

Anti-Inflammatory and Anti-Obesity Properties of Food Bioactive Components: Effects on Adipose Tissue

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ABSTRACT: Obesity is an epidemic and costly disease affecting 13% of the adult population worldwide. Obesity is associated with adipose tissue hypertrophy and hyperplasia, as well as pathologic endocrine alterations of adipose tissue including local and chronic systemic low-grade inflammation. Moreover, this inflammation is a risk factor for both metabolic syndrome (MetS) and insulin resistance. Basic and clinical studies demonstrate that foods containing bioactive compounds are capable of preventing both obesity and adipose tissue inflammation, improving obesity-associated MetS in human subjects and animal models of obesity. In this review, we discuss the anti-obesity and anti-inflammatory protective effects of some bioactive polyphenols of plant origin and omega-3 polyunsaturated fatty acids, available for the customers worldwide from commonly used foods and/or as components of commercial food supplements. We review how these bioactive compounds modulate cell signaling including through the nuclear factor- κ B, adenosine monophosphate-activated protein kinase, mitogen-activated protein kinase, toll-like receptors, and G-protein coupled receptor 120 intracellular signaling pathways and improve the balance of pro- and anti-inflammatory mediators secreted by adipose tissue and subsequently lower systemic inflammation and risk for metabolic diseases.

Keywords: obesity, inflammation, polyphenols, omega-3 fatty acids

INTRODUCTION

Obesity is a disease of a complex etiology (1,2), which has become a major health problem in the United States and worldwide. Multiple factors contributing to obesity pathogenesis include genetic background, environment, and lifestyle. Importantly, obesity is closely linked with chronic low-grade inflammation (3,4), which in turn may trigger other chronic pathophysiologic conditions such as type 2 diabetes, metabolic syndrome (MetS), and heart diseases (1). Currently, 35.0% men, 40.4% women, and 17.0% of children and adolescent aged 2 to 19 years old in the US are obese (5,6). Moreover, over 600 million adults are obese worldwide according to the World Health Organization (7). Due to its epidemic rates, the obesity emerges as a major health care challenge in most regions of the world.

ADIPOSE TISSUE INFLAMMATION

Obesity is a result of adipose tissue expansion by adipocyte hypertrophy and/or hyperplasia especially in pre-adipocytes, stroma vascular cells, and stem cells (8). Adipose tissue is a loose connective tissue mainly composed of adipocytes. Besides adipocytes (lipid filled cells), adipose tissue contains fibroblast and immune cells linked together by collagen fibers (9). Two morphologically, anatomically and physiologically distinct adipose tissue types are brown adipose tissue (BAT) and white adipose tissue (WAT) (9). WAT is the most abundant type found in most of organisms and is crucial for energy storing (10). Moreover, WAT has also been well characterized as an endocrine organ (11), which controls a wide range of biological functions. Adipose tissue also acts as a thermal regulator and as a protector for important organs (8). In addition to energy storage and heat production, adipose tissue secretes a wide range of cytokines (9,12,13), collectively names 'adipokines' (10,14). These in-

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clude pro-inflammatory monocyte chemoattractant protein (MCP)-1, interleukin (IL)-8, IL-6, IL-1, tumor necrosis factor (TNF)- α , and anti-inflammatory IL-10 (15).

Adipose tissue also produces hormones such as angiotensin (Ang)-II (16), known for regulating blood pressure and fluid balance. Other adipose-derived proteins control energy homeostasis (leptin), glucose homeostasis (adiponectin and vistafin), immune regulation (resistin), and angiogenesis and cardiac contractility (apelin) (17,18). In healthy lean individuals, the adipocytes are small in size, insulin sensitive, and primarily secrete anti-inflammatory mediators such as adiponectin, IL-10, IL-4, IL-13, IL-1 receptor antagonist (IL-1Ra), apelin, and transforming growth factor beta (TGF β) (19,20). By contrast, in obesity, adipocytes are large and the adipose tissue of individuals with obesity is infiltrated by a large number of pro-inflammatory M1 macrophages (21), and secretes cytokines such as TNF- α , IL-6, visfatin, leptin, MCP-1, Ang-II, and plasminogen activator inhibitor-1 (20). As most of these compounds are pro-inflammatory, the "obese" adipose tissue is often referred to as inflamed. Low-grade inflammation in adipose tissue, which is a hallmark of obesity pathophysiology, is strongly associated with significant alterations in the profile of secreted adipokines (22,23).

The etiology of obesity-associated insulin resistance (IR) is intertwined with dyslipidemia, partially caused by enhanced secretion of free fatty acids (FFAs) by "obese" adipocytes, as illustrated in clinical studies comparing obese vs. lean women (24-26). Further, excessive production of pro-inflammatory adipokines by "obese" adipose tissue also causes IR both directly by inhibiting insulin signaling pathway or indirectly through activation of pathways of inflammation (22). As an example, TNF- α secreted by adipose tissue macrophages is directly involved in IR through serine phosphorylation of insulin receptor substrate (IRS)-1 (27). TNF- α also alters adipocyte differentiation and lipid metabolism, thus contributing indirectly to IR (22). Furthermore, Weyer et al. (28) and Arita et al. (29) have shown that plasma adiponectin levels are decreased in individuals with obesity, and inversely correlate with the degree of IR and hyperinsulinemia. These studies suggest that the metabolic syndrome and chronic low-grade inflammation are intertwined with the pathogenesis of obesity.

BIOACTIVE COMPOUNDS OF FOOD

The risk of chronic inflammation and metabolic syndrome are increased in obesity due to pathologic alterations of WAT metabolism and pro-inflammatory bias of secreted adipokines, which have systemic effects on the organism health status (30). Various strategies were de-

veloped to cure and/or prevent obesity; and most used approaches are based on suppressing appetite, normalizing the lipid metabolism, and increasing the energy expenditure (31). Numerous other therapeutic drugs, such as phentermine, diethylpropion, sibutramine, and loarcaserine, were developed for obesity treatments; however, some of them exert gastrointestinal and other adverse effects, such as oily stools, high blood pressure, variation in pulse rate, headache, dizziness, nausea, depression, and other serious psychological disorders (32,33). Accordingly, dietary interventions using natural bioactive food compounds have emerged as promising therapeutic tools for obesity and metabolic diseases, with limited deleterious side effects.

Composition of the diet may affect metabolic and endocrine functions as well as overall energy balance (8). Bioactive compounds are generally natural "extra nutritional" constituents which can be found in small quantities in plants and lipid-rich foods (34). The foods containing bioactive compounds improve body metabolism and energy balance. For example, in animal foods, fatty fish such as salmon, mackerel, and herring are enriched in omega-3 (ω -3) polyunsaturated fatty acids (PUFAs). Fruits, vegetables, nuts, seeds, herbs, and spices are plant based foods that are enriched with bioactive phytochemicals. Phenolic compounds, flavonoids, plant sterols, and carotenoids of plant origin have some well-documented protective effects against the prevention of chronic diseases such as coronary heart disease (35). The US Department of Health and Human Services and the US Department of Agriculture recommend a daily dose of 9 servings (about 4.5 cups) of fruits and vegetables, including 4 servings (about 2 cups) of fruits, and 5 servings (about 2.5 cups) of vegetables, based on a 2,000 kcal diet according to the guidelines for Americans to improve overall health and prevent chronic diseases (36).

In this review, we have selected bioactive compounds that are commonly used in foods and supplements in the US and other countries for improving health against diseases including obesity; these are summarized in Table 1, and their major mechanisms of action are summarized in Fig. 1. Several other reviews have covered other bioactive compounds as well as some of those discussed here (8,37).

GINGER

Ginger (*Zingiber officinale*), which belongs to *Zingiberaceae* family, is native to Southern Asia, where it is most commonly used as a spice, especially in the Southeast-Eastern Asian countries (38). Experimental data shows that ginger has multiple health benefits such as digestive stimulant action, antidiabetic effects, lipid lowering and

Table 1. Summary of some major functional foods, their biological effects and signaling mechanisms

| Food | Functional compound | Biological function | Signaling pathways or mechanisms | Reference |
|---------------------|----------------------------|--|---|----------------------------|
| Ginger | Ginger extract | Anti-obesity/Anti-inflammatory | ↑ PPAR- δ | 42 |
| | Gingerols | Anti-inflammatory | ↓ PGEs, COX1&2, lipoxygenase, leukotrienes, PG synthetase | 43, 45 |
| Turmeric | Zingerone | Anti-inflammatory | ↓ NF- κ B | 48 |
| | Curcumin | Anti-inflammatory | ↓ Phosphorylation of MAPK, Wnt/ β -catenin, NF- κ B, PAI-1 | 57, 58, 60, 61 |
| | | Anti-obesity | ↓ FASN | 59 |
| Garlic | Garlic extract | Anti-obesity | ↑ FA oxidation, AMPK | 57, 51 |
| | | Anti-inflammatory | ↓ Adipose tissue, TG, Free FA, weight gain, SREBP-1C, PPAR- γ | 68, 69, 71 |
| | Alliin | Anti-inflammatory | ↑ IL-10 | 74 |
| | | Anti-inflammatory | ↓ TNF- α , IL-1 α , IFN- γ | 74 |
| Soy beans | Isoflavones (soy proteins) | Anti-obesity | ↓ Phosphorylation of ERK1/2, IL-6, MCP-1 | 73 |
| | | Anti-inflammatory | ↓ Regulate adipose tissue body weight, BMI, adiposity, fat pad, SREBP-1C, ACC, FASN | 78, 80, 81, 88, 90, 91, 93 |
| | Polyphenols ¹⁾ | Anti-inflammatory | ↓ TNF- α , MCP-1, IL-6, lipid accumulation | 85, 86, 94 |
| Anti-inflammatory | | ↑ Adiponectin | 88 | |
| Bilberry | Polyphenols ¹⁾ | Anti-inflammatory | ↓ Adipocyte differentiation, PPAR, SREBP-1C, NF- κ B, CRP, IL-6, IL-15 | 96, 97 |
| Grape | Polyphenol (procyanidin) | Anti-inflammatory | ↓ NF- κ B, TNF- α , IL-6 | 98, 99 |
| Grape, wine | Resveratrol | Anti-obesity | ↑ Adiponectin | 101 |
| | | Anti-obesity | ↓ Lipogenesis | 101 |
| Strawberry | Anthocyanins ²⁾ | Anti-inflammatory | ↑ FA oxidation | 102 |
| Blueberries | Anthocyanins ²⁾ | Anti-inflammatory | ↓ IL-6 | 103 |
| Red sweet cherries | Anthocyanins | Anti-inflammatory | ↓ NF- κ B, IL-6, TNF- α , CRP | 104, 105 |
| | | Anti-obesity | ↑ Adiponectin | 105 |
| Tart cherry | Anthocyanins | Anti-inflammatory /Anti-obesity | ↓ Inflammation | 106 |
| Omega-3-fatty acids | ALA | Anti-inflammatory | ↓ Obesity | 105 |
| | | Anti-inflammatory | ↓ NF- κ B, adiposity | 106 |
| | EPA | Anti-inflammatory | ↓ IL-6, TNF- α , IL1- β , XBP1, sXBP1 | 108, 112 |
| | | Anti-obesity | ↓ PGE2, COX, MCP-1, IL-6, TNF- α , TLRs, NF- κ B | 120, 125, 126 |
| DHA | Anti-obesity | ↑ GPR120, PPAR- γ , adiponectin | 14, 121, 122 | |
| | Anti-obesity | ↑ Mitochondrial biogenesis, β -oxidation, AMPK | 117, 118, 123, 107, 106 | |
| | | | ↓ Adiposity, lipogenesis, visceral fat, body weight | 14, 116 |

PPAR, peroxisome proliferator-activated receptor; PGE, prostaglandin E; COX, cyclooxygenase; PG, prostaglandin; NF- κ B, nuclear factor- κ B; MAPK, mitogen-activated protein kinase; PAI-1, plasminogen activator inhibitor type-1; FASN, fatty acid synthase; FA, fatty acid; AMPK, adenosine monophosphate-activated protein kinase; TG, triglyceride; SREBP-1C, sterol regulatory element-binding protein 1C; TNF, tumor necrosis factor; IL, interleukin; IFN, interferons; ERK, extracellular-signal-regulated kinase; MCP-1, monocyte chemoattractant protein; BMI, body mass index; ACC, acetyl-coenzyme A carboxylase; CRP, C-reactive protein; ALA, α -linolenic acid; XBP, X-box-binding protein; sXBP, spliced X-box-binding protein; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; GPR120, G-protein coupled receptor 120.

¹⁾Anthocyanidins, quercetin, epicatechin, and resveratrol.

²⁾Pelargonidin sulfate and pelargonidin-3-*O*-glucoside.

anti-obesity effects, anti-inflammatory effects, protective effects on gastro-intestinal tract, cancer prevention properties, protective effects on liver, kidney, ulcerative colitis, and the absorption of micronutrients (39). Ginger contains both volatile and nonvolatile compounds. Volatile compounds/oil is responsible for the ginger odor (40).

Ginger reduces body weight by downregulating the absorption of lipids via inhibiting the fat hydrolysis processes (41). In particular, the calorie burning can also be increased by consuming ginger extract (39). The anti-inflammatory properties of ginger were shown using both

in vitro and *in vivo* models. Misawa et al. (42) studied the anti-obesity properties of ginger extract using C57BL/6 mice. Their study demonstrated that ginger extract can decrease high fat diet (HFD)-induced obesity via activation of the peroxisome proliferator-activated receptor (PPAR)- δ pathway in skeletal muscle and the liver which induces the utilization of fats and the expression of the genes in the skeletal muscle which regulates the oxidation of fatty acid. Furthermore, ginger extract reduced the infiltration of macrophages in adipose tissue of mice fed with ginger extract-enriched high fat diet, compared to

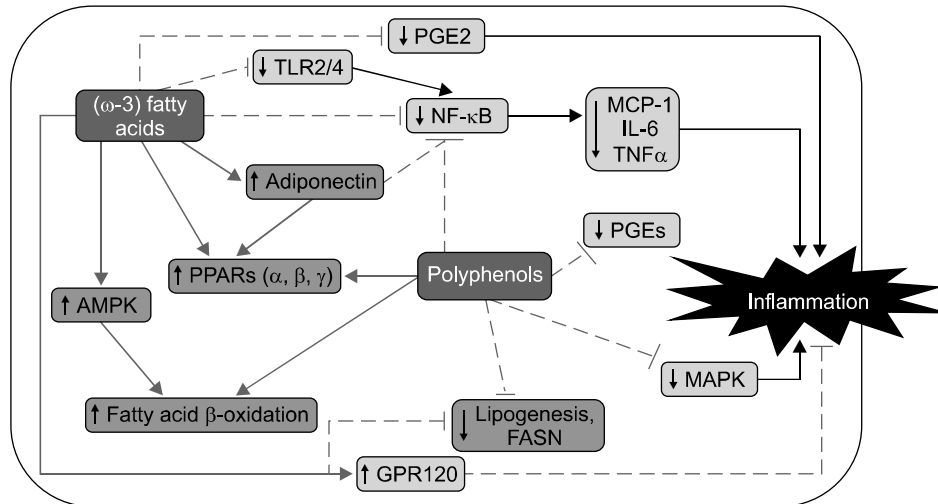


Fig. 1. Summary of major signaling mechanisms mediating effects of omega-3 (ω -3) fatty acids and some polyphenols. Bioactive compounds such as omega-3 fatty acids and polyphenols discussed in this review modulate cell signaling including various mechanisms including the nuclear factor- κ B (NF- κ B), adenosine monophosphate-activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK), toll-like receptors (TLRs), and G-protein coupled receptor 120 (GPR120) intracellular signaling pathways. These effects lead to reduction of inflammation and possibly obesity and associated metabolic diseases. PGE, prostaglandin E; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α ; PPAR, peroxisome proliferator-activated receptor; FASN, fatty acid synthase.

HF diet alone (42). Inhibition properties of cyclooxygenase (COX) and lipoxygenase and synthesis of leukotrienes by ginger extract were demonstrated both *in vitro* and *in vivo* (43).

Gingerols, shogaols, and paradols are structurally similar compounds of polyphenolic nature found in ginger, which possess major anti-inflammatory properties. Gingerols are the main ginger pungent constituents. They may be converted to shogaols by dehydration (43). Gingerols inhibited prostaglandin (PG) biosynthesizing enzyme (PG synthetase) and leukotrienes biosynthesis enzyme (arachidonate 5-lipoxygenase) in rat basophilic leukemia (RBL-1) cells (44), and inhibited lipopolysaccharide (LPS) induced COX-2 expression in U937 cells (45). Saravanan et al. (46) reported anti-obesity properties of gingerol through the inhibition of dietary fat absorption in the gastrointestinal tract, and its hypophagic and hypolipidaemic activity in male rats in the HFD-induced model of dietary obesity. Ability of gingerols to improve adipocyte differentiation and insulin-dependent glucose uptake was showed in *in vitro* studies using mouse 3T3-L1 pre-adipocytes (47). Furthermore, the MCP-1 secretion in the same cells, as well as secretion of such mediators of inflammation as TNF- α and nitric oxide (NO) in macrophages, can be significantly inhibited by another ginger phenolic bioactive, zingerone (vanillyacetone) (48). Taken together, these studies demonstrated that ginger components are able to reduce inflammation, lipid storage and absorption and increasing lipid oxidation.

TURMERIC

Turmeric (*Curcuma longa*) is widely consumed as a spice in India and other Asian countries. Also, it has been used for thousands of years in a medicine of Ayurveda, which means "science of long life". First records about the turmeric as a versatile medicine are dated 3,000 B.C. (49). Nutritional analysis of turmeric has shown that 100 g turmeric contain 354 kcal; 19 g total fat, including 3 g saturated fat; 65 g of carbohydrates, 38 mg of sodium; about 2.5 g potassium; 21 g fiber, 3 g sugar, 8 g protein, and no cholesterol (49). More than 100 bioactive components have been identified in turmeric (50). The volatile oil is the main component containing turmerone and other coloring agents known as curcuminoids, a group of chemically related bioactive low molecular weight polyphenols (49). Turmeric has well documented anti-inflammatory, anti-obesity, anti-angiogenesis, anti-carcinogenic and antioxidant activities (51,52). Most protective effects of turmeric are attributed to curcuminoids, consisting of 77% curcumin, 17% demethoxycurcumin, and 3% bide-methoxycurcumin (53). Curcumin has been the most studied component of turmeric (54,55).

A randomized control trial conducted by Di Pierro et al. (56) among overweight people with metabolic syndrome showed the ability of curcumin to reduce weight and omental adipose tissue. Both *in vitro* and *in vivo* studies have shown the positive influences of curcumin on obesity and its associated metabolic syndrome (8,37). In mice with dietary obesity, supplementing the diet with curcumin decreased adiposity and body weight (51), and increased the oxidation of fatty acid and adenosine mon-

ophosphate activated protein kinase (AMPK) activity in adipocytes (57). *In vitro*, curcumin inhibited the adipocyte differentiation via suppressing the phosphorylation of mitogen-activated protein kinases [mitogen-activated protein kinases (MAPKs); extracellular-signal-regulated kinase (ERK), c-Jun N-terminal kinases, and p38] in 3T3-L1 adipocytes (57). MAPK cascades are crucial for the development of adipocytes from 3T3-L1 precursors. In differentiated adipocytes, curcumin further interferes with adipogenesis, through the Wnt/ β -catenin signaling pathway (58). Curcumin reduces lipogenesis in fat cells by decreasing the expression of fatty acid synthase (FASN) (59). Moreover, curcumin ameliorated obesity-associated inflammation by preventing the stimulation of nuclear factor κ B (NF- κ B), a critical pro-inflammatory transcription factor (60,61). Downregulation of the NF- κ B reduced expression of TNF- α and MCP-1, thus preventing the infiltration of macrophages into adipose tissue. Curcumin reduced the expression of such potential inflammatory molecules and increased the expression of anti-inflammatory adiponectin (61). Curcumin treatment in C57/BL6 mice increased fatty acid oxidation and AMPK activity in adipocytes (57), and decreased adiposity and body weight (51).

Overall, these studies indicate that curcumin exerts anti-obesity and anti-inflammatory effects in part through adipose tissue, by reducing adiposity, lipid storage, and increasing lipid oxidation.

GARLIC

Garlic (*Allium sativum*) belongs to the *Alliaceae* family. Garlic is most popularly used as both a spice and a medicine. It was originated from Central Asia, but it is also currently grown in Mexico, Europe, and North Africa (62). The bioactive components of this plant have been studied for their hypocholesterolemic, hypoglycemic, antioxidant, anticancer, and anti-obesity beneficial biological effects (63). Alliin, ajoene, allicin, diallyl disulfide, diallyl trisulfide, allyl methanethiosulfinate, S-allylcysteine, and other numerous sulphur compounds of garlic have been implicated in its anticancer effects (64-66). Allicin (diallyl-dithiosulfinate) is often referred to as the most important garlic bioactive component (62). As the therapeutic efficacy of most of garlic organosulphur bioactives can be compromised during food processing, and cooking protocols are particularly important for garlic containing foods.

Many published studies reported beneficial effects of garlic against obesity, heart diseases, hyperglycemia, and high blood pressure (63,67-70). It was observed that in obese mice, garlic decreases total body adiposity and ameliorates the obesity-associated dyslipidemia via reduc-

ing blood triglycerides, FFAs, and total cholesterol (69). Using 3T3-L1 pre-adipocytes, Kim et al. (71) have demonstrated the ability of the garlic compound thiocremonone to interfere with adipocyte differentiation. The anti-adipogenic effects of this sulfur compound are mediated via downregulating the transcription factor PPAR- γ and activating the AMPK. The latter finding was further corroborated by the observation that thiacremonone-induced AMPK activation results in up-regulation of the UCP-2 gene, related to energy expenditure by BAT (71). In a rat model of HFD-induced obesity, administration of 250 mg/kg body weight of aged black garlic with the animal diet reduced weight gain and dyslipidemia (68,72). Ha et al. (68) further showed that garlic extracts modulate lipid and cholesterol metabolism by lowering the liver sterol regulatory element-binding protein 1C (SREBP-1C) mRNA levels.

Anti-inflammatory properties of alliin, a simple L-cysteine derivative in garlic have been extensively studied. Alliin reduced LPS-stimulated inflammation in 3T3-L1 adipocytes by decreasing the phosphorylation of ERK1/2. This effect is associated with decreased gene expression of IL-6 and MCP-1 inflammatory markers (73). Human peripheral blood leukocytes, treated with garlic extracts *in vitro*, exhibited suppression of TNF- α , IL-1 α , interferons (IFN)- γ , and other pro-inflammatory cytokines production along with upregulation of anti-inflammatory IL-10 (74). The above studies demonstrate beneficial effects of garlic components in metabolic diseases by reducing obesity and inflammation and increasing energy expenditure.

SOYBEAN

Soybean (*Glycine max*), an East Asian legume, is well known for its high quality protein, which contains all nine essential amino acids. The nutritional value of soybean protein may be considered equivalent to meat and animal proteins (75). Soy proteins contain isoflavones, which are phytochemicals, also referred to phytoestrogens, due to their ability to bind estrogen receptors and mediate estrogenic or antiestrogenic effects in mammals (76). Isoflavones are diphenolic compounds capable of reducing oxidative stress (77). Genistein, daidzen, and glycerin are the main isoflavones of soy. Genistein is the major isoflavone in soy and the most reviewed phytoestrogen in soy. All three soy isoflavones regulate adipose tissue without affecting food consumption (78). Furthermore, several studies show favorable role of soy in enhancing health and preventing diseases, such as cholesterol and triglyceride lowering effects (79), reducing adiposity, improving IR as well as protecting against cancer and osteoporosis and ameliorating the symptoms of men-

opause (80,81). In 1999, the Food and Drug Administration endorsed the claim that 25 g of soy protein per day (approximately 50 mg/d of isoflavones) may lower the risk of heart disease (82). This amount of isoflavones corresponds to the typical daily consumption in Asian countries, however, less than 1 mg of isoflavones is consumed daily in Western countries (83,84).

Many studies reported beneficial effects of soybeans on inflammation in many health conditions (85). Soy proteins inhibit secretion of inflammatory cytokines (TNF- α , MCP-1, and IL-6) and reduce the inflammatory responses in mature murine adipocytes *in vitro* (86). This finding is in line with inhibiting of LPS-induced inflammation by soy peptides and pancreatic soybean hydrolysates in RAW 264.7 macrophages, reported by Vermont et al. (87). Similarly, Zhang et al. (88) observed that 150 to 450 mg/(kg \times d) isoflavone administered with HFD to rats sharply decreased the adiposity and pro-inflammatory adipokine (IL-6, TNF- α , and resistin) levels, and improved blood adiponectin. These alterations in body structure and adipokine profiles correlated with improved insulin sensitivity in animals treated with dietary soy isoflavones (88). A recent randomized clinical trial demonstrated that a nutritional intervention using 30 g soy protein/d as an alternative to animal protein improved body weight, body mass index, and biomarkers associated with cardiovascular risk; including total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, and apolipoprotein B (89). *In vivo* experiments in rodent obesity models have shown that dietary isoflavones significantly reduced body weight and fat pad weight (90,91). Xiao et al. (92) have shown that soy isoflavones promote lipid clearance in the liver, a major lipogenesis and lipid β -oxidation organ, in weanling Sprague-Dawley rats. It was shown in the same study, that SREBP1 transcription factor expression and its other target genes (acetyl-coenzyme A carboxylase, ATP-citrate lyase, and FASN) were reduced by soy isoflavones (93). Consistent with these findings, soy isoflavones also decrease lipid gathering in differentiated 3T3-L1 cells (94).

Overall, available data demonstrate that soy isoflavones reduce adiposity and inflammation, by reducing lipogenesis, adipogenesis, and improving lipid clearance and may contribute in this manner to metabolic improvements in obesity.

GRAPE, CHERRIES AND BERRIES

Grape, cherries and berries are popular fruits which contain large amounts of polyphenols such as anthocyanins, proanthocyanidins, and resveratrol. Historically, foods, rich in anthocyanins, have been used as a medicine. Anthocyanins (cyanidin-3-glucoside) improve hyperglycemia

and insulin sensitivity by inducing the expression of glucose transporter type 4 and decreasing the retinol binding protein 4 (RBP4), which is accompanied by the reduced expression of MCP-1 and TNF- α inflammatory cytokines in white adipose tissue in type 2 diabetic mice (95). Anthocyanidins and bilberry extracts similarly inhibited differentiation of 3T3-L1 adipocytes *in vitro* and regulated expression of insulin pathway genes, and reduced the IRS-1 phosphorylation. Moreover, both anthocyanidins and bilberry extracts decreased the expression of PPAR- γ (96). In another study, polyphenol-rich bilberry juice reduced expression of NF- κ B pathway genes, C-reactive protein (CRP), IL-6, IL-15, and monokine induced by IFN- γ (97). This study also determined effects of polyphenols on LPS-induced NF- κ B activation in monocyte cell line and found that quercetin, epicatechin, and resveratrol in bilberry repressed NF- κ B activation (97).

A mix of procyanidin (members of proanthocyanidin) flavonoids extracted from grape has shown anti-inflammatory effects on human macrophage-like cell lines and adipocytes (98). This polyphenol rich extract was able to reduce NF- κ B pathway and increased the anti-inflammatory adiponectin production (98). Moreover, supplementing the animal diet with grape procyanidins resulted in reduction of TNF- α and IL-6 production in the mesenteric white adipose tissue of male Zucker *fa/fa* rats prone to spontaneous obesity (99).

Resveratrol, a naturally occurring stress-response polyphenol abundant in grape, grape juice and red wine, reduced the RBP4 and resistin gene expression in 3T3-L1 adipocytes (100). Both these adipokines have been implicated in IR in mice (30,31). Resveratrol also reduced lipogenesis and enhanced fatty acid oxidation in adipocytes (101).

In a clinical study, strawberry anthocyanins, pelargonidin sulfate, and pelargonidin-3-O-glucoside reduced the postprandial inflammation and plasma IL-6, and increased insulin sensitivity in overweight human subjects (102).

Blueberries, another anthocyanin-rich berry, improved the insulin sensitivity in obese insulin-resistant adults (100). In a Zucker rat model of spontaneous obesity, blueberries revealed a wide spectrum of anti-inflammatory activities, including reduced expression of NF- κ B, IL-6, and TNF- α in the liver and adipose tissue and lowered concentrations of IL-6, TNF- α , and CRP in plasma while upregulating adiponectin (103).

Consumption of cherries mitigates obesity-associated inflammation and metabolic syndrome. In genetically obese and diabetic *db/db* mice, a diet supplemented with red sweet cherry powder, ameliorated inflammation and hyperglycemia (104). Anthocyanins, purified from methanol extract of sweet cherries, prevented adipocyte differentiation of 3T3-L1 cells and improved HFD-induced obesity in C57BL/6J (B6) mice. Mice, whose diet was en-

riched with cherry anthocyanins, improved dyslipidemia and hyperglycemia and reduced plasma levels of chronic inflammatory markers (105). Supplementing the HFD with freeze-dried tart cherries administered to Zucker rats for 90 days, reduced expression of NF- κ B and its downstream target genes and decreased total body adiposity, compared to control animals (106).

OMEGA-3 POLYUNSATURATED FATTY ACIDS (ω -3 PUFAs)

Dietary fats play a versatile role in whole body homeostasis as a source of energy, components of cell membranes and metabolic precursors for hormones and immune system mediators. Depending on their molecular structure, the dietary fats fall into one of three main categories, namely saturated fatty acids, monounsaturated fatty acids, and PUFAs. According to the location of the first double bond from the methyl ($-\text{CH}_3$) end of the molecule, long chain PUFAs are further classified into two major groups: ω -3 and omega-6 (ω -6) fatty acids. ω -3 and ω -6 PUFAs are both essential food constituents as they cannot be synthesized in mammals (107).

Examples for the dietary sources rich in ω -3 fatty acids are fatty marine fish, nuts, and plant oils. However marine fats are rich specifically in very long chain ω -3 fatty acids. The composition of ω -3 PUFAs found in plant sources is mostly enriched with short-chained α -linoleic acid (ALA) which contains 18 carbon atoms (C18:3). Canola (rapeseed), walnut, soybean (up to 10% ALA in total fatty acids) and flaxseed (over 50% ALA in total fatty acids) oils are most widely distributed plant ω -3 PUFA sources. Health benefits of ALA are related with its ability to reduce systemic inflammation. In clinical studies, supplementing the diet with ALA inhibited the IL-6, IL-1 β and TNF- α production in peripheral blood mononuclear cells and decreased plasma TNF- α (108). These effects were accompanied by increased proportions of long-chained ω -3 PUFAs: eicosapentaenoic acid (EPA) and docosapentaenoic acid in membranes of neutrophils, monocytes and lymphocytes (108-110). This phenomenon may be explained by the fact that, in mammalian organisms, short chain ALA is converted to some extent to long chain EPA, decosahexaenoic acid (DHA), and other ω -3 PUFAs after a series of elongation, desaturation, and β -oxidation reactions (107,111). Another recent study reported that ALA supplementation decreased expression of genes associated with endoplasmic reticulum stress such as X-box-binding protein (XBP)1 (20%), spliced XBP1 (70%) in subcutaneous adipose tissue in patients with type 2 diabetes (112).

The fatty sea fish species like mackerel, sardines, mullet, salmon, tuna, trout, bluefish, herrings, and ancho-

vies are the major sources of animal fats rich in long chain ω -3 PUFAs (15). Compared to ω -3 PUFA-rich plants, the animal sources of ω -3 PUFAs contain more significant fractions of long-chained EPA (C20:5) and DHA (C22:6). EPA and DHA provide stronger and more rapid health protective effects than ALA due to their high ability to be incorporated into plasma and membrane lipids (113, 114). Moreover, DHA and EPA serve metabolic precursors for biosynthesis of lipid anti-inflammatory mediators such as resolvins, protectins, and maresins (107,115). In most of the countries which have accepted a westernized lifestyle, the diet mainly contains short chain ALA, but lacking in long chain omega-3 PUFAs (111).

Experimental studies have shown that adipose tissue is an anatomical location where the anti-inflammatory effects of ω -3 PUFAs are exerted. In individuals with obesity and laboratory animals, the adipocytes are filled with lipids, are insulin resistant and involved in the pathogenesis of the MetS. Some studies, especially in animals, showed that dietary ω -3 PUFAs are capable of decreasing body adiposity (116,117). Furthermore, these fatty acids increased mitochondria biogenesis and β -oxidation of fatty acid in adipose tissue (117,118). In addition, DHA has ability to inhibit adipocyte differentiation and induce apoptosis in preadipocytes *in vitro* (119). These mechanisms contribute to anti-obesity effects of long chain ω -3 PUFAs. These fatty acids also reduce inflammation by decreasing the secretion of MCP-1, IL-6, and TNF- α *in vitro* from LPS-induced human adipose tissue or mature adipocyte cultures (120). Mechanisms mediating actions of long chain ω -3 fatty acids such as EPA and DHA is in part through their lipid mediators protectins and resolvins (120). Further, these fatty acids may act by binding with G protein-coupled receptor 120 (GPR120). Indeed, it was demonstrated that long chain ω -3 fatty acids inhibit the NF- κ B pathway in RAW 264.7 mouse macrophages and reduce macrophage-induced adipose tissue inflammation and insulin resistance through GPR120 (121).

The long chain ω -3 PUFAs serve as ligands for PPAR- α and PPAR- γ , the members of the PPAR transcription factors family, which functions in different aspects of regulating energy balance, including lipid metabolism (107, 115,118). EPA and DHA increase secretion of adiponectin in adipose tissue and reduce body weight, in part through PPAR- γ activation in mice fed with a fish oil diet (15, 122). ω -3 PUFAs reduce adiposity and progress of obesity through other key regulatory transcription factors such as PPARs (α , β , and γ) which are involved in adipogenesis and lipid metabolism in mature adipocytes (123). In addition, these fatty acids activate the AMPK pathway, thus inhibiting lipogenesis, and stimulating lipid oxidation, and glucose uptake by adipose tissue (124). Moreover, ω -3 PUFAs inhibit gluconeogenesis in the liver, stimulate glucose transport, and induce mitochondrial

biogenesis in skeletal muscle (107). EPA suppresses the liver lipogenesis and steatosis in mice fed with a high fat diet, and prevents visceral fat accumulation and obesity (116). Moreover, ω -3 PUFAs inhibit the inflammatory mediators such as prostaglandins-2 by inhibiting COX activity (125). Obesity-associated inflammation may also be directly modulated by ω -3 PUFAs due to their ability to downregulate the expression of toll-like receptors (TLRs). In mice suffering from LPS-induced systemic inflammation, supplementing the diet with EPA and DHA rich fish oil resulted in decreased levels of IL-1 β , IL-6, and TNF- α accompanied by reduced expression of TLR4 gene as well as the genes of NF- κ B, MyD88 and other components of TLR4 pathway (126). These data were generated using lean animals fed regular diet. But the protective effects exerted by long chain ω -3 PUFAs against the inflammation, associated with obesity, may be mediated by similar mechanisms, because this kind of inflammation is partially caused by increased intestinal permeability and elevated plasma LPS (127). In sum, the complex spectrum of anti-obesity and anti-inflammatory benefits and diverse mechanisms mediating effects of ω -3 PUFAs point to a promising role for these macronutrients in and for additional research in this area, especially in humans.

CONCLUSION

Obesity is a complex multifactorial disease with the incidence and prevalence rates growing epidemically and globally. Adipose tissue is the anatomic site of manifestation of major pathophysiologic effects of obesity and its associated inflammation. Chronic low-grade inflammation compromises the healthy secretion profile of pro- and anti-inflammatory adipokines and increases the risk of developing insulin resistance, heart and vascular diseases, respiratory disorders, and cancers. Various strategies including lifestyle modifications, dietary supplements and eating patterns have been developed to reduce obesity and inflammation. Numerous clinical and basic, *in vivo* and *in vitro*, studies demonstrate the link between the health benefits of the foods containing bioactive compounds and their ability to regulate gene expression in adipose tissue, thus modulating the secretion of adipose cytokines and hormones. The molecular mechanisms of bioactive food compounds are being characterized extensively. Along with its metabolic and inflammation-related complications, the obesity can be ameliorated by including the foods enriched with bioactive compounds into the diet. Bioactive food compounds discussed in this review have a promising potential as an anti-inflammatory components of science-based novel therapeutic diets, which may help patients with obesity. More basic and clinical

studies to evaluate the anti-obesity impacts of bioactive food compounds individually or in combination, are warranted. Moreover, educating the people worldwide about nutritional advantages of natural foods, advocating particularly those which are traditional for particular countries and cultures, may be invaluable for preventing the incidence of western diet-induced obesity. This in turn will help halt the obesity epidemic, and ultimately improve the quality of life while reducing the economic burden of obesity.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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