Potential Mechanisms by Which Polyphenol-Rich Grapes Prevent Obesity-Mediated Inflammation and Metabolic Diseases

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Keywords

phenolic phytochemicals, flavonols, anthocyanins, antioxidant, anti-inflammatory, insulin resistance

Abstract

Obesity and metabolic disease–related health problems (e.g., type 2 diabetes, atherosclerosis, and hypertension) are the most prevalent nutrition-related issues in the United States. An emerging feature of obesity and type 2 diabetes is their linkage with chronic inflammation that begins in white adipose tissue and eventually becomes systemic. One potential strategy to reduce inflammation and insulin resistance is consumption of polyphenol-rich foods like grapes or their by-products, which have anti-inflammatory properties. Polyphenols commonly found in grape products have been reported to reduce inflammation by (*a*) acting as an antioxidant or increasing antioxidant gene or protein expression, (*b*) attenuating endoplasmic reticulum stress signaling, (*c*) blocking proinflammatory cytokines or endotoxin-mediated kinases and transcription factors involved in metabolic disease, (*d*) suppressing inflammatory- or inducing metabolic-gene expression via increasing histone deacetylase activity, or (*e*) activating transcription factors that antagonize chronic inflammation. Thus, polyphenol-rich grape products may reduce obesity-mediated chronic inflammation by multiple mechanisms, thereby preventing metabolic diseases.

Contents

OBESITY, INFLAMMATION, AND METABOLIC DISEASES

Factors Influencing White Adipose Tissue Growth, Development, and Overexpansion that Lead to Obesity

Obesity is a global health issue, with more than 500 million people classified as obese and 1.5 billion overweight, including 43 million children under the age of five (**http://www.who.int/mediacentre/factsheets/fs311/en/index.html**). In the United States, obesity is rapidly increasing among all age groups. Currently, in all but two states at least 20% of the population is classified as obese (**http://www.cdc.gov/obesity/data/trends.html**). Diets high in calories, especially from sugars, saturated fatty acids (SFAs), and long-chain

omega-6 polyunsaturated fatty acids (PUFAs), and sedentary lifestyles lacking physical activity contribute significantly to this obesity epidemic. Endogenous and exogenous factors that enhance preadipocyte proliferation or adipocyte hypertrophy have the capacity to increase white adipose tissue (WAT) mass and the development of obesity (reviewed in 66, 116).

Metabolic Consequences of Expanding White Adipose Tissue and Its Impact on Liver, Muscle, and Pancreas

The rapid rise in obesity is accompanied by a similar increase in cardiovascular disease (CVD), hypertension, and insulin resistance or type 2 diabetes (**http://www.who.int/mediacentre/factsheets/fs311/en/index.html**). For instance, ~80% of people with type 2 diabetes are overweight or obese (13), suggesting a strong positive relationship between the two diseases (**http://www.cdc.gov/nccdphp/dnpa/obesity/consequences.htm**). Obese patients with type 2 diabetes have elevated levels of tumor necrosis factor alpha (TNFα) in their blood (133), WAT (50), and muscle (97). Furthermore, impaired glucose disposal is positively correlated to TNFα expression (97, 104, 133). Metabolic endotoxemia [e.g., elevated lipopolysaccharide (LPS) level in circulation] is also associated with obesity (14).

This cluster of obesity-related, metabolic diseases is known as the metabolic syndrome. One emerging feature of the metabolic syndrome is its linkage with chronic inflammation in WAT that becomes systemic. It is characterized by engorged adipocyte death (107), increased cytokine/chemokine production and inflammatory signaling, and recruitment of leukocytes (reviewed in 48). Thus, excess WAT is an overactive endocrine organ secreting an array of inflammatory adipokines that contribute to the metabolic syndrome (reviewed in 44). Furthermore, as WAT mass increases, its lipid- and glucose-buffering capacity decreases. This results in elevated blood levels of free fatty acids (FFAs), very-low-density lipoprotein (VLDL) (hyperlipidemia), glucose (hyperglycemia), and insulin (hyperinsulinemia), as well as ectopic lipid accumulation in skeletal and cardiac muscle, liver (steatosis), and pancreas (**Figure 1**). Understanding the mediators of this inflammation and their mechanisms of action is essential in order to develop effective strategies to prevent chronic inflammatory signaling from WAT.

WAT: white adipose tissue

TNF: tumor necrosis factor

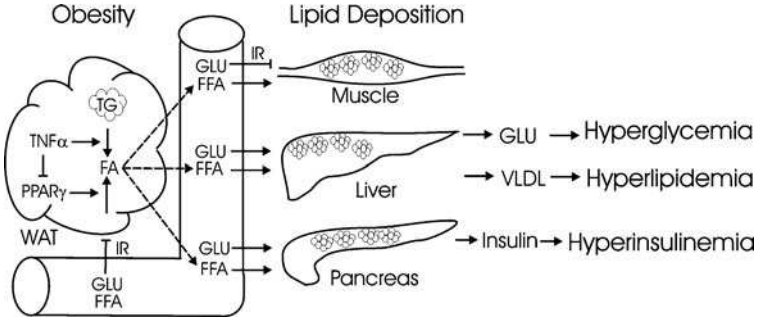

Figure 1

Decreased lipid- and glucose-buffering capacity of adipocytes leads to hyperglycemia, hyperlipidemia, and hyperinsulinemia. Nutrient overload in white adipose tissue (WAT) leads to insulin resistance [IR; i.e., decreased free fatty acids (FFAs) and glucose (GLU) uptake] coupled with increased secretion of FFAs and proinflammatory adipokines such as tumor necrosis factor alpha (TNFα). Elevated FFAs are deposited ectopically in muscle, liver, and pancreas, leading to hyperglycemia, hyperlipidemia, and hyperinsulinemia, respectively. TG, triglyceride; PPARγ, peroxisome proliferator-activated receptor gamma; VLDL, very-low-density lipoprotein.

ROS: reactive oxygen species

MAPKs: mitogen-activated protein kinases

ERK: extracellular signal-related kinase

JNK: c-Jun-NH2-terminal kinase

AP: activating protein

PPAR: peroxisome proliferator-activated receptor

MCP: monocyte chemoattractant protein

MΦ: macrophages

Proinflammatory Role of Free Fatty Acids and Adipokines

Free fatty acids, especially SFAs, contribute significantly to chronic inflammation (reviewed in 58). For example, palmitate activates protein kinase C (PKC) signaling, generates ceramide and reactive oxygen species (ROS), and increases oxidative or endoplasmic reticulum (ER) stress, all of which are associated with chronic inflammation or insulin resistance. Dietary constituents like SFA may also alter gut microflora, leading to elevated blood levels of LPS or TNFα that cause endotoxemia (14).

Tumor necrosis factor alpha, LPS, SFA, or FFA instigate inflammation and insulin resistance by triggering ROS-mediated oxidative or ER stress and serine/threonine kinase phosphorylation signaling that active inflammatory mitogen-activated protein kinases (MAPKs), including extracellular signal-related kinase (ERK) and c-Jun-NH2-terminal kinase (JNK), IκBα kinase (IKK), and transcription factors nuclear factor-kappa B (NF-κB) and activating protein (AP)-1 (reviewed in 45). Collectively, these proteins induce inflammatory gene transcription, antagonize peroxisome proliferator-activated receptor gamma (PPARγ) activity, or directly impair insulin receptor substrate (IRS)-1 signaling, leading to insulin resistance. Furthermore, engorged adipocytes release chemokines such as monocyte chemoattractant protein (MCP)-1 that attract monocytes and stimulate their recruitment and differentiation into macrophages (MΦ) via chemotaxis (reviewed in 77). Monocyte chemoattractant protein-1 has also been reported to convert alternatively activated MΦ (M2) into classically activated MΦ (M1), further increasing inflammation and insulin resistance (**Figure 2**). Such an inflammatory scenario in perivascular WAT can lead to plaque formation and smooth muscle migration and proliferation in the vascular endothelium and wall, thereby increasing the development of CVD (reviewed in 95).

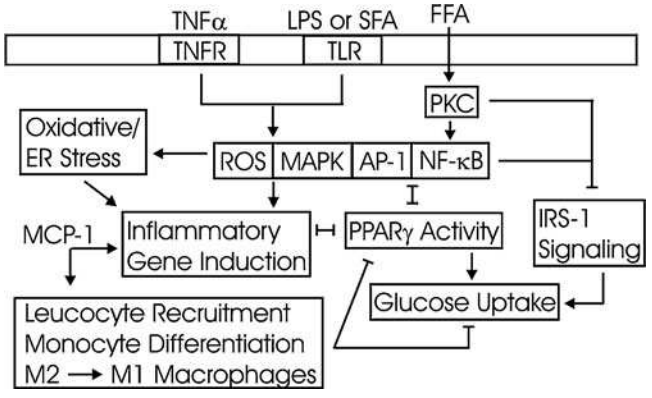

Figure 2

Mechanisms by which tumor necrosis factor alpha (TNFα), lipopolysaccharide (LPS), saturated fatty acids (SFAs), and free fatty acids (FFAs) promote inflammation and insulin resistance. Elevated levels of TNFα, LPS, SFA, or FFA activate their cognate cell surface receptors or diffuse into the cell, thereby activating protein kinases such as protein kinase C (PKC) and mitogen-activated protein kinases (MAPKs) or enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase that produce reactive oxygen species (ROS), thereby triggering oxidative or endoplasmic reticulum (ER) stress signals or activating inflammatory transcription factors such as nuclear factor-kappa B (NF-κB) and activating protein (AP)-1. Together, these inflammatory signals induce inflammatory gene expression, enhance leukocyte recruitment and differentiation including activating monocytes into classically activated M1-macrophages (MΦ), antagonize peroxisome proliferator-activated receptor gamma (PPARγ) activity, and impair insulin receptor substrate (IRS)-1 signaling, leading to insulin resistance. MCP-1, monocyte chemoattractant protein-1; TLR, toll-like receptor; TNFR, TNFα receptor.

Thus, a positive energy balance expands WAT, generating adipokines such as TNFα and MCP-1 as well as FFA that recruit and activate MΦ and activate inflammatory cascades. These responses antagonize PPARγ activity, leading to decreased glucose and FA uptake and metabolism, causing ectopic lipid accumulation (lipodystrophy), hyperglycemia, and hyperlipidemia. Proposed mechanisms by which these inflammatory signals reduce PPARγ activity include (*a*) decreased PPARγ mRNA levels, (*b*) increased phosphorylation of serine residue 112 of PPARγ by ERK, leading to PPARγ ubiquination and proteosome degradation, (*c*) decreased PPARγ DNA binding, and (*d*) decreased PPARγ transcriptional activity (**Figure 3**) (reviewed in 129). Discovery of dietary strategies, including the consumption of polyphenol-rich grapes or grape products, to reduce obesity-related chronic inflammation could potentially attenuate metabolic diseases.

TYPES AND ABUNDANCE OF PHENOLIC PHYTOCHEMICALS IN GRAPES

Types of Phenolic Phytochemicals in Grapes and Grape Products

Grapes and their by-products are consumed worldwide. There are more than 50 varieties of seeded and seedless grapes in black, blue, blue-black, golden, red, green, purple, and white colors. Common grape products include table grapes, wine, raisins, juices, and preservatives. The average annual consumption of fresh grapes in the United States is about eight pounds per person (**http://www.ers.usda.gov/Data/FoodConsumption/**). Most of the grapes consumed in the United States are grown in California. Table grapes contain essential nutrients such as water, carbohydrates, proteins, fats, vitamins, minerals, and fiber (reviewed in 127) and nonessential compounds including phytochemicals. Phenolic phytochemicals in grapes (**Table 1**) possess biological activities that have been reported to promote health (reviewed in 125). Some of the early health benefits of consuming red wine (e.g., decreased the risk of CVD), referred to as the "French Paradox" (92, 103), have been attributed to its phenolic phytochemicals including resveratrol. Ironically, the resveratrol content of grapes and red wine is relatively low compared to other polyphenols (**Table 1**).

The predominant phenolic phytochemicals in grapes are flavonoids such as flavonols, flavan-3-ols (monomers, oligomers, or polymers), and anthocyanidins/anthocyanins, and to a much lesser extent nonflavonoids such as stilbenes, phenolic acids/hydroxybenzoates, and hydroxycinnamates (**Tables 1** and **2**; 15, 17, 18, 29, 30, 41, 43, 56, 71, 78, 84, 85, 88, 90). Quercetin is the major flavonol in grapes (**Figure 4*A***) and usually occurs as *O*-glucosides in the D-glucose isoform such as quercetin 3-*O*-glucoside (**Figure 4*B***). Grape flavan-3-ols are mainly represented by monomeric catechins such as (+)-catechin (**Figure 4*C***) and oligomeric procyanidins, also known as proanthocyanidins or condensed tannins, such as procyanidin B2 (**Figure 4*D***). Anthocyanins (i.e., anthocyanidins with sugar groups) in grapes are primarily 3-*O*-glucosides such as malvidin (**Figure 4*E***) and malvidin 3-*O*-glucoside (**Figure 4*F***), which are found in red grapes. *Trans*-resveratrol (**Figure 4*G***) is probably the most well-known and studied stilbene found in grapes and red wine. Phenolic acids, also known as hydroxybenzoates, are commonly represented by gallic acid (**Figure 4*H***) in grapes. In grapes or grape products, hydroxycinnamates usually undergo esterification with tartaric acid such as caffeic acids (**Figure 4*I***) and its tartaric acid esters such as caftaric acid (**Figure 4*J***).

The phenolic phytochemical content of grapes varies due to grape type, color, and ripeness, and climatic, geographical, and cultural factors. In general, flavonols and anthocyanidins/anthocyanins represent colored

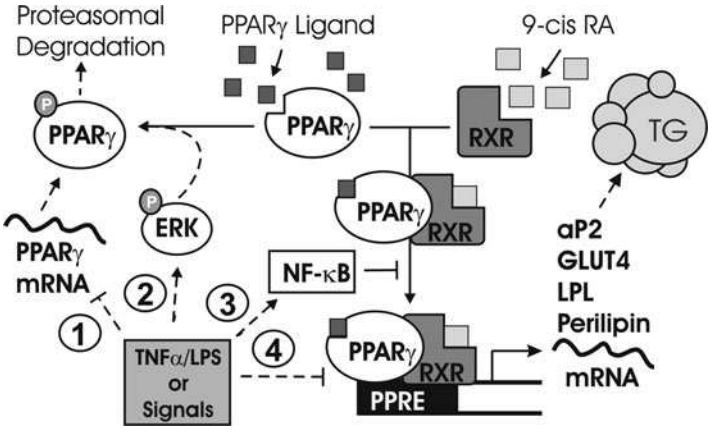

Figure 3

Mechanisms by which tumor necrosis factor alpha (TNFα) or lipopolysaccharide (LPS) antagonizes peroxisome proliferator-activated receptor gamma (PPARγ) activity. Tumor necrosis factor α and LPS or their signals antagonize PPARγ activity by (*a*) decreasing PPARγ mRNA levels, (*b*) phosphorylation (P) of PPARγ on serine 112 by extracellular signal-related kinase (ERK), leading to PPARγ ubiquination and proteosomal degradation, (*c*) activating nuclear factor-kappa B (NF-κB), which antagonizes PPARγ activity and its DNA binding capacity, or (*d*) activating nuclear corepressors, which decrease PPARγ transcriptional activity and target gene expression. Collectively, this leads to insulin resistance in white adipose tissue, thereby elevating circulating free fatty acids (lipodystrophy) and glucose (hyperglycemia) that promote ectopic lipid deposition in liver, skeletal muscle, heart, and pancreas. 9-cis RA, 9-cis retinoic acid; aP2, adipocyte fatty acid–binding protein; GLUT4, insulin-dependent glucose transporter 4; LPL, lipoprotein lipase; PPRE, peroxisome proliferator response element; RXR, retinoid X receptor, TG, triglyceride.

Table 1 The content of polyphenols analyzed in freeze-dried table grape powder (GP)[a]

Polyphenols	Compounds	Content (mg/kg GP)
Anthocyanins	Malvidin	145.2
	Cyanidin	125.0
	Peonidin	31.7
Flavonols	Quercetin	32.6
	Isorhamnetin	6.8
	Kaempferol	5.6
Flavan-3-ols	Catechin	19.7
	Epicatechin	12.6
Stilbenes	Resveratrol	1.75

[a]Data are from California Table Grape Commission Information Sheet (2005), **http://agbioresearch.msu.edu/rfp/ca_grape2009.pdf**.

phenols and flavan-3-ols, phenolic acids/hydroxybenzoates, and hydroxycinnamates represent noncolored phenols in grapes or grape products (**Table 2**). These polyphenols are present mainly in skins and seeds and contribute to the astringency, bitterness, and color of the grapes and wine. Polyphenols also impact the quality of the wine produced and potential health benefits associated with wine consumption.

Relatively High Abundance of Anthocyanidins/Anthocyanins and Flavonols in Grapes

Grapes are particularly rich in anthocyanidins/anthocyanins (e.g., malvidin, cyanidin, and peonidin) and to a lesser extent flavonols (e.g., quercetin) (**Tables 1** and **2**). The average of daily anthocyanidin/anthocyanin and flavonol intake from all foods in the United States is approximately 12.5 mg (124) and 20.0 mg (68, 99) per person, respectively. Average adult plasma levels of flavonols such as quercetin and isorhamnetin, a metabolite of quercetin, are approximately 53.9 nM and 3.0 nM, respectively (34). However, anthocyanidins/anthocyanins such as malvidin 3-*O*-glucoside were undetectable in the plasma of adult subjects (12, 40). Also, variation in plasma levels of polyphenols or their metabolites between individuals is high at baseline and after intervention (34, 75).

The bioavailability of these anthocyanidins/anthocyanins and flavonols has been reported to be poor based on in vitro (11, 30, 37, 130) and in vivo studies (reviewed in 32, 96). However, phenolic phytochemicals may be rapidly metabolized by cells and therefore difficult to detect within the circulation or cells following consumption or supplementation (105). Also, despite having relatively low abundance and poor bioavailability, some polyphenols have potent biological actions (i.e., resveratrol; 5, 6, 62). Because of the relative high abundance and biological activity of grape anthocyanidins/anthocyanins and flavonols, the following sections focus on potential mechanisms by which they reduce chronic inflammation associated with obesity and related metabolic diseases.

MECHANISMS BY WHICH ANTHOCYANIDINS/ANTHOCYANINS AND FLAVONOLS, MAJOR PHENOLIC PHYTOCHEMICALS IN GRAPES, REDUCE CHRONIC INFLAMMATION

Acting as an Antioxidant or Increasing Antioxidant Gene or Protein Expression

Reactive oxygen species and reactive nitrogen species (RNS) can be generated by enzyme systems such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase (NOS), respectively, or transition metals, and are notorious mediators of oxidative stress and inflammation. Reactive oxygen species trigger redox-sensitive kinases such as apoptosis signal-regulating kinase 1 (ASK1) that activate downstream MAPKs, NF-κB, and AP-1, which in turn induce inflammatory gene expression. Phenolic phytochemicals have a strong antioxidant potential owing to the abundance of hydroxyl groups associated with their aromatic rings. Phenolic phytochemicals also have the capacity to increase the levels of anti-inflammatory

Table 2 Phenolic phytochemicals found in grapes and grape products

Resource	Phenolic phytochemicals	References
Whole grapes	Flavonol glycosides (quercetin, kaempferol, myricetin, laricitrin, isorhamnetin, syringetin), anthocyanins[a] (malvidin, peonidin, petunidin, cyanidin, delphinidin, pelargonidin), flavan-3-ols (catechin, epicatechin), phenolic acids (protocatechuic acid, gallic acid), hydroxycinnammates (caftaric acid, coutaric acid, fertaric acid), stilbenes (*trans*-resveratrol)	(15, 17, 78)
Grape seed	Flavan-3-ols (catechin, catechin gallate, epicatechin, epicatechin gallate, procyanidin gallate, B1, B2, other dimers, trimers, and tetramers)	(18, 84)
Grape skin	Flavonol glycosides (quercetin, kaempferol, myricetin, laricitrin, isorhamnetin, syringetin), anthocyanins[a] (malvidin, peonidin, petunidin, cyanidin, delphinidin, pelargonidin), flavan-3-ols (catechin, epicatechin, gallocatechin, procyanidin B1, B2, B4, other dimers, C1, other trimers, and tetramers), phenolic acids (protocatechuic acid, gallic acid), hydroxycinnammates (caftaric acid, coutaric acid, fertaric acid), stilbenes (*trans*-resveratrol, *cis*-resveratrol, resveratrol dimmers and tetramers), flavanonol glycosides (taxifolin)	(15, 17, 18, 84)
Grape stem	Flavonols (quercetin glucoside), flavan-3-ols (catechin, catechin gallate, epicatechin, procyanidin B1 and B2), hydroxycinnammates (caffeic acid, coumaric acid), stilbenes (*trans*-resveratrol, *trans*-resveratrol glucoside, resveratrol dimers, trimers, and tetramers), flavanonols (taxifolin glucoside)	(71, 90)
Grape leaf	Flavonols (quercetin, rutin, kaempferol, myricetin), flavan-3-ols (catechin), phenolic acids (gallic acid, ellagic acid), stilbenes (resveratrol), flavanones (naringin)	(29, 84)
Red grape juice	Flavonols (quercetin glucoside, rutin, myricetin), anthocyanins[a] (malvidin, peonidin, petunidin, cyanidin, delphinidin), flavan-3-ols (catechin, procyanidin B2)	(30)
Red wine	Flavonol glycosides (quercetin, kaempferol, myricetin, isorhamnetin), anthocyanins[a] (malvidin, peonidin, petunidin, cyanidin, delphinidin), flavan-3-ols (catechin, catechin gallate, epicatechin, epicatechin gallate, procyanidin B1, B2, B4, and trimers), phenolic acids (protocatechuic acid, gallic acid, ellagic acid, vanillic acid, syringic acid), hydroxycinnammates (caffeic acid, caftaric acid, coutaric acid, ferulic acid, fertaric acid, coumaric acid, sinapic acid), stilbenes (*trans*-resveratrol, *trans*-resveratrol glucoside)	(41, 43, 85, 88)
Raisin	Flavonol glycosides (quercetin, kaempferol), phenolic acids (protocatechuic acid), hydroxycinnammates (caftaric acid, coutaric acid)	(56)

[a]Anthocyanidins/anthocyanins are detected only in red grapes.

genes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and heme oxygenase (HO)-1 via activation of the transcription factor nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2) (reviewed in 91). Thus, polyphenols have an inherent capacity to reduce ROS and other free radicals, thereby preventing their activation of oxidative stress and inflammation. Consistent with this antioxidant potential, Sprague-Dawley rats consuming a high-fructose diet supplemented with a grape skin extract (21 mg/kg body weight for six weeks) were protected against ROS production, possibly due to reduced levels of NADPH oxidase, thereby preventing cardiac hypertrophy and hypertension induced by a high-fructose diet (2).

In vitro, pretreatment with freeze-dried grape powder (300 μg/ml) restored glutathione (GSH) content in human hepatoma cells (Huh7 cells) and primary mouse hepatocytes treated with hydrogen peroxide (H_2O_2) (126). The flavonols quercetin and kaempferol (5–50 μM) decreased the levels of oxidized GSH, peroxides, superoxide anions, and nitric oxide in parenchymal liver cells (Chang liver cells) treated with a mixture of inflammatory cytokines (28). Quercetin pretreatment (25 μM) of primary cultures of rat neurons exposed to H_2O_2 increased GSH levels, the nuclear translocation of Nrf2, and the expression of γ-glutamate-cysteine ligase catalytic subunit (GCLC), the rate-limiting enzyme for GSH synthesis, compared with those treated with

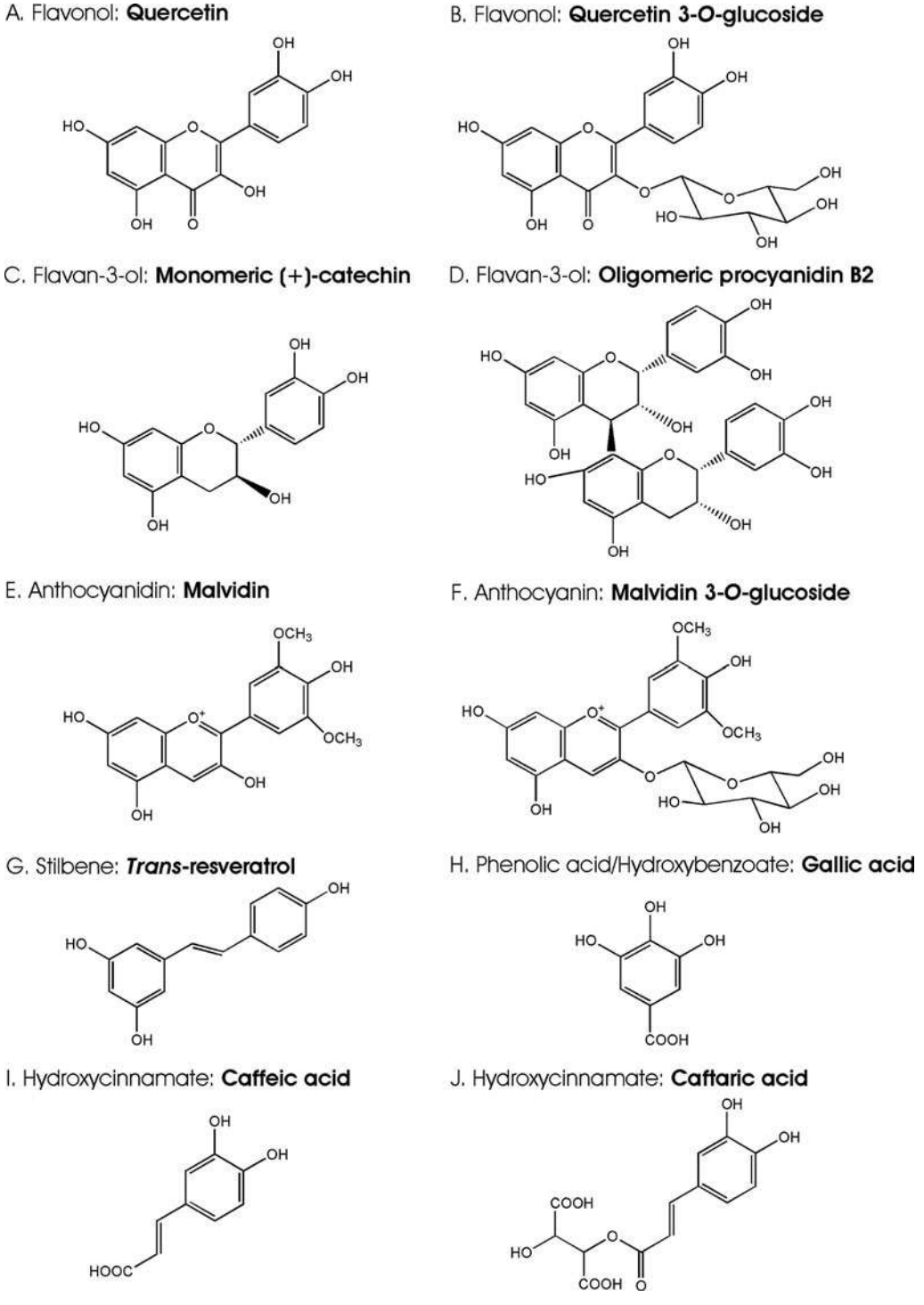

Figure 4

Structures of polyphenols commonly found in grape products.

H_2O_2 only (3). However, cells treated with doses of quercetin higher than 25 μM for 24 hours showed signs of cytotoxicity.

Quercetin and isorhamnetin (10 μM) pretreatment of murine macrophages (RAW264.7 cells) treated with LPS decreased the expression of inflammatory genes and inducible NOS and increased the protein levels of HO-1 (10). However, cells treated with doses of these flavonols equal to or greater than 25 μM for 24 hours showed signs of cytotoxicity. Quercetin pretreatment (10–50 μM) of immortalized human keratinocytes (HaCaT cells) treated with H_2O_2 increased mitochondrial membrane potential and cell viability and reduced the percentage of apoptotic cells compared with controls (122). Quercetin pretreatment (10 and 100 μM) of human hepatoma cells treated with H_2O_2 or $CuSO_4$ (to initiate the Fenton reaction for the production of hydroxyl radicals) acutely decreased ROS production (60). However, long-term treatment with high levels of quercetin (100 μM) decreased cell viability, suggesting pro-oxidant actions of quercetin at high levels. Pretreatment with the anthocyanin cyanidin 3-glucoside (10–40 μM) of murine adipocytes (3T3-L1 cells) exposed to H_2O_2 or TNFα decreased ROS production and insulin resistance compared with controls (46). Quercetin and rutin (1–25 μM), a quercetin metabolite, blocked oxidized low-density lipoprotein (LDL)-mediated apoptosis of human umbilical vein endothelial cells via modulation of Janus kinase/signal transducers and activators of the transcription signaling pathway (23). Rutin, but not quercetin, inhibited JNK and p38 signaling by decreasing the activation of ASK1, a redox-sensitive kinase that triggers inflammatory MAPK signaling.

Collectively, these data suggest that grape polyphenols or their metabolites have the capacity to protect cells against oxidative damage by (*a*) neutralizing ROS and RNS or transition metals that produce ROS, RNS, and oxidize GSH, (*b*) decreasing the activity of enzymes such as NAPDH oxidase and NOS that produce ROS and RNS, respectively, (*c*) suppressing inflammatory signaling cascades including ASK1 and downstream MAPK, and (*d*) activating transcription factors such as Nrf2 that induce the transcription of antioxidant enzymes such as GPx, SOD, HO-1, and GCLC (**Figure 5**). However, high levels of these polyphenols may be cytotoxic.

Attenuating Endoplasmic Reticulum Stress Signaling

The development of obesity and the metabolic syndrome has been linked to ER stress and inflammation (reviewed in 49). Endoplasmic reticulum stress activates the unfolded protein response (UPR), which involves activation of three ER membrane–associated proteins: (*a*) double-stranded RNA-activated protein kinase (PKR)-like eukaryotic initiation factor 2α (eIF2α) kinase (PERK), (*b*) inositol-requiring enzyme 1 (IRE1), and (*c*) activating transcription factor 6 (ATF6). Studies on flavonols suggest that kaempferol (10 μM) or quercetin (25–150 μM) attenuate ER stress in a rat cardiac muscle cell line (H9c2 cells) and isolated rat hearts (59) or in human colon cancer cell lines (Caco-2 and LS180 cells) (76), respectively, by blocking PERK-mediated eIF2α phosphorylation, IRE1-mediated X-box-binding protein 1 activation, and ATF6 expression (**Figure 5**). In contrast, freeze-dried grape powder (300 μg/ml) did not prevent ER stress-mediated apoptosis of human hepatoma cell line (Huh7 cell) and primary mouse hepatocytes (126). Research investigating the inhibitory effects of anthocyanidins/anthocyanins on ER stress is lacking, and the preventive effects of grape anthocyanidins/anthocyanins and flavonols on ER stress and chronic inflammation are unknown.

Blocking Pro-Inflammatory Cytokines or Endotoxin-Mediated Kinases and Transcription Factors Involved in Metabolic Diseases

Anthocyanins and flavonols modulate inflammation and insulin resistance associated with obesity. For example, Zucker fatty rats

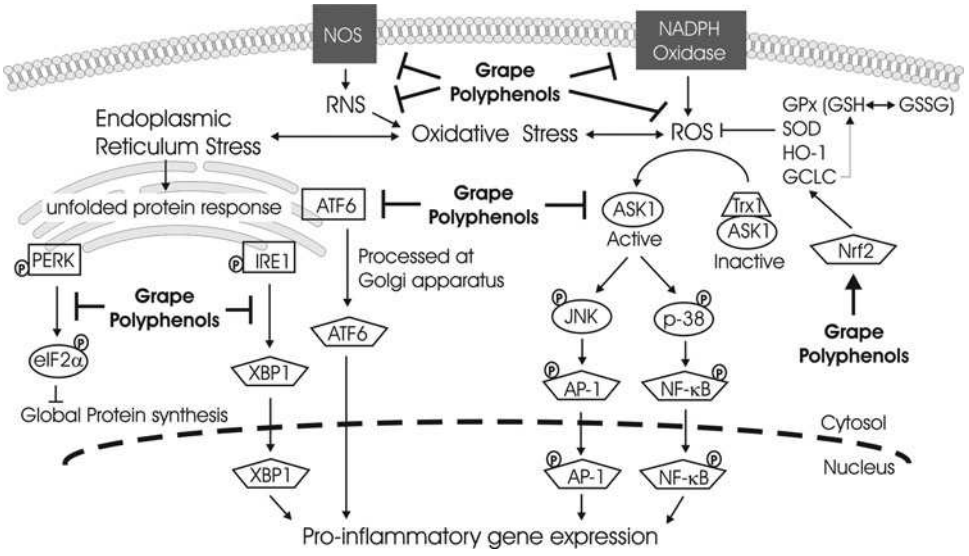

Figure 5

Potential mechanisms by which grape polyphenols prevent chronic inflammation associated with obesity. Grape polyphenols may attenuate oxidative or endoplasmic reticulum (ER) stress-mediated inflammation associated with obesity by (*a*) inhibiting the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase or nitric oxide synthase (NOS) that generate reactive oxygen species (ROS) or reactive nitrogen species (RNS), respectively, (*b*) acting as a classic antioxidant by directly scavenging ROS and RNS, (*c*) preventing ROS-mediated activation of apoptosis signal-regulated kinase 1 (ASK1), a redox-sensitive, inflammatory signaling pathway, (*d*) increasing the expression of antioxidant genes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), heme oxygenase (HO)-1, and γ-glutamate-cysteine ligase catalytic subunit (GCLC) via activation of transcription factor nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), or (*e*) blocking ER stress-mediated unfolded protein response including double-stranded RNA-activated protein kinase (PKR)-like eukaryotic initiation factor 2α (eIF2α) kinase (PERK)-mediated eIF2α, inositol requiring enzyme 1 (IRE1)-mediated X-box binding protein 1 (XBP1), and activating transcription factor 6 (ATF6) signaling pathways that trigger proinflammatory gene expression. AP-1, activating protein-1; GSH, reduced glutathione; GSSG, oxidized glutathione; JNK, c-Jun-NH2 terminal kinase; NF-κB, nuclear factor-kappa B; P, phosphorylated; Trx1, thioredoxin-1.

fed a high-fat diet supplemented with an anthocyanin-rich, 1% tart cherry powder (w/w) for 12 weeks had lower WAT and plasma levels of TNFα and interleukin (IL)-6 and WAT NF-κB activity compared with controls (101). Dahl salt-sensitive, hypertensive rats supplemented with 3% grape powder in the diet (w/w) for 18 weeks had lower plasma levels of TNFα and IL-6, decreased cardiac tissue oxidative damage (102), and reduced expression of inflammatory genes and NF-κB DNA binding activity in cardiac tissue (100) compared with high-sugar controls (3% fructose:glucose; 1:1). C57BL/6J mice fed a high-fat diet supplemented for eight weeks with an anthocyanin-rich, 4% blueberry powder (w/w) had lower indices of inflammation (e.g., decreased gene expression of markers of WAT MΦ and inflammation) and oxidative stress and greater insulin sensitivity compared with control mice (33). C57BL/6J mice fed a high-fat diet supplemented with 0.8% quercetin in the diet (w/w) for eight weeks had lower plasma levels of interferon γ, IL-1α, and IL-4 compared with controls (106). Finally, Zucker fatty rats receiving a daily dose of quercetin (2 or 10 mg/kg body weight, o.p.) for 10 weeks had lower inflammatory markers, improved insulin sensitivity and blood lipid profiles, and decreased blood pressure compared with placebo controls (94).

IL: interleukin

In vitro, cyanidin 3-glucoside (10–40 μM) prevented TNFα-mediated JNK activation, IRS-1 phosphorylation at serine residue 307, and insulin resistance in 3T3-L1 adipocytes (46). Notably, grape seed flavan-3-ols/procyanidins (50 and 100 mg/liter) modulated LPS- and TNFα-induced inflammatory signal and gene expression in human MΦ (differentiated THP-1 monocytes) and Simpson-Golabi-Behmel Syndrome adipocytes, respectively (19). Moreover, oligomerized grape seed polyphenols (10 and 20 μg/ml) attenuated activation of inflammatory signaling and production of inflammatory cytokines in a murine cell line of adipocytes (HW mouse white adipocytes) cocultured with a murine MΦ cell line (RAW264 cells) (98).

Consistent with these data, our lab demonstrated that grape powder extract (GPE; 30–100 μg/ml), made from grape powder provided by the California Table Grape Commission, attenuated inflammatory gene expression (i.e., IL-6, IL-1β, IL-8, and MCP-1) in primary human adipocytes induced by conditioned media collected from LPS-treated MΦ (differentiated U937 monocytes) (81). Furthermore, quercetin (3–30 μM), the most abundant polyphenol in GPE (81), prevented inflammation in human MΦ and primary human adipocytes treated with MΦ conditioned media (82). We showed that pretreatment of human MΦ with quercetin (3–30 μM) prevented MΦ-mediated insulin resistance in primary human adipocytes (82). We also demonstrated that GPE (10–60 μg/ml) and quercetin (3–60 μM) attenuated TNFα-mediated inflammation and insulin resistance in primary human adipocytes by blocking activation of ERK, JNK, NF-κB, and AP-1 signaling and negative regulators of insulin signaling (e.g., protein tyrosine phosphatase (PTP)-1B and phosphorylation of serine residue 307 on IRS) (25, 26). Furthermore, the quercetin content of the cells increased within one hour of treatment with 30 μM quercetin, suggesting that quercetin is rapidly taken up by human adipocytes (26). No signs of cytotoxicity were observed for these doses of GPE or quercetin.

Quercetin (1–5 μM) suppressed carcinogen-mediated inflammation by directly binding to MEK, which prevents activation of inflammatory MEK/MAPK signaling in JB6 P+ cells, a JB6 promotion-sensitive mouse skin epidermal cell line (65). Moreover, kaempferol (1 and 3 μM) inhibited TNFα-mediated inflammation by directly blocking nuclear translocation and DNA binding of NF-κB and AP-1 in A549 cells, an alveolar epithelial cell carcinoma cell line (21). Taken together, these data suggest that grape polyphenols, especially anthocyanins and flavonols, inhibit proinflammatory cytokine- and metabolic endotoxin-triggered activation of inflammatory MEK/MAPK, NF-κB, and AP-1 signaling, which increase inflammatory gene expression (e.g., TNFα, IL-6, IL-8, IL-1β, and MCP-1) and negative regulators of insulin signaling (**Figure 6**). Therefore, grape polyphenols may be useful in preventing inflammatory-mediated insulin resistance and other related metabolic diseases.

Suppressing Inflammatory- or Inducing Metabolic-Gene Expression via Increasing Histone Deacetylase Activity

Sirtuins (SIRT), class III histone deacetylases, are nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases. Sirtuins deacetylate not only histones, but also nonhistone proteins including transcription factors by transferring an acetyl group from the targeted protein to NAD^+, generating deacetylated histones or nonhistone proteins, nicotinamide, and *O*-acetyl-ADP-ribose. This NAD^+ dependency contributes to the role that SIRT play in the regulation of chromatin structure and gene expression, cell survival, and energy homeostasis. In a SIRT1 in vitro screening assay (51), several polyphenols such as *trans*-resveratrol and quercetin (100 μM) were shown to activate SIRT1.

In vitro (0.01–10 μM) and in vivo (2.5–400 mg/kg body weight/day) studies have reported that resveratrol activated SIRT1, thereby (*a*) decreasing inflammatory gene

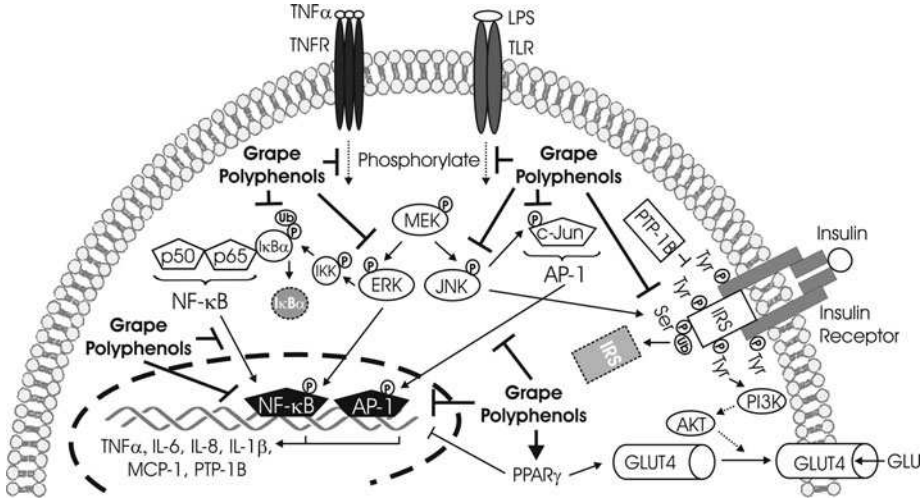

Figure 6

Grape polyphenols may prevent inflammation and insulin resistance associated with obesity by blocking activation of mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF-κB), and activating protein (AP)-1. Grape polyphenols may prevent inflammatory tumor necrosis factor alpha (TNFα)/TNF receptor (TNFR) or lipopolysaccharide (LPS)/toll-like receptor (TLR) signaling to MAPK kinases (MEK) and their downstream, extracellular signal-related kinase (ERK) and c-Jun-NH2 terminal kinase (JNK). This would attenuate the activation of inflammatory transcription factors NF-κB and AP-1, which are potent inducers of inflammatory gene expression [e.g., TNFα, interleukin (IL)-6, IL-8, IL-1β, and monocyte chemoattractant protein (MCP)-1] and negative regulators of insulin signaling [e.g., phosphorylation of serine residue 307 on insulin receptor substrate (IRS) and protein tyrosine phosphatase (PTP)-1B], and which suppress insulin signaling necessary for insulin-dependent glucose transporter 4 (GLUT4) translocation to the plasma membrane. AKT, AKT/protein kinase B; GLU, glucose; IKK, IκBα kinase; PI3 K, phosphatidylinositol 3-kinases; P, phosphorylated; PPAR, peroxisome proliferator-activated receptor; Ser, serine; Tyr, tyrosine; Ub, ubiquinated degradation.

expression by deacetylation/inactivation of NF-κB (39, 79, 128, 132) and (*b*) improving insulin sensitivity by deacetylation/activation of PPARγ coactivator-1 alpha (PGC-1α) (62, 111), a regulator of PPAR activity (reviewed in 20). Activation of PPARα or PPARβ/δ by PGC-1α also enhances energy expenditure (reviewed in 38, 110). Consistent with these data, quercetin supplementation (12.5 and 25 mg/kg body weight/day) for seven days increased SIRT1 and PGC-1α expression and mitochondrial biogenesis in male ICR mice (31). These findings suggest that resveratrol and quercetin prevent inflammation by activating SIRT1, which deacetylates NF-κB (inactive form) and PGC-1α (active form), thereby suppressing inflammatory- and inducing metabolic-gene expression, mitochondrial biogenesis, and oxidative phosphorylation via activation of PPAR (**Figure 7**). However, more research is needed on the regulation of SIRT1 by grape polyphenols to determine which specific anthocyanidins and flavonols are involved.

Activating Transcription Factors that Antagonize Chronic Inflammation

The PPARs (i.e., PPARα, PPARβ/δ, and PPARγ) are ligand-dependent, nuclear transcription factors that regulate energy homeostasis, glucose and lipid metabolism, and immune response (reviewed in 7). Activation of PPARs has been reported to suppress inflammatory gene expression by directly interfering with transcriptional activation of NF-κB or AP-1 (reviewed in 93). For example, upon

activation by ligand binding, PPARγ can be SUMOylated by binding to SUMO1, a small ubiquitin-like modifier. The SUMOylated PPARγ subsequently binds to nuclear receptor corepressors, which interferes with clearance of the corepressor complex of NF-κB, thereby transrepressing LPS-mediated NF-κB activation (83).

Several studies reported that anthocyanin-rich cherries or berries increase the level of PPARγ gene, protein, or activity. For example, the supplementation with 1% tart cherry in the diet (w/w) for 12 weeks or 3% grape powder in the diet (w/w) for 18 weeks suppressed inflammation and improved metabolic diseases by increasing PPARγ gene expression in Zucker fatty rats (101) or by increasing PPARα/γ mRNA levels and protein activity in Dahl salt-sensitive, hypertensive rats (100), respectively. Consistent with these data, our lab (26) and others (36) showed that by increasing PPARγ activation, quercetin or kaempferol (3–60 μM) attenuated inflammation or insulin resistance in adipocytes. These findings suggest that grape polyphenols increase the expression or activation of PPARs that antagonize inflammatory transcription factors, thereby blocking inflammation and the development of metabolic diseases (**Figures 6** and **7**).

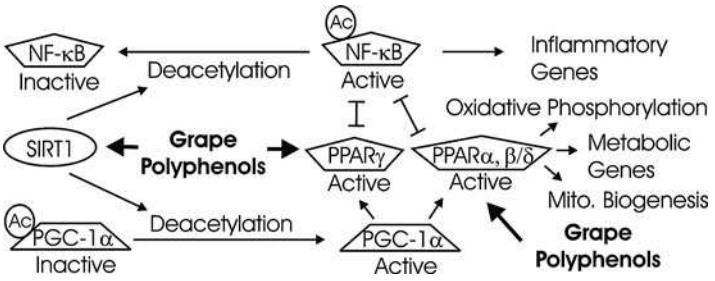

Figure 7

Grape polyphenols may activate sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor (PPAR) that antagonize inflammation and improve the metabolic diseases associated with obesity. Grape polyphenols may prevent inflammation and improve metabolic diseases associated with obesity by activating SIRT1. SIRT1 has been reported to (*a*) deacetylate/inactivate nuclear factor-kappa B (NF-κB), resulting in the suppression of inflammatory gene expression, and (*b*) deacetylate/activate PPARγ coactivator-1 alpha (PGC-1α), resulting in the activation of PPARs. Activation of PPARα and PPARβ/δ increases oxidative phosphorylation, metabolic gene expression, and mitochondrial (Mito) biogenesis. Activation of PPARγ may antagonize NF-κB transcriptional activation of inflammatory genes, thereby attenuating inflammation associated with obesity.

CONCLUSIONS AND IMPLICATIONS

Potential Health Benefits of Consuming Grapes or Grape Products

Cardiovascular disease. Inflammatory mediators released from excess WAT cause endothelial dysfunction, plaque initiation and progression, and plaque rupture, leading to CVD (reviewed in 63). Supplementation with quercetin (64 mg/kg body weight/day for 10 and 20 weeks) attenuated inflammation and endothelial dysfunction in a mouse model of atherosclerosis (ApoE-/- knockout mice) (69). Randomized, clinical trials with proanthocyanidin-rich cocoa powder (40 g cocoa powder in 500 ml skim milk/day for four weeks) (73) and anthocyanin- and flavonol-rich bilberry juice (330 ml/day for four weeks) (57) showed decreased plasma markers of inflammation in adults with high CVD risk who consumed these polyphenol-rich products.

Consumption of red grape juice (50 ml concentrate twice per day for two weeks) reduced serum markers of inflammation and oxidative stress/oxidized-LDL and improved dyslipidemia in hemodialysis patients (16). Consumption of raisins (one cup per day for six weeks) reduced systolic blood pressure and inflammatory cytokines and improved lipid profiles in men and postmenopausal women (89). Furthermore, consumption of grape seed flavan-3-ols procyanidins (0.32 mg/g diet/day for 19 weeks) attenuated inflammatory markers in liver, WAT, and circulation in high-fat-fed, obese male Zucker fatty rats (114). Also, consumption of whole table grape powder (3% in the diet, w/w, for 18 weeks) attenuated systolic blood pressure, cardiac hypertrophy, and diastolic dysfunction in Dahl salt-sensitive hypertensive rats (102). Finally, Pérez-Jiménez & Saura-Calixto (86) reviewed 75 trials including human and animal studies that investigated the relationship between consumption of grapes or

grape products and their effects on lowering risk factors for CVD including (*a*) inflammation, (*b*) oxidative stress/LDL oxidation, (*c*) endothelial dysfunction, (*d*) platelet aggregation, (*e*) dyslipidemia, and (*f*) hypertension. They concluded from these studies that grapes and grape products have antihypertensive, antihyperlipidemic, antiatherosclerotic, and antioxidant effects. Therefore, supplementation with grapes or grape products rich in polyphenols may be a useful dietary strategy for the attenuation of CVD associated with obesity and inflammation.

Insulin resistance or diabetes. Obesity-associated, low-grade inflammation causes insulin resistance (**Figures 1** and **2**). Insulin resistance is a prediabetic state characterized by decreased tissue sensitivity to insulin and hyperinsulinemia. These chronic perturbations in glucose disposal lead to the development of noninsulin-dependent diabetes (type 2) and eventually pancreatic beta cell failure, resulting in insulin-dependent diabetes (type 1) (reviewed in 108). Elevated inflammatory TNFα, LPS, SFA, or FFA contribute to obesity-associated insulin resistance as shown in **Figure 2**.

Grape polyphenols such as flavan-3-ols/procyanidins or stilbenes/resveratrol improved glucose intolerance in type 1 diabetic rat models (1, 22, 35, 87, 109). Resveratrol (0.04% in the diet w/w for 12–48 weeks, or 2.5–400 mg/kg body weight/day for 15–16 weeks) improved glucose and lipid homeostasis in high-fat-fed C57BL/6J obese mice (6, 62, 111). Consumption of 150 ml of muscadine grape wine or dealcoholized grape wine per day for 28 days improved fasting blood glucose and insulin levels in subjects with type 2 diabetes (4). Overall, results suggest that grapes or grape products are good candidates for dietetic management of type 2 diabetes because of their abundant polyphenol content and low glycemic index (134). However, clinical studies investigating the effect of grape consumption on insulin resistance or type 2 diabetes are limited.

Cancer. Obesity-associated inflammation contributes to cancer initiation or progression (reviewed in 27, 52, 80). García-Lafuente et al. (42) summarized the potential anti-inflammatory mechanisms of flavonoids found in fruits and vegetables that are linked to the prevention or treatment of cancer. For example, resveratrol prevents certain cancers due to its ability to inactivate inflammatory signaling, including protein kinases such as MEK/MAPK and transcription factors such as NF-κB and AP-1, and to modulate carcinogenic signaling by down-regulation of cyclooxygenase (COX)-2 and iNOS (47, 54, 72, 113; reviewed in 8, 112, 117).

Interestingly, the anticarcinogenic effects of red wine extract may be due to not only resveratrol but to flavonols as well (65). For example, flavonol/quercetin (9, 24, 64, 67, 123) and anthocyanidin/delphinidin (53, 61, 120, 131) exert anti-inflammatory and anticancer activity. However, most studies used pharmacological doses of these polyphenols. Future studies are needed to investigate the relationship between physiologically relevant doses of polyphenols from grapes and grape products and their ability to prevent or treat certain types of cancer.

Neurodegenerative diseases linked to obesity. Grapes and grape products have been reported to have antiaging and antineurodegenerative effects due to their antioxidant properties (reviewed in 55). Moreover, rats fed 6.5 ml/kg body weight per day white or red wine or 2.5 mg/kg body weight per day resveratrol for two weeks had higher expression levels of genes and proteins related to longevity (74). Consumption of red wine containing 0.2 mg/liter of resveratrol for seven months attenuated the development of Alzheimer's disease (AD) in Tg2576 AD transgenic mice due to reduced aggregation of brain amyloid beta-protein (119). Grape powder or extract also has been reported to modulate the pathogenesis of neurodegenerative disease (70, 115, 118, 121). However, the extent to which polyphenols in grapes other than resveratrol extend lifespan

or prevent neurodegenerative diseases is unknown, as are their mechanisms of action.

Potential Risks of Excess Consumption of Grapes or Grape Products

Overconsumption of grapes or grape products could lead to (*a*) excess weight gain due to the high sugar content of grapes, (*b*) immunosuppression due to the anti-inflammatory actions of polyphenols, (*c*) impairment of micronutrient absorption or metabolism, and (*d*) alcohol toxicity associated with excess wine consumption. Of these four, the deleterious effects of excess alcohol consumption (e.g., gastrointestinal cancers, cirrhosis, pancreatitis, malabsorption, nonsteroidal anti-inflammatory drug interactions, impaired judgment, alcoholism, mania) are well-documented risks. Thus, moderation is the key with regard to consuming grapes or their by-products, especially alcoholic beverages made from grapes. Detrimental effects of consuming high levels of supplements made from grapes or their by-products are not well reported in the literature.

Future Research

Potential mechanisms by which polyphenol-rich grape products reduce chronic inflammation and metabolic diseases associated with obesity are summarized in **Figure 8**. The following research foci on polyphenol-rich grape products warrant further investigation: (*a*) identify the most bioactive components in grapes or grape products and their mechanisms of action; (*b*) investigate the bioavailability and efficacy of individual grape bioactive components versus whole foods, beverages, extracts, or supplements; (*c*) examine additive or synergistic effects of grape polyphenols in vitro and in vivo; (*d*) design and carry out well-controlled cell, animal, and human studies with purified single and mixed grape compounds known to be taken up by specific tissues; and (*e*) determine potential side effects of consuming high levels of grapes or grape products, grape supplements, or individual or mixtures of grape polyphenols.

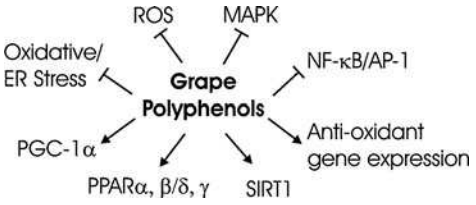

Figure 8

Summary of potential mechanisms by which polyphenol-rich grape products reduce chronic inflammation and metabolic diseases associated with obesity. AP-1, activating protein-1; ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; PPAR, peroxisome proliferator-activated receptor; PGC-1, PPARγ coactivator-1; ROS, reactive oxygen species; SIRT, sirtuins.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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