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Beneficial Effects of Plant Polyphenols on Obesity

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Abstract

Plant polyphenols are found in foods such as tea, apples, onions, berries, citrus fruits, plums, broccoli, cocoa, and coffee. Epigallocatechin-3-gallate, chlorogenic acid, curcumin, quercetin, and resveratrol are representative polyphenols and have been extensively studied for their health benefits. This review article provides evidence derived from epidemiological, clinical, and laboratory studies on the anti-obesity effects of plant polyphenols, and discusses their mechanisms of action. Most cell-based and animal studies have described their anti-obesity effects, although human studies have shown conflicting results, indicating that further studies are required to determine whether polyphenols indeed have preventive and therapeutic significance in obesity and related diseases. Basic research has suggested that the primary mechanisms of action of plant polyphenols include involvement of reactive oxygen species (ROS), 5'-AMP-activated protein kinase (AMPK), and the transcription factor NF-κB. The involvement of ROS in AMPK activation has been well documented, and the pro-oxidative properties of plant polyphenols can lead to the activation of AMPK, resulting in the modulation of various signaling pathways involved in adipogenesis, lipogenesis, and lipolysis. NF-κB is another key mediator of the mechanisms of action of plant polyphenols, and can modulate the protein and gene expression of pro- and anti-inflammatory cytokines that play important roles in obesity. The polyphenols described in this review are established antioxidants, and their ROS-scavenging properties may mitigate ROS-dependent NF-κB activation. At present, the factors that direct these polyphenols to act as either pro-oxidants or antioxidants remain unclear, although polyphenol concentration and the presence of metal ions have been suggested. Furthermore, the observation that activated AMPK can downregulate NF-κB may provide an alternative explanation for the activities of plant polyphenols. Future studies are required to confirm the mechanisms of action of these polyphenols, and may subsequently contribute to their evidence-based application in human health.

Keywords: Polyphenol; Obesity; ROS; AMPK; NF-κB; Health Benefit

Introduction

Plant polyphenols are found in foods such as tea, apples, onions, berries, citrus fruits, plums, broccoli, cocoa, and coffee [1]. In the United Kingdom, the mean daily intake of flavanols such as tea catechins, apple epicatechin, cocoa procyanidins; flavonols such as onion quercetin; flavanones such as citrus fruit hesperidin; hydrocinnamic acids such as coffee chlorogenic acid (CGA); and anthocyanins such as berry cyanidins is approximately 590, 61, 25, 478, and 20 mg, respectively [1] (Figure 1). Recent studies have demonstrated the beneficial health effects of polyphenols in obesity and obesity-related chronic diseases. Wang et al. evaluated the effect of commonly consumed polyphenols, including green tea catechins, particularly (-)-epigallocatechin-3-gallate (EGCG), resveratrol (RSV), and curcumin, on obesity and obesity-related inflammation [2] (Figure 1). Furthermore, the beneficial effects of CGA and quercetin on health are well documented.

Green tea, a product of the leaves of *Camellia sinensis* plants, has been consumed by humans for thousands of years and used as a folk remedy for a wide array of diseases. EGCG is contained almost exclusively in green tea leaves, from which black tea and oolong tea are also produced. One 200 mL cup of green tea contains approximately 140 mg of EGCG, although black and oolong teas contain significantly less EGCG because it is converted to other catechin derivatives during production [3].

Globally, coffee is the second most commonly consumed beverage after tea, and contains approximately 2,000 chemicals [4]. Several coffee components such as caffeine and polyphenols exert beneficial effects on health. CGA or 3-caffeoylquinic acid is the representative polyphenol in coffee, and found also in *C. sinensis* and other plants [5].

Curcumin, a yellow pigment, is an active component of the Indian spice turmeric (*Curcuma longa*) and is widely used in cooking, cosmetics, dyes, and medicines [6]. Isolated in 1815 by two German scientists, Vogel and Pelletier, the first study on the biological activity of curcumin as an antibacterial agent was published in 1949 in *Nature*, and the first clinical trial of curcumin was reported in *The Lancet* in 1937 [7]. Curcumin comprises 2%–8% of turmeric, and is consumed by Asian populations at doses up to 100 mg/day [2]. Curcumin has also been used as a herbal remedy in traditional Indian and Chinese medicine, with multiple studies demonstrating its beneficial effects in human disease [8].

Quercetin is a flavonol found in green tea, red onions, apples, and other sources [1,9]. The median flavonoid intake is 3-4 mg/day, ranging from 0.41-4 mg/day. On average, approximately 95%

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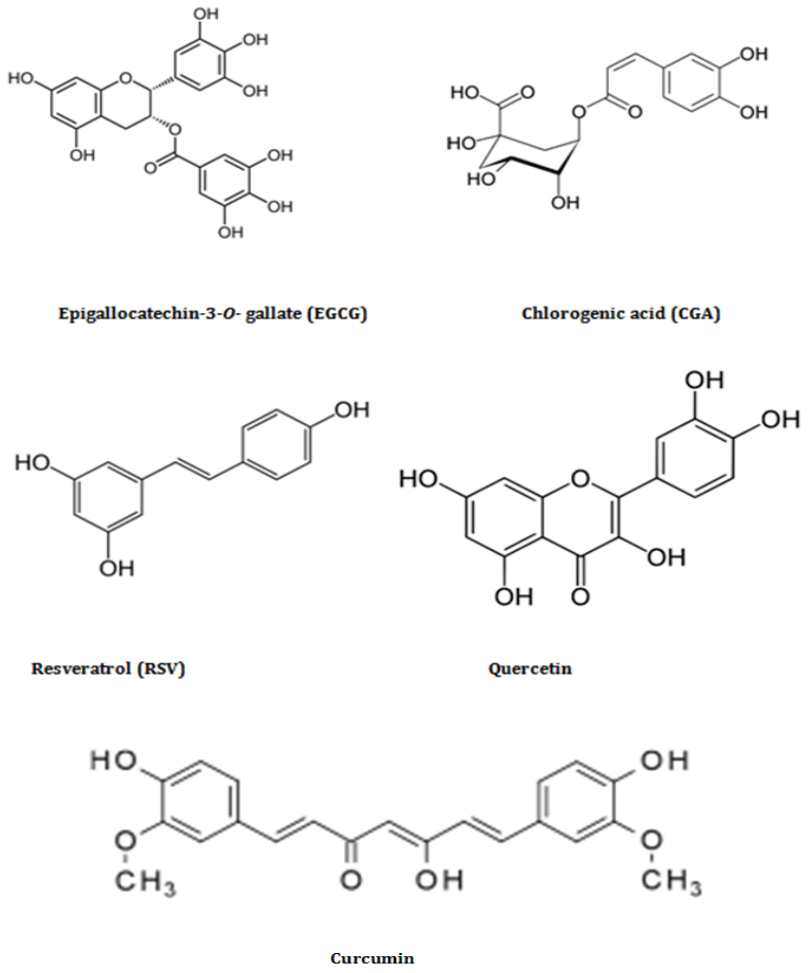

Figure 1: Chemical structures of selected dietary polyphenols

of the total flavonoid intake is quercetin. Examples of quercetin content, expressed as mg/100 g, are 233.84 in raw capers, 50.73 in raw yellow peppers, 39.21 in raw red onions, 7.67 in raw blueberries, 3.69 in Golden Delicious apples with skin, 2.49 in brewed green tea, and 1.04 in red table wine. Quercetin is largely utilized as a nutritional supplement and as a phytochemical remedy for a variety of conditions such as diabetes and obesity, circulatory dysfunction, inflammation, and mood disorders [10].

RSV (3, 4', 5-trihydroxystilbene) is a naturally occurring polyphenolic compound found in many plants sources, including grapes, peanuts, and berries, and exists in two isomeric forms: *cis*- and *trans*-RSV. Trans-RSV is naturally found in grapes, mainly in the skin and in the leaf epidermis of the grape vine [11]. *Trans*-RSV is the main form of RSV found in red grape juice (3.38 mg/L) [2]. Apart from grapes, *trans*-RSV is found in more than seventy other plant species and in foods such as mulberries, peanuts, and cocoa. *cis-RSV* is present in red wine but not in grapes, as it is converted from *trans*-RSV during fermentation, and is not commonly found in foods [2]. Therefore, in this review, RSV represents *trans*-RSV.

In this review article, we summarize the recent evidence on the anti-obesity effects of plant polyphenols and discuss their mechanism of action, focusing on EGCG, CGA, curcumin, quercetin, and RSV.

Anti-obesity effects of green tea/EGCG

Epidemiological observational studies on green tea/EGCG

Several epidemiological studies have shown the beneficial effects of tea consumption on metabolic syndrome (MetS) and/or its component, obesity. In an epidemiological study with 6,472 adult participants in the United States, Vernarelli and Lambert found that tea consumers had a lower mean waist circumference and lower body mass index (BMI) (25 versus 28 kg/m^2 in men; 26 versus 29 kg/m^2 in women) than non-consumers after controlling for age, physical activity, total energy intake, and other confounding factors, suggesting that hot tea consumption was inversely associated with obesity [12].

A cross-sectional, population-based survey among 8,821 adults conducted in Poland found that, after adjusting for

potential confounding factors, higher tea consumption was inversely associated with MetS (odds ratio (OR): 0.79, 95% confidence interval (CI): 0.92). Specifically, tea consumption was inversely correlated with central obesity and fasting plasma glucose in women, but not in men [13].

In contrast, two epidemiological studies in Japanese populations found no beneficial association between green tea consumption and MetS and its components, including waist circumference [14, 15].

Clinical studies on green tea/EGCG

Multiple human intervention studies have examined the effect of tea consumption on MetS and its components. For example, Nagao, et al. showed that, in a randomized clinical trial on 240 Japanese subjects with visceral fat-type obesity who consumed green tea containing 583 mg of catechins (catechin group) or 96 mg of catechins (control group) per day for 12 weeks, MetS indexes such as body weight, BMI, body fat ratio, and waist circumference decreased to a greater extent in the catechin group than in the control group [16].

Chen, et al. examined the effect and safety of high-dose green tea extract (GTE), at a daily dosage of 856.8 mg, on weight reduction. In a randomized, double-blind trial on 102 women with central obesity, significant weight loss, from 76.8 ± 11.3 kg to 75.7 ± 11.5 kg after 12 weeks, was observed following GTE intervention, with significant decreases in BMI and waist circumference [17].

Legeay, et al. reviewed six human intervention studies and identified four studies showing an association between higher consumption of EGCG and decreased body weight [18]. In one example, a randomized, double-blind clinical trial on 46 obese patients, the BMI (31.71 ± 2.29) of patients who consumed 379 mg/day of GTE for 3 months was significantly lower than that of patients in the placebo group (33.36 ± 2.66), although there was no significant difference in BMI between the groups at baseline [19].

A systematic review conducted by Amiot, et al. summarized ten clinical studies on the effects of green tea and pu-erh tea extracts on MetS and identified eight studies reporting significant improvements in BMI and seven reporting improvements in weight circumference [20]. Furthermore, Yang, et al. identified several studies that supported the preventive effect of green tea and pu-erh tea on MetS through the mitigation of obesity [21].

Green tea may also be beneficial in the treatment of obesity, as suggested by Suliburska, et al. [19]. These authors found that 3 months of supplementation with 379 mg of GTE per day in obese patients resulted in decreased BMI, waist circumference, and levels of total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and triglycerides(TGs).

In contrast to these findings providing clinical information on the beneficial effects of tea in obesity, a randomized clinical trial showed that two kinds of Japanese-branded green tea did not affect body weight [22].

Laboratory studies and mechanism of action of green tea/EGCG

A comprehensive review article by Huang, et al. on the anti-obesity effects of green tea summarized the mechanisms of action of green tea catechins [23]. These include 1) interference with energy absorption and metabolism to inhibit the proliferation of preadipocytes and induce apoptosis in the preadipocyte and matured adipocyte; 2) inhibition of preadipocyte differentiation and the adipogenesis of maturing adipocytes; 3) inhibition of the activity of gastrointestinal digestive enzymes, luminal emulsification, and micellar solubilization of lipids; 4) interference with the uptake and intracellular processing of lipids and secretion of chylomicrons in enterocytes; 5) enhancement of fecal excretion; 6) downregulation of hepatic gene expression of lipogenic enzymes and related transcription factors; 7) upregulation of hepatic mRNA levels of β-oxidation genes; 8) stimulation of fatty acid oxidation and glucose uptake in skeletal muscle; 9) stimulation of the expression of lipolysis and fatty acid oxidation-related genes in adipose tissue; and 10) suppression of glucose intake and expression of lipogenesis-related genes in adipose tissue.

Yang, et al. in their comprehensive review, also supported the above mechanisms of action of the anti-obesity effects of green tea, including the inhibition of pancreatic lipase, lipid transporters, and micellar solubilization of lipids [21]. In addition, these authors proposed the "AMPK hypothesis," in which the activation of 5'-AMP-activated protein kinase (AMPK) represents the main mechanism by which EGCG influences energy metabolism to alleviate MetS and its components [21]. AMPK activated by phosphorylation can modulate the protein and gene expression of enzymes involved in lipid and carbohydrate metabolism. The following findings may primarily be explained by one or more of the mechanisms described by Huang, et al. and Yang, et al. [21,23].

In an animal experiment in which mice were fed either a low-fat diet (5% TGs), high-fat diet (HFD; 30% TGs), or HFD supplemented with 0.1%-0.5% (w/w) tea catechins for 11 months, tea catechin supplementation was associated with a significant reduction in HFD-induced body weight gain, visceral and liver fat accumulation, and the development of hyperinsulinemia and hyperleptinemia. Tea catechins also increased the mRNA expression of acyl-CoA oxidase (ACO) and medium-chain acyl-CoA dehydrogenase and increased β-oxidation activity in the liver, suggesting that catechin-mediated stimulation of hepatic lipolysis is responsible for its anti-obesity effects [24].

When mice were maintained on either a control diet (CD) or HFD for 16 weeks and supplemented with either water or decaffeinated GTE (50 mg/kg/day), the weight gain in the CD+GTE group was lower than that in the CD+water group. From the eighth week, the weight gain in the HFD+water group was higher than that in the CD group, and the weight gain in the HFD+GTE group was lower than that in the HFD+water group. The HFD+GTE group showed higher adiponectin levels and increased protein expression of AdipoR2, SIRT1, pLKB1, and pAMPK than the HFD+water group, which may explain the reduced expression

of *ACC, FASN, SREBP-1*, and *carbohydrate-responsive-element-binding protein* (*ChREBP*) genes. These results suggest the involvement of AMPK activation via LKB1 in the mechanism of action of decaffeinated GTE [25].

In a drug-induced rat model of MetS, Razavi, et al. showed that intraperitoneal (i.p.) administration of GTE (25, 50, and 100 mg/kg/day for 11 days) significantly decreased body weight gain and average food and water intake, improved the lipid profile and fasting blood glucose levels, and decreased hyperleptinemia and hypertension induced by the drug. The anti-obesity effect of GTE appeared to be related to its lowering effect on leptin [26].

In an experiment using cultured mouse mesenchymal stem cells that differentiate into adipocytes, cells were incubated with varying concentrations of EGCG (1–50 μM) in the presence or absence of adipogenic medium for 9 days. The results demonstrated that EGCG inhibited cell proliferation and migration, prevented differentiation to the adipogenic lineage, and decreased the expression of adipsin, an adipogenic marker gene. These findings demonstrated the anti-adipogenic effects of EGCG, and its potential role in therapeutic intervention for obesity [27].

In a cell-based experiment, Kim, et al. found that EGCG reduced the TG content in adipocytes and increased autophagy. However, unlike the effects of starvation, EGCG did not affect protein kinase A signaling or brown adipocyte marker expression in adipocytes, or inhibit the mammalian target of rapamycin (mTOR) pathway. EGCG did cause AMPK phosphorylation, however, indicating its induction of an energy-depleted state. EGCG also increased the association between lipophagy-related RAB7 and lipid droplets, and the knockdown of *Rab7* attenuated the EGCG-dependent reduction in lipid content. These findings indicate that EGCG upregulated autophagic lipolysis in adipocytes and may be useful as a caloric restriction agent to prevent obesity [28].

When mice were fed CD or HFD supplemented with or without 0.5% polyphenolic GTE for 8 weeks, GTE supplementation was found to reduce HFD-induced adiposity in white adipose tissue (WAT) and brown adipose tissue (BAT), and HF-induced inflammation in WAT. GTE reduced the adipocyte size in WAT and the lipid droplet size in BAT. The results also indicated that browning activation in WAT and whitening reduction in BAT instigated by GTE participated in the improvement of metabolic and inflammatory disorders mediated by GTE in HFD conditions. These findings indicate the potential of GTE for use as a nutritional tool to activate browning and to decrease fat storage in all adipose tissues, leading to the attenuation of obesity [29].

Glutamate dehydrogenase (GDH) senses mitochondrial energy supply and regulates insulin secretion. In an experiment to investigate the interplay between GDH and the cytosolic energy sensing enzyme AMPK, Pournourmohammadi, et al. used EGCG as a possible inhibitor of GDH in isolated islets and myotubes [30]. As a result, EGCG was found to reduce insulin secretion stimulated by glucose. In human islets, EGCG inhibited both basal and nutrient-stimulated insulin secretion. EGCG prevented the decrease in AMPK phosphorylation raised by glutamine/BCH (the allosteric GDH activator). EGCG attenuated the stimulative effect of GDH on insulin-induced 2-deoxyglucose uptake in primary human myotubes. Thus, EGCG may be useful in prevention of obesity by resensitizing insulin-resistant muscle through blunting hyper-secretion of insulin in hypermetabolic states.

Green tea consumption may increase the proportion of favorable intestinal bacteria, such as *Bifidobacterium* species [21]. Henning, et al. demonstrated that supplementation with decaffeinated green tea polyphenols (GTPs) and black tea polyphenols induced weight loss in association with alteration of the microbiota and an increase in hepatic AMPK phosphorylation in diet-induced obese mice, in which GTP and black tea polyphenols diets caused a decrease in cecum *Firmicutes* species and increase in *Bacteroidetes* species [31].

With respect to black tea polyphenols, detailed information is available in the review article by Pan, et al. [32].

Effects of coffee/CGA on obesity

Epidemiological observational studies on coffee/CGA

Several epidemiological studies have indicated the beneficial effects of coffee on obesity. A 1999 population-based health check study among 1,902 Japanese people aged over 40 years found that the majority of MetS components, including waist circumference, were inversely related to coffee consumption but not to green tea consumption, after adjusting for confounding factors, with statistical significance [14]. In a cross-sectional study on 137 patients with non-alcoholic fatty liver disease (NAFLD) and 108 controls, Catalano, et al. found that coffee consumption was inversely associated with obesity and insulin resistance [33].

A cross-sectional population-based survey among 8,821 Polish adults found that high coffee drinkers had lower BMI, waist circumference, systolic and diastolic blood pressure, and TGs, and higher HDL-cholesterol (HDL-C) than those drinking less than 1 cup/day. After adjusting for confounding factors, coffee consumption was inversely associated with MetS risk (OR: 0.75, 95% CI: 0.66–0.86). Among the specific components of MetS, high coffee consumption was associated with lower waist circumference, hypertension risk, and TG level [15].

A Mendelian randomization study in 93,179 individuals from large general population cohorts found that high coffee intake was associated with low risk of obesity, MetS, and type 2 diabetes. Higher coffee intake of up to 4 cups/day was associated with a lower risk of obesity, with ORs of 0.82, 0.86, 0.86, 0.83, 0.95, and 1.02 for 0.1–1, 1.1–2, 2.1–3, 3.1–4, 4.1–5, and > 5 cups/day, respectively, as compared with non-coffee drinkers [34].

These findings indicate a beneficial effect of coffee consumption. However, an epidemiological study in 17,953 Korean adults, aged 19–65 years, found that after multivariable adjustment, the ORs of those who consumed coffee ≥ 3 times/day relative to those who consumed coffee < 1 time/week were 1.37 (95% CI: 1.15-1.63) for obesity, 1.33 (1.11-1.59) for abdominal obesity, 1.28 (1.09-1.51) for hypo-HDL cholesterolemia, and 1.37

(1.10–1.72) for MetS. Instant coffee drinkers, however, were observed to have elevated risks of these metabolic conditions [35].

Clinical studies on coffee/CGA

Several clinical studies have reported the effects of coffee or CGA on obesity. A systematic review and meta-analysis of randomized clinical trials found a significant reduction (mean difference: −2.47 kg; 95% CI: −4.23, −0.72) in body weight in a green coffee extract (GCE)-treated group compared with a placebo group. However, the magnitude of the effect was moderate, and there was significant heterogeneity among the studies [36]. In a randomized, double-blind, 12-week intervention study in 30 overweight people, Thom found that the average loss in body weight among subjects who consumed CGA-enriched coffee was 5.4 kg, while in the normal instant coffee group, the average loss was 1.7 kg [37].

Ohnaka, et al. conducted a randomized clinical trial in which overweight men with a mild-to-moderate elevation of fasting plasma glucose were randomly allocated to a 16-week intervention. The participants consumed 5 cups of caffeinated or decaffeinated instant coffee per day, or no coffee. The results showed that waist circumference decreased by 1.5 cm in the caffeinated coffee group, increased by 1.3 cm in the decaffeinated coffee group, and decreased by 0.6 cm in the non-coffee group. Body weight changes from baseline were -1.1 kg in the caffeinated coffee group, 0.5 kg in the decaffeinated coffee group, and −0.6 kg in the non-coffee group. The authors proposed that caffeine was responsible for the decrease in waist circumference and body weight in the caffeinated coffee group, in view of its role in thermogenesis and fat oxidation [38].

These findings support the beneficial effects of coffee/CGA on body weight reduction. However, in a placebo-controlled, double-blind, crossover intervention study in 18 healthy male subjects, the consumption of 185 mL per day of a test beverage with or without CGA (329 mg) for 4 weeks showed no differences in body weight, BMI, or body fat [39]. Thus, further studies are required to confirm the beneficial effects of coffee and CGA in obesity.

Laboratory studies and mechanism of CGA action

Several laboratory studies have provided evidence for the anti-obesity effect of coffee and its mechanism of action. Hsu, et al. found that the addition of coffee phenols to culture medium decreased the growth of 3T3-L1 preadipocytes. The IC50 value of CGA was 72.3 μM. Treatment of preadipocytes with CGA caused cell cycle arrest in the G1 phase. These findings suggest that coffee phenols exert anti-obesity effects [40].

Murase, et al. showed that coffee polyphenols (CPP) suppressed diet-induced body fat accumulation by downregulating sterol regulatory element-binding protein (SREBP-1c) and related molecules in C57BL/6J mice. When mice were fed a control diet, HFD, or HFD supplemented with 0.5%–1.0% CPP for 2-15 weeks, CPP supplementation reduced body weight gain and fat accumulation in abdominal and liver tissues. The mRNA levels of SREBP-1c, ACCs, stearoyl-CoA desaturase-1, and pyruvate dehydrogenase kinase-4 in the liver were lower in CPP-fed mice than in HFD-fed and control mice. Experiments in cultured cells identified CGA and dicaffeoyl quinic acids as active substances of CPP associated with its beneficial effects. CPP and CGA decreased the nuclear active form of SREBP-1, ACC activity, and cellular malonyl-CoA levels. These findings indicate that CPP/CGA can enhance energy metabolism and reduce lipogenesis by down regulating SREBP-1c and related molecules, leading to the suppression of body fat accumulation [41].

When HFD-induced obese mice were supplemented with CGA or caffeic acid at a dose of 0.02% (wt/wt), both CGA and caffeic acid lowered body weight, visceral fat mass, and plasma leptin and insulin levels compared with a high-fat control group. Reductions in TG (in plasma, liver, and heart) and cholesterol (in plasma, adipose tissue, and heart) concentrations were also observed. TG content in adipose tissue was significantly lowered, whereas plasma adiponectin levels were elevated by CGA supplementation compared with the high-fat control group. CGA and caffeic acid inhibited the activity of fatty acid synthase (FASN), hydroxy-3-methylglutaryl CoA reductase (HMGCR), and acyl-CoA:cholesterol acyltransferase, and increased fatty acid β-oxidation activity and peroxisome proliferator-activated receptors-α (PPAR-α) expression in the liver compared with the HFD group. CGA appeared to exert a more potent effect on body weight reduction and regulation of lipid metabolism than caffeic acid [42].

In Sprague-Dawley rats fed HFD, CGA suppressed HFD-induced increases in body weight and visceral fat-pad weight, serum lipid levels, and serum and hepatic free fatty acid (FFA) levels. CGA altered the mRNA expression of the transcription factors *PPARα* and *liver X receptor α (LXRα)*, as well as target genes involved in hepatic fatty acid uptake, β-oxidation, fatty acid synthesis, and cholesterol synthesis [43].

Ma, et al. conducted two sets of animal experiments. In one experiment, 6-week old C57BL/6 mice were fed a regular chow or HFD for 15 weeks with i.p. injection of CGA (100 mg/kg) or vehicle twice per week, and in another, obese mice were treated with CGA (100 mg/kg, i.p., twice weekly) or vehicle for 6 weeks. The results showed that CGA prevented the development of diet-induced obesity but did not affect body weight in obese mice. CGA also prevented HFD-induced hepatic steatosis and insulin resistance, suppressed the hepatic expression of *PPAR-γ, Cd36, Fabp4,* and *Mgat1* genes, and attenuated inflammation in the liver and WAT, accompanied by a decrease in the mRNA levels of macrophage marker genes including *F4/80, Cd68, Cd11b, Cd11c, TNF-α, monocyte chemoattractant-1 (Mcp-1), and Ccr-2*, encoding inflammatory proteins. These findings provide direct evidence in support of CGA as a potent compound for the prevention of diet-induced obesity and obesity-related MetS [44].

When hyperlipidemia was induced in Wistar rats using HFD, administration of a CGA complex derived from green coffee beans, CGA7 (50, 100, and 150 mg/kg body weight), resulted in decreased TGs and FFA levels in plasma and liver compared with the control group. CGA7 administration also led to the activation

of AMPK and the subsequent increase in the levels of carnitine palmitoyltransferase-1, and decreased ACC activity. These results suggest that CGA7 may represent a suitable active ingredient in nutrition for obesity management [45].

Maki, et al. found that coffee intake significantly suppressed HFD-induced metabolic changes such as increased body weight and the accumulation of adipose tissue, and the upregulation of glucose, FFA, TC, and insulin levels in the blood. In the early phase of adipogenesis, 3T3-L1 cells treated with coffee extract displayed delayed cell cycle entry into the G2/M phase, termed mitotic clonal expansion. Coffee extract also inhibited the activation of CCAAT/enhancer-binding protein β (C/EBP-β) by preventing its phosphorylation by extracellular signal-regulated kinase (ERK), and suppressed adipogenesis-related events such as mitotic clonal expansion and C/EBP-β activation through the downregulation of insulin receptor substrate-1 (IRS-1). The stability of the IRS-1 protein was markedly decreased by treatment with coffee extract due to proteasomal degradation. These results demonstrated an anti-adipogenic function for coffee intake, and identified IRS1 as a novel target for coffee extract in adipogenesis [46].

Santana-Galvez, et al. proposed a potential mechanism of action for CGA, whereby it may act as an anti-oxidant to reduce ROS, which stimulates inflammation leading to fat accumulation, weight gain, and insulin resistance [47]. The anti-oxidative activity of CGA may also stimulate nitric oxide (NO) production, leading to an improvement in endothelial function and blood pressure. CGA may also improve lipid metabolism by down regulating transcriptional factors such as LXRα and PPAR-γ and the gene expression of *FASN, ACC*, and *HMGCR*, and by up-regulating PPAR-α, adiponectin, and AMPK phosphorylation [47].

Although these results support the favorable effects of coffee and/or its extracts in obesity, other studies failed to show such effects. For example, Cheong, et al. carried out a study in three groups of C57BL/ mice: (i) normal diet, (ii) HFD, and (iii) HFD supplemented with 0.5% w/w GCE rich in CGA. The results showed that groups (ii) and (iii) displayed MetS symptoms more profoundly than group (i), and that GCE did not attenuate HFD-induced obesity, glucose intolerance, insulin resistance, or systemic oxidative stress [48].

Tsumura-Suzuki obese diabetic mice are a newly developed MetS model that spontaneously exhibits obesity, diabetes, hyperlipidemia, and non-alcoholic steatohepatitis with liver nodules. Experimental results showed that coffee supplementation did not affect obesity or hyperlipidemia in these mice [49].

Anti-obesity effects of curcumin

Epidemiological observational studies on curcumin

No comprehensive epidemiological studies have been reported to date showing the effect of curcumin on obesity. Future studies may reveal beneficial effects in obesity and other diseases, however, particularly in Asian populations with high levels of curcumin consumption.

Clinical studies on curcumin

Multiple clinical studies have reported the health benefits of curcumin consumption. In a randomized, controlled clinical study in MetS patients with BMI between 25.0 and 29.9, among forty four subjects that showed a < 2% weight loss after 30 days of diet, twenty two patients were treated for further 30 days with curcumin (in the form of an enteric-coated nutritional supplement containing 800 mg/dose/day of *Curcuma longa* extract [95% curcumin]) complexed with sunflower phospholipids and blended with 8 mg/dose/day of piperine, while the other twenty two patients received vehicle. The results indicated that curcumin administration increased weight loss from 1.88% to 4.91%, enhanced the percentage reduction of body fat (from 0.70% to 8.43%), increased waistline reduction (from 2.36% to 4.14%), improved hip circumference reduction (from 0.74% to 2.51%), and enhanced the reduction of BMI (from 2.10% to 6.43%) with statistical significance. The phospholipids vehicle alone did not exert any significant effect [50].

Disilvestro, et al. conducted an intervention study in healthy middle-aged people (40–60 years old) using a low dose of curcumin (80 mg/day) in a lipidated form expected to have high absorption. Thirty-eight subjects were given either curcumin or placebo for 4 weeks. The results indicated that curcumin significantly lowered plasma TG values, salivary amylase levels, plasma β-amyloid protein concentrations, plasma soluble intercellular adhesion molecule readings, and plasma alanine aminotransferase (ALT) activity. Furthermore, curcumin increased plasma myeloperoxidase without increasing C-reactive protein (CRP) level, salivary radical scavenging capacity, plasma catalase activity, or plasma NO level. These findings demonstrate that curcumin can produce a variety of potentially health-promoting effects in healthy middle-aged individuals [51].

Kunnumakkara, et al. found that curcumin was effective in reducing the symptoms of anxiety and depression associated with obesity [7]. Curcumin has also been found to modulate circulating levels of IL-1β, IL-4, and vascular endothelial growth factor (VEGF), exhibiting an immunomodulatory effect and suppressive effect on oxidative stress in obese patients [7]. Mohammadi, et al. investigated the effect of curcuminoid supplementation in 30 obese individuals for 30 days, and observed a significant reduction in serum TGs [52].

In a recent meta-analysis of seven randomized trials of turmeric/curcumin in patients at risk of cardiovascular disease (CVD), Qin, et al. found some beneficial health effects and a significant improvement in serum TG and LDL-C levels. As examples, three of the studies included in the analysis are described here. Rhamani, et al. found that in a randomized, double-blind, placebo-controlled trial in patients with NAFLD, supplementation with an amorphous dispersion curcumin formulation (equivalent to 70 mg curcumin) for 8 weeks was associated with a significant reduction in liver fat compared with the placebo control. There were also significant reductions in BMI and serum levels of TC, LDL, TG, ALT, aspartate aminotransferase (AST), glucose, and glycated hemoglobin compared with the

placebo group [53]. In a double-blind, randomized clinical trial in male patients with MetS who consumed turmeric (2.4 g/day), improvements were observed in BMI, waist circumference, and body-fat percentage compared with baseline at 4 weeks, and turmeric consumption reduced LDL-C and CRP levels at 8 weeks [54].

Usharani, et al. conducted a randomized, placebo-controlled, 8-week study in 72 patients with type 2 diabetes, in which patients received NCB-02 (a standardized preparation of curcuminoids). The results showed that, compared with baseline, there was a significant improvement in endothelial function after treatment with NCB-02 (-2.69 ± -3.02% versus -8.19 ± 5.73%, respectively). Similarly, patients who received NCB-02 showed significant reductions in the levels of malondialdehyde, ET-1, IL-6, and TNF-α. Thus, curcumin had a favorable effect on endothelial dysfunction in association with reductions in pro-inflammatory cytokines and markers of oxidative stress [55].

Dyslipidemia is a leading risk factor for CVD and a common feature of obesity. In a randomized, double-blind, placebo-controlled, crossover trial in 30 participants, curcumin supplementation (1 g/day for 30 days) reduced serum TG levels significantly, without affecting other parameters, including BMI and body fat [52]. A similar clinical study in 30 obese individuals found that curcuminoid supplementation was associated with a significant decrease in the serum pro-oxidant/antioxidant balance. However, no significant change was observed in serum concentrations of Hsp27 or oxidized LDL. These findings suggest that supplementation with oral curcuminoids (1g/day) can effectively reduce oxidative stress burden [56].

In a clinical trial in 33 patients with coronary artery disease, patients were randomly assigned to receive curcumin or placebo (500 mg capsules) four times daily for 8 weeks. Serum TG levels significantly decreased in the curcumin group (2.7%), but decreased in the placebo group only to a non-significant extent (2.35%). However, no significant differences were found in other laboratory parameters examined between the curcumin and placebo groups. Therefore, curcumin did not show an appreciable effect on markers of inflammation in patients with coronary artery disease [57].

A systematic review of seven randomized trials of turmeric and curcumin in patients at risk of CVD identified evidence of their beneficial effects on serum TG and LDL-C levels, although no significant difference was found with respect to serum HDL-C levels. When the analysis was restricted to more homogenous studies based on the subjects underlying disease, a beneficial effect of turmeric and curcumin on serum TC levels was observed in subjects with MetS [6].

By contrast, results of a 6-month, randomized, double-blind trial in which elderly subjects consumed 4 g/day curcumin, 1g/day curcumin, or placebo showed that the consumption of either dose of curcumin did not significantly affect TG, TC, LDL-C, or HDL-C levels over 1 month or 6 months [58].

A meta-analysis of eight randomized clinical trials found a significant reduction in circulating TNF-α concentrations following curcumin supplementation, suggesting a beneficial effect of curcumin, since TNF-α is a key inflammatory mediator and its reduction is a therapeutic target in several inflammatory diseases [59].

Laboratory studies and mechanism of action of curcumin

Several cellular and animal experiments have shown the beneficial effects of curcumin on obesity [2]. For example, in a study in which C57BL/6J mice received low-fat diet or HFD with or without curcumin for 28 weeks, curcumin significantly attenuated the effect of HFD on glucose disposal, body weight gain, and the development of insulin resistance. Curcumin also inhibited the expression of lipogenic genes, including *NF-κB, SRBP-1c, ChREBP* and *LPK* in the liver, and blocked the effects of HFD on macrophage infiltration and the inflammatory pathway in adipose tissue [60].

Weisberg, et al. found that dietary curcumin ameliorated diabetes in HFD-induced obese and ob/ob male C57BL/6J mice and also reduced body weight gain and macrophage infiltration in WAT, increased adipose tissue adiponectin production, and decreased hepatic NF-κB activity, hepatomegaly, and markers of hepatic inflammation [61]. In obesity, dietary curcumin was shown to improve glycemia in HFD-induced diabetic C57BL/6J and ob/ob mice, and to increase adiponectin and decrease hepatic NF-κB activity and markers of hepatic inflammation [61].

Obesity is an adverse effect of olanzapine, an atypical antipsychotic drug used for the treatment of schizophrenia and bipolar disorder. Curcumin has been shown to cause a significant reduction in olanzapine-induced body weight gain and to improve locomotor effects in Sprague-Dawley rats [62].

Several studies have shown the ability of curcumin to inhibit the expression of obesity-related proteins such as Wnt/β-catenin and MAPK. For example, Ahn, et al. found that in 3T3-L1 cells, curcumin inhibited the mRNA expression of AP2 (a mature adipocyte marker) and increased the mRNA expression of Wnt10b, Fz2 (Wnt direct receptor), and LRP5 (Wnt co-receptor). Curcumin also increased the mRNA levels of c-Myc and cyclin D1, well-known Wnt targets, and inhibited mitogen-activated protein kinase (MAPK) phosphorylation associated with the differentiation of 3T3-L1 cells into adipocytes. These findings suggest that the Wnt signaling pathway participates in curcumin-induced suppression of adipogenesis in 3T3-L1 cells [63].

Ejaz, et al. reported that mice fed HFD supplemented with curcumin showed a reduction in body weight gain, adiposity, and microvessel density in adipose tissue, which coincided with the reduced expression of VEGF and its receptor VEGFR-2. Curcumin also increased AMPK phosphorylation, reduced glycerol-3-phosphate acyl transferase-1, and increased carnitine palmitoyltransferase-1 expression, which led to increased oxidation and decreased fatty acid esterification [64]. In accordance with these findings, Kim, et al. showed that curcumin activated AMPK and suppressed hepatic glucogenic

gene expression, effects which might explain some of the glucose-lowering effects of curcumin [65]. Tian et al. showed that curcumin attenuated miR-17-5p expression and stimulated *Tcf*712 expression in 3T3-L1 cells, and suggested that *Tcf*712 is a target of miR-17-5p; the repressive effect of Tcf712 on adipogenic differentiation was subsequently confirmed in 3T3-L1 cells [66].

Hypoxia in adipose tissue is a major cause of inflammation and insulin resistance in obesity. In 3T3-L1 adipocytes, hypoxia increased the secretion of MCP-1 and leptin and reduced adiponectin, while mRNA levels of resistin and toll-like receptor-4 (TLR-4) were upregulated. Increased serine phosphorylation of IRS-1 and decreased expression of IRS-2 in the hypoxic group were observed. Curcumin protected adipocytes from hypoxia-induced inflammation and insulin resistance by reducing inflammatory adipokine, NF-κB/c-jun N-terminal kinase (JNK), and serine phosphorylation of IRS-1 receptors, and by improving adiponectin secretion [67].

A comprehensive review article by Kunnumakkara, et al. enumerated the molecular targets of curcumin, including transcription factors, inflammatory mediators, protein kinases, and enzymes such as protein reductases and histone acetyl transferase, growth factors, receptors, adhesion molecules, and apoptotic regulators [7]. Curcumin may exert its manifold effects via epigenetic regulation, of which the major targets are nuclear factor-related factor-2 (Nrf2), β-catenin, NF-κB, p38 MAPK, cyclooxygenase (COX)-2, FOXO3, inducible NOS, ROS, cyclin D1, VEGF, glutathione, TNF-α, and ERK. Although not described in their review, it is important to note that curcumin can also activate AMPK [68].

Martin, et al. reported similarities between caloric restriction and epigenetic diets, such as those containing curcumin, EGCG, or RSV, a claim supported by the following findings [69]. In an experiment on ob/ob male C57BL/6J mice, diets containing curcumin caused a significant decrease in WAT, hepatomegaly, hepatic NF-κB activity, and markers of hepatic inflammation, while simultaneously increasing adipose tissue adiponectin production, leading to the reversal of several symptoms commonly associated with obesity. These findings were consistent with a study on the effects of caloric restriction in ten patients with a BMI greater than 30; within two weeks of initiation of the diet, levels of the anti-oxidant uric acid increased significantly, while pro-inflammatory cytokine TNF-α and brain-derived neurotropic factor decreased. The results are also consistent with the observation, in a study with almost 500 obese female participants, that caloric restriction, weight loss, and exercise all significantly decreased the levels of inflammatory biomarkers such as high-sensitivity CRP, serum amyloid A, and IL-6, and leukocyte and neutrophil counts. A literature search indicated that curcumin inhibits histone deacetylase, histone acetyltransferase, and DNA methyltransferase activities; amyloid β production; and the expression of TNF-α and IL-1β, while curcumin induces ROS [69].

Wang, et al. reviewed and summarized the effects of curcumin on obesity, and found that it could downregulate or inactivate transcription factors, enzymes, cytokines, and other components of signaling pathways [2]. These included C/EBP-α, PPAR-γ, SREBP-1c, FASN, MAPK, ACC, glycerol-3-phosphate acyl transferase-1, NF-κB, IL-2, IL-6, TNF-α, COX-2, JNK, ERK1/2, NO, MCP-1, VEGF, VEGFR-2 SREBP-1c, ChREBP, LPK, and TGF-β. The study also showed that curcumin upregulates or activates LXR-α, ABCA1, CPT-1, AMPK, ACC, NrF2, SIRT1, HSP70, HSP90, FOXO1α, IL-4, and adiponectin.

Anti-obesity effects of quercetin

Epidemiological observational studies on quercetin

Few epidemiological studies have reported on the effect of quercetin on obesity. A cohort study among 5,133 Finnish men and women aged 30-69 years with no history of heart disease at baseline found that the relative risks between the highest and lowest quarters of flavonoid intake adjusted for age, smoking, serum cholesterol concentration, blood pressure, and BMI were 0.69 (95% CI: 0.53-0.90) and 0.54 (95% CI: 0.3-0.87) for total and coronary mortality, respectively [70]. The relative risks for coronary mortality between the highest and lowest quarters of apple intake were 0.57 (95% CI: 0.36-0.91) and 0.81 (95% CI: 0.61-1.09) for women and men, respectively. The corresponding values for onions were 0.50 (95% CI: 0.30-0.82) and 0.74 (95% CI: 0.53-1.02), respectively. However, no association was found between flavonoid intake and BMI [70].

Clinical studies on quercetin

Several human intervention studies have demonstrated the favorable effects of quercetin on obesity. For example, a double-blind crossover study in 49 healthy male subjects with different apolipoprotein E (ApoE) genotype variants found that daily consumption of 150 mg quercetin for 8 weeks significantly decreased waist circumference and postprandial systolic blood pressure compared with the placebo group. Quercetin also caused a significant decrease in postprandial TG concentrations and increase in HDL-C concentrations. Of note, quercetin also caused a moderate but significant increase in TNF-α level, a finding that conflicts with the outcomes of several other studies [71].

In a 12-week, randomized, double-blind, placebo-controlled study in overweight and obese Korean subjects, participants received either placebo or onion peel extract capsules containing 100 mg of quercetin per day. Quercetin-rich onion peel extract supplementation significantly reduced body weight and percentage of body fat as well as the levels of blood glucose and leptin, indicating a beneficial role of quercetin in obesity [72].

In a double-blinded, placebo-controlled cross-over trial in 93 overweight or obese subjects aged 25-65 years with MetS traits, the consumption of 150 mg quercetin/day resulted in an increase in mean fasting plasma quercetin concentrations from 71 to 269 nmol/L. Compared with placebo, quercetin decreased systolic blood pressure, serum concentrations of HDL-C, and plasma concentrations of atherogenic oxidized LDL, while TC, TGs, LDL:HDL-C and TG:HDL-C ratios, TNF-α, and CRP were unaltered. These findings provide evidence that quercetin has a protective effect against CVD in obese patients [73].

However, several studies have failed to demonstrate the anti-obesity effects of quercetin. In a 12-week, double-blinded study to investigate the effect of quercetin on disease risk factors in 1,002 adults varying widely in age and BMI, the consumption of supplements (500 mg quercetin, 125 mg vitamin C, and 5 mg niacin; or 1,000 mg quercetin, 250 mg vitamin C, and 10 mg niacin) had a negligible influence on disease risk factors such as inflammatory markers, blood pressure, and blood lipid profiles [74]. Similarly, high-dose quercetin supplementation (500 or 1,000 mg/day) for 12 weeks in a large, heterogeneous group of adults did not affect body mass or composition [75].

A placebo-controlled, crossover trial on 93 overweight–obese subjects (aged 25–65 years) with MetS in relation to apoE genotype found that the daily consumption of 150 mg quercetin did not affect body weight, waist circumference, fat mass, fat-free mass, or serum CRP levels, although different effects depending on apoE phenotype were observed in systolic blood pressure, HDL-C levels, and LDL-C:HDL-C ratio [76].

Laboratory studies and action mechanism of quercetin

An in vitro experiment showed that the exposure of 3T3-L1 preadipocytes to quercetin attenuated adipogenesis and decreased the expression of adipogenesis-related factors and enzymes. Quercetin exposure upregulated the levels of pAMPK and its substrate ACC. Treatment of 3T3-L1 adipocytes with quercetin induced apoptosis and concomitantly decreased ERK and JNK phosphorylation. These findings indicate that quercetin exerts anti-adipogenesis activity by activating the AMPK signaling pathway in 3T3-L1 preadipocytes, while the quercetin-induced apoptosis of mature adipocytes was mediated by modulation of the ERK and JNK pathways [77].

Jung, et al. found that quercetin supplementation in mice reduced HFD-induced gains in body weight, liver weight, and WAT weight compared with mice fed HFD only, and also reduced HFD-induced increases in serum lipids including cholesterol, TGs, and thiobarbituric acid-reactive substance. Quercetin supplementation also altered the expression profiles of several lipid metabolism-related genes, including *Fnta, Pon1, Pparg, Aldh1b1, Apoa4, Abcg5, Gpam, Acaca, Cd36, Fdft1* and *FASN*, relative to the expression in control mice, suggesting that the anti-obesity effects of quercetin may be related to the regulation of lipogenesis at the transcription level [78].

In streptozotocin-induced diabetic rats that exhibited increases in indexes such as blood glucose, kidney weight and body weight, urine albumin excretion, serum creatinine, blood urea nitrogen, and creatinine clearance compared with a control group, quercetin treatment improved all these parameters, except for blood glucose. Quercetin also attenuated the over-expression of TGF-β1 and connective tissue growth factor in the renal tissues of diabetic rats [79].

In a review article, Nabavi, et al. summarized the possible mechanisms by which quercetin may exert an anti-obesity effect. These included 1) suppression of the expression of genes including PPAR-γ, a transcription factor that regulates HFD-induced fat accumulation in the liver; 2) increased plasma adiponectin concentration, reduction of plasma nitrate and nitrite levels, and enhancement of visceral adipose tissue endothelial NO synthase expression; 3) upregulation of the expression of Nrf2 and heme oxygenase-1; 4) suppression of NF-κB activation and ERK1/2 phosphorylation, leading to anti-inflammatory effects in adipose tissue; 5) suppression of the expression of inflammatory genes, such as those coding for TNF-α, IL-6, IL-8, IL-1β, interferon-γ inducible protein-10, and COX-2; 6) serine phosphorylation of IRIS-1 and protein tyrosine phosphatase-1B gene expression; 7) enhancement of AMPK catalytic subunit phosphorylation and expression of its positive regulator SIRT1, which is related to the attenuation of adipogenesis and decreased expression of adipogenesis-related factors; 8) direct binding to the glucose transporter GLUT4 and GLUT2 to inhibit glucose-uptake; and 9) scavenging of ROS [80].

Leiherer, et al. demonstrated that quercetin decreased gene expression of the adipokines ANGPTL4, adipsin, and PAI-1 as well as of the glycolysis-associated enzymes ENO2, PFKP, and PFKFB4 in human SGBS adipocytes. The fasting-induced adipose factor ANGPTL4, produced predominantly in adipose tissue, is a target of PPAR and is inhibited by AMPK activation. PAI-1 is also a target of PPAR. The ability of quercetin to activate AMPK, thus leading to decreased PPAR expression, might explain the observed decrease in expression of ANGPTL4 and PAI-1. *ENO2, PFKP*, and *PFKFB4* genes are HIF-1-dependent, and the anti-oxidant property of quercetin, which could decrease the expression of HIF-1, might explain the reduced expression of these genes [81].

In a review article, Chen et al. discussed several effects of quercetin on obesity and related diseases [82]. Based on the finding that obese adults have altered circulating levels of inflammatory cytokines such as IL-1β, IL-6, TNF-α, and CRP, the authors claimed that quercetin's anti-inflammatory effects may lead to the prevention of obesity, and cited literature providing key findings as follows. Quercetin inhibited the *in vitro* production of COX and lipoxygenase enzymes, which are typically induced by inflammation. Quercetin also suppressed the expression of *IL-6, IL-8, IL-1β* and *TNF-α* in cultured orbital tissues derived from Graves' orbitopathy samples compared with untreated control tissue. Quercetin at 10 μM downregulated the production of COX-2, NF-κB, and NO by fibroblasts, and at 50 and 100 μM, reduced the secretion of IL-6 and TNF-α in LPS-stimulated RAW 264.7 macrophages. Quercetin blocked TNF-α secretion in macrophages most efficiently at the concentrations of 25 and 50 μM, and stimulated the anti-inflammatory cytokine IL-10 at concentrations < 50 μM. At 25 μM, quercetin blocked IL-1β, IL-6, IFN-γ, and TNF-α secretion in human whole blood induced by LPS. Furthermore, by inhibiting NF-κB activation, quercetin at < 10 μM inhibited the production of NO, IL-6, MCP-1, TNF-α, iNOS, and COX-2 in RAW 264.7 cells. A 6-week regiment of 150 mg of quercetin taken daily by human subjects significantly lowered TNF-α serum concentrations. Quercetin has also been shown to reduce pancreatic histopathological damage and lower the mRNA and protein level of NF-κB, IL-1β, IL-6, and TNF-α in rats [10].

Given the potent anti-oxidant activity of quercetin, which

potentially enables it to quench free radicals, its basic mechanism of action appears to be related to the modulation of ROS signaling [10] (Table 1).

Anti-obesity effects of RSV

Epidemiological observational studies on RSV

Difficulties in accurately estimating RSV exposure may have contributed to the dearth of cohort studies on its effects [83]. Among the studies that have been reported, 24-hour urinary RSV has been shown to be an effective biomarker of both RSV and wine intake. Moderate wine consumption has been shown to reduce CVD risk, an observation that has been dubbed the 'French paradox' and proposed to be attributable to alcohol and polyphenolic compounds such as RSV [84]. A large cross-sectional study among 1,000 participants in Spain found that high levels of total urinary RSV metabolites were associated with improvements in HDL and TG plasma concentrations and heart rate, suggesting that RSV intake may help decrease the risk of CVD and related diseases [85]. In a population-based cohort study, Siedlinski, et al. found that RSV intake was associated with higher forced vital capacity levels, but that SIRT1 single-nucleotide polymorphisms were not significantly associated with level or course of lung function via wine or RSV intake [86].

Table 1: Modulatory effects of EGCG, CGA, curcumin, quercetin, and RSV on ROS, AMPK, and NF-κB

Polyphenols	ROS	AMPK	ROS	NF-κB
	Stimulation/upregulation	Stimulation/upregulation	Suppression/downregulation	Suppression/downregulation
EGCG	Kim, et al. [28]	Yang, et al. [21]	Yang, et al. [95]	Hayakawa, et al. [99]
	Yang, et al. [95]	Kim, et al. [28]	Hayakawa, et al. [99]	Ohishi, et al. [100]
	Towler, et al. [98]	Suzuki, et al. [96]	Ohishi, et al. [100]	Liu, et al. [109]
CGA	Rakshit, et al. [110]	Sudeep, et al. [45]	Santana-Gálvez et al. [47]	Shan et al. [116]
	Yang, et al. [111]	Santana-Galvez, et al. [47]	Cha, et al. [114]	Zatorski, et al. [117]
	Hou, et al. [112]	Zhou, et al. [113]	Wang, et al. [115]	Ye, et al. [118]
Curcumin	Martin, et al. [69]	Ejaz, et al. [64]	Wang, et al. [2]	Wang, et al. [2]
	Chang, et al. [119]	Kim, et al. [65]	Kunnumakkara, et al.[7]	Kunnumakkara, et al. [7]
	Gersey, et al. [120]	Pan, et al. [68]	Nabavi, et al. [80]	Shao, et al. [60]
Quercetin	Kim, et al. [121]	Ahn, et al. [77]	D'Andrea, et al. [10]	D'Andrea, et al.[10]
	Kim, et al. [122]	Nabavi, et al. [80]	Nabavi, et al. [80]	Nabavi, et al. [80]
	Kim, et al. [123]	Leiherer, et al. [81]	Bahar, et al. [124]	Chen, et al. [82]
RSV	Hussain, et al. [125]	Wang, et al. [2]	Seidman, et al. [128]	Wang, et al. [2]
	Andre, et al. [126]	Baur, et al. [90]	Mathieu, et al. [129]	Kim, et al. [94]
	Li, et al. [127]	Price, et al. [92]	Mamalis, et al. [130]	Gines, et al. [131]

Clinical studies on RSV

Several clinical studies have examined the potential health benefits of RSV. Following a literature search, Wang, et al. summarized five randomized clinical trials published from 2009 to 2013, among which four reported favorable effects of RSV [2]. These include the downregulation of inflammatory markers such as TNF-α and PAI-1 (3 studies), TGs (1 study), LDL-C (1 study), and NF-κB (1 study); and the upregulation of adiponectin (2 studies), AMPK (1 study), and SIRT1 (1 study). However, one study, conducted by Poulsen et al., showed that the consumption of RSV (500 mg for 28 days) by 24 obese but otherwise healthy males resulted in non-significant changes in markers of obesity such as total body mass, lean body mass, total body fat mass, and visceral and abdominal subcutaneous fat volumes, suggesting that RSV may exert different effects between humans and other species [87].

A comprehensive review by Wahab, et al. described clinical studies on the effects of RSV, including 17 studies in patients with chronic diseases and 21 studies in healthy subjects who had been supplemented with RSV but no other medicine [88]. The findings confirmed the beneficial actions of RSV, including the downregulation of inflammatory cytokines such as TNF-α; reduction in body weight, BMI, fat weight, LDL-C levels, and adipocyte size; and elevation of adiponectin levels and adipose tissue lipolysis. The authors also described the negative findings of Poulsen, et al. as did Wang, et al. [2]. In addition, Wahab, et al. cited a pilot study by Gualdoni, et al. that reported somewhat conflicting results [88]. Ten healthy volunteers who had consumed 5 g RSV showed a significant increase in TNF-α levels 24 hours after treatment compared with baseline. Studies in human peripheral blood mononuclear cells or isolated monocytes confirmed the potentiation by RSV of TNF-α production by different TLR agonists. Moreover, significant increases in NF-κB activity and phosphorylation of p105, indicative of alternative NF-κB pathway activation, were observed [89].

Laboratory studies and mechanism of action of RSV

A notable study is that reported by Baur, et al. who showed that RSV shifted the physiology of middle-aged mice on a high-

calorie diet toward that of mice on a standard diet, and also increased their survival [90]. RSV increased AMPK and PGC-1α activities, increased mitochondrial number, and improved motor function. DNA microarray and pathway analysis revealed that RSV countered the effects of the high-calorie diet in 144 out of 153 significantly altered signaling pathways. Although this experiment demonstrated the enhancement of SIRT1 enzymatic activity by RSV without altering its gene expression, a subsequent study showed that RSV restored its mRNA levels that were decreased following hemorrhagic shock in the rat kidney to the levels of those in a sham group [91].

Price, et al. reported different dose-dependent activities of RSV on AMPK and SIRT1. Mice treated with a moderate dose of RSV showed AMPK activation and increased mitochondrial biogenesis and function in skeletal muscle, whereas SIRT1 knockout mice displayed none of these effects. A mouse model over expressing SIRT1 mimicked these effects, demonstrating the requirement of SIRT1 for AMPK activation. In contrast, a high dose of RSV activated AMPK in a SIRT1-independent manner, demonstrating that RSV dosage is a critical factor [92]. These findings indicate that RSV exerts dose-dependent effects on AMPK and SIRT1 signaling pathways.

In a literature review, Wang, et al. examined 14 cell-based studies and 12 animal studies that had examined the effects of RSV on obesity [2]. Most of the cell-based experiments used 3T3-L1 pre-adipocytes, which can be differentiated to adipocytes. The results of these studies demonstrated that RSV caused increased levels of adiponectin; upregulation of AMPK, SIRT1, and SIRT3; reduction of TG levels and lipid accumulation; downregulation of FASN and PPAR-γ; amelioration of drug-induced increases in TNF-α production; and NF-κB activation. The review also cited a study showing that RSV reduced the phosphorylation of AMPK, a finding in contrast to that of other studies. The results of the animal experiments supported several anti-obesity effects of RSV. For example, in one study, male rats were randomized into three groups: a control group given free access to regular dry rat chow, a steatosis group, and an RSV (10 mg/day) group given free access to a high carbohydrate, fat-free modified diet. The results showed that body weight and fat deposition were decreased in the RSV group compared with the steatosis group, and that increased levels of SOD, glutathione peroxidase, and catalase and decreased levels of NOS were observed in the livers of rats in the RSV group. Thus, RSV decreased the severity of NAFLD in rats through a mechanism of action that involved the inhibition of TNF-α and anti-oxidant activities [93]. The authors also described three studies showing the upregulation of AMPK and PGC-1α by RSV, and two studies reporting its ability to reduce oxidative stress.

An animal experiment conducted by Kim et al. found that, compared with HFD-fed mice, mice fed a diet supplemented with 0.4% RSV showed decreased body weight gain (-48%), visceral fat-pad weight (-58%), and plasma levels of TGs, FFA, TC, glucose, TNF-α, and MCP1. RSV also reversed the HFD-induced upregulation of galanin-mediated signaling molecules (GalR1/2, PKCδ, Cyc-D, E2F1, and ERK) and key adipogenic genes (*PPARγ-2, C/EBPα, SREBP-1c, FASN, LPL, AP2* and leptin) in epididymal adipose tissues. RSV also attenuated the HFD-induced upregulation of pro-inflammatory cytokines (TNF-α, IFN-α, IFN-β, and IL-6) and their upstream signaling molecules (TLR2/4, MyD88, Tirap, TRIF, TRAF6, IRF5, p-IRF3, and NF-κB) in adipose tissue [94].

From findings in cell-based, animal, and human experiments, Wahab, et al. discussed the mechanism of action of RSV [88]. High doses of RSV (≥ 1,000 mg/day) may inhibit cytochrome P450 isoenzymes such as CYP3A4, CYP2C9, and CYP2D6, and the induction of CYP1A2 may lead to interactions with a number of other drugs, a potentially adverse effect of RSV supplementation in patients receiving concomitant medication. These authors also listed molecular targets of RSV retrieved through the STITCH 5.0 database. These include SIRT1, estrogen receptor-1, PPAR-γ, SIRT5, prostaglandin-endoperoxide synthase-1, AKT1, SIRT3, p53, PTEN (phosphatase and tensin homolog), NAD(P)H dehydrogenase, quinone 2, nicotinamide phosphoribosyltransferase, IGF-1, FOXO3, FOXO1, HO1, PPAR-α, nuclear factor (erythroid-derived 2)-like 2, and cytochrome P450, family 1, subfamily A, polypeptide 1.

These findings support mechanisms of action of RSV such as 1) the inhibition of preadipocyte differentiation and adipocyte proliferation by stimulating adipocyte apoptosis, or the inhibition of lipogenesis and promotion of lipolysis and fatty acid β-oxidation by modulating AMPK, SIRT1, and PGC-1α; 2) the downregulation of PPAR-γ and C/EBPα expression, leading to the activation of AMPK and subsequent downregulation of lipogenic genes including FASN, LPL, SREBP-1c, and ACC; and 3) the reduction of NF-κB activity, leading to the downregulation of TNF-α and the TNF-α-induced release of IL-6, MCP-1, and other inflammatory cytokines [2].

However, some outcomes cannot be explained by these proposed mechanisms, likely due to differences in study design such as the dose of RSV, duration of experiments, passage number of cultured cells, and age of animals. Differences in the results may also be attributable to genetic differences and epigenetic effects of RSV. Martin, et al. reviewed five studies that supported the use of RSV as an epigenetic dietary compound leading to DNA modification [69]. These include studies demonstrating that RSV modulates histone deacetylase and decreases the nuclear level of hTERT.

Discussion

This review has presented several sources of evidence for the health benefits of dietary polyphenols, specifically of EGCG, CGA, curcumin, quercetin, and RSV. Most cell-based and animal experiments to date have described favorable effects of these compounds, and epidemiological cohort and intervention studies have supported these findings. However, some studies have reported conflicting results, possibly because of confounding factors such as the method of quantifying consumption, beverage temperature, cigarette smoking, alcohol consumption, and differences in genetic and environmental factors such as race, sex, age, and lifestyle [95-97]. Intestinal microbiota and genetic polymorphisms may also have influenced the study outcomes

[95, 96]. Therefore, more rigorous human studies are required to establish the anti-obesity effects of polyphenols.

Although several mechanisms of action have been proposed for polyphenols, those involving AMPK and NF-κB are most likely to explain the activities of the five polyphenols discussed in this review. The AMPK system acts as a sensor of cellular energy status and is activated by an increase in the cellular AMP: ATP ratio, caused by metabolic stresses that either interfere with ATP production (eg. deprivation of glucose or oxygen) or accelerate ATP consumption (eg. muscle contraction) [98]. All five polyphenols can activate AMPK, leading to the downregulation or upregulation of various signaling pathways, termed the "AMPK hypothesis" by Yang, et al. [21] (Table 1). This includes the downregulation of adipogenetic and lipogenetic genes such as PPAR-γ, C/EBPα, SREBP, PGC-1 and FASN and the upregulation of lipolysis-related genes such as PPAR-α, NRF-2, LPL and ATGL [21,96,99]. As the involvement of ROS in AMPK activation has been well documented, and that the pro-oxidative properties of these polyphenols have been established, it is possible that polyphenols act as pro-oxidants to activate AMPK, resulting in the modulation of various signaling pathways [99].

NF-κB is another key mediator that is downregulated by the polyphenols discussed in this review, leading to the suppression of pro-inflammatory cytokines such as TNF-α, IL-1β, COX-2, NO, and MMP-9 (Table 1). These polyphenols are known anti-oxidants, and their ROS-scavenging properties can mitigate the ROS-dependent stimulation of the NF-κB signaling pathway [99,100].

At present, the conditions that can direct these polyphenols to function as either pro-oxidants or anti-oxidants remain unclear, although the contribution of polyphenol concentrations and metal ions has been suggested [96,99]. The simplest explanation is that ROS-mediated AMPK activation causes the downregulation of NF-κB and, therefore, that the pro-oxidant properties of polyphenols can explain most of their health-promoting effects [101-103]. In addition, as discussed above, starvation/energy deprivation has been shown to share certain characteristics with the consumption of polyphenols, in that both conditions activate AMPK. This fact might be explained by the capacity of starvation/energy deprivation to enhance intracellular ROS, leading to AMPK activation [104-106].

It is also interesting to note that the differences in actions between these polyphenols might be attributable to differences in their protein-binding properties, as exemplified by the specific binding of EGCG to the cell surface 67 kDa laminin receptor [107,108].

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