at least in part, by inhibition of oxidative stress and inflammation (131). Resveratrol significantly decreased cellular infiltration, fibrosis, and expression of inflammatory cytokines in the myocardium in myosin-induced autoimmune myocarditis of rats (132).

Despite the promise of resveratrol as a potential therapeutic for numerous CVD, the number of clinical studies investigating the cardioprotective effects of resveratrol is still limited. Moreover, there is still a great deal of uncertainty on the beneficial effects of resveratrol on inflammatory markers in patients with CVD. In one study, one-year daily intake of a resveratrol-enriched grape extract modulated the expression of key pro-inflammatory cytokines and inflammation-related microRNAs in peripheral blood mononuclear cells of T2D and hypertensive patients with coronary artery disease (133). In addition, chronic daily consumption of a resveratrol-rich grape supplement improved the inflammatory status in patients at high CVD risk (134, 135). This effect was mediated by increasing adiponectin (136, 137) and IL-10 levels, and suppressing several well-known inflammatory mediators including TNF-α, IL-6/IL-10 ratio, PAI-1, hs-CRP, soluble ICAM-1 (137), and IL-6 (135). On the other hand, receiving 10 mg resveratrol capsule daily for 3 months did not alter CRP and TNF-α in patients with stable coronary artery disease. However, it improved left ventricle diastolic function and endothelial function and reduced LDL-cholesterol level (138). In summary, preclinical studies using resveratrol have demonstrated that this polyphenol can ameliorate inflammatory state in CVD, but there are some controversies about the clinical studies, thus there is a need for large and well-controlled clinical trials in this regard.

Resveratrol and inflammation in central nervous system

Inflammation is a complex responsive cascade in the central nervous system (CNS) by which it defends against potentially injurious stimuli. An increasing body of literature has demonstrated that activated microglia and infiltrating monocytes, along with inflammatory cytokines secreted from these cells, have an important role in the initiation and progression of neuro-inflammation (139, 140). According to several studies, resveratrol has been considered to ameliorate neuro-inflammation in the CNS (141, 142).

Firstly, resveratrol as an inhibitor of neuro-inflammation has been investigated in several animal model studies (143-147). For instance, resveratrol had a decreasing effect on the levels of inflammatory factors in the hippocampus of kindled mice and rats (148, 149). It has been reported that the antidepressant function of resveratrol was partially mediated by decreasing the levels of pro-inflammatory cytokines through the NF-κB signaling pathway in the brain areas of animal models (150, 151). Secondly, there are also several cell models of neuro-inflammation such as CNS-resident microglia, BV-2 murine microglia, N9 microglia and CNS-infiltrating peripheral macrophages, which have been used in studies investigating the cellular mechanisms underlying the anti-inflammatory effects of resveratrol in the CNS (152-155). Moreover, astrocytes as the most abundant cells in the CNS and producers of pro-inflammatory cytokines (156, 157) can also be affected by resveratrol (158).

There is also evidence that HFD and obesity can result in high levels of FFAs and cytokines in blood (159-161). Following the arrival of FFAs, cytokines and immune cells in the hypothalamus, neuro-inflammation is triggered which in turn leads to interruption of satiety signals and adverse impacts on cognition (162). Although the exact mechanisms by which obesity induces neuro-inflammation is still unclear, there is evidence for intracellular disturbances and stresses such as ER stress, oxidative stress, and autophagic defects in this regard (163). Moreover, diabetic neuropathy is one of the common complications of diabetes and clinical manifestations such as numbness, burning and tingling sensation and intractable pain are attributed to this disorder. The pathophysiological factors of diabetic neuropathy may include hyperglycemia, oxidative stress, lipid peroxidation, nitrosative stress, poly (ADP-ribose) polymerase (PARP) over activation, defective neurotrophism and autoimmune-mediated nerve destruction which can trigger neuro-inflammation. Following this condition, permanent nerve damage can happen through decreasing nerve functionality and nerve blood perfusion (164, 165).

It has been described that resveratrol attenuated hypothalamic inflammation through a decrease in mRNA levels of IκB and IKKβ and protein level and acetylated NF-κB subunit RelA/p65 in a mouse model of T2D (166). Furthermore, resveratrol reduced TNF-α levels in hippocampus of HFD fed diabetic mice (42). It was also described that the Jak-Stat pathway as an activator of the pro-inflammatory factors including IL-15 and IL-22 showed lower expression following resveratrol supplementation in hippocampus of diabetic mice (167). In addition, DNA fragmentation, oxidative stress and levels of malondialdehyde, peroxynitrite, NF-κB, TNF-α, IL-6 and COX-2 indicated a significant decrease following resveratrol treatment in diabetic rats (168, 169). Another study reported that the neuroprotective effect of resveratrol was enhanced in combination with 4-amino 1,8 naphthalimide (4-ANI) as an PARP inhibitor in experimental diabetic neuropathy (170).

A number of studies have reported the possible role of resveratrol in protecting against brain damage following ischemia, stroke, seizure, and epilepsy (171). Rats treated with resveratrol indicated increased heme oxygenase neuroprotective enzyme and decreased intracellular heme levels as a pro-oxidant following stroke (172). Moreover, resveratrol as a cardio- and neuro-protector ameliorated blood-brain barrier disruption and brain damage following recurrent stroke through activation of SIRT-1 and attenuating the inflammatory and oxidative stress markers in adult rats (173). Additionally, resveratrol decreased the volume

of infarction following focal cerebral ischemia in rats (174). As discussed above, based on animal models and cell culture studies, it seems that resveratrol mitigates meta-inflammation pertaining to several CNS conditions. However, these results should be confirmed in human studies.

Conclusion

Existing evidence supports the role of low-grade chronic inflammation or metabolic inflammation as a probable mechanism connecting obesity and T2D. Multiple mechanisms including inflammatory cytokines, macrophage infiltration into tissues, excessive FFAs, production of ROS, hypoxia and ER stress, inflammasome activation and alteration in gut microbiota have been implicated in triggering meta-inflammation. Therefore, it is worth mentioning that strategies targeting meta-inflammation could be promising approaches for the treatment and prevention of obesity-related disorders.

Resveratrol, due to its protective roles in the regulation of inflammatory responses, is of particular interest for ameliorating diseases linked with meta-inflammation. The specific mechanisms linked to resveratrol in the context of meta-inflammation are still uncertain, but several mechanisms have been attributed to the anti-inflammatory activities of this polyphenol. These mechanisms include (1) suppression of NF-kB signaling pathway by either inhibiting NF-kB p65 phosphorylation or by repressing NF-kB binding activity or by restoration of its inhibitor; Ik-Ba; (2) down-regulation of ERK/p38 MAPK signaling pathway; (3) suppression of TLR-mediated pathways; (4) inhibition of NLRP3 inflammasome activation; (5) inhibition of ROS production; (6) suppression of infiltration of immune cells into tissues; and (7) inhibition of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, and CRP) production. The modulation of these processes by resveratrol is associated with protective effects against meta-inflammation-induced tissue injury in adipose tissue, liver, pancreas, skeletal muscle, kidney, heart and brain.

In the case of human studies, the anti-inflammatory properties of resveratrol have been reported in several pre-clinical studies; however, some studies have reported opposing results. The conflicting data may be related to the poor bioavailability of resveratrol in humans and dissimilarities in study design and use of different doses of resveratrol. Therefore, long-term follow-up studies are needed to generalize the beneficial effects of resveratrol in meta-inflammation-related abnormalities to humans..

Conflict of Interest

The authors declare that they have no conflict of interest.

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