Review

Phenolic compounds: Evidence for inhibitory effects against obesity and their underlying molecular signaling mechanisms

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Phenolic compounds are widely present in the plant kingdom. Many epidemiological studies have indicated that consumption of some plant-derived foodstuffs with high phenolic content is associated with the prevention of some diseases and that these compounds may have similar properties to antioxidants, antimutagenic agents, antithrombotic agents, anti-inflammatory agents, anti-HIV-1, and anticancer agents. However, obesity is an important topic in the world of public health and preventive medicine. Relationships between body mass index, waist circumference, or waist-to-hip ratio and the risk of development of some diseases (such as heart disease, dyslipidemia, hypertension, non-alcoholic fatty liver disease, diabetes, kidney failure, cancer, stroke, osteoarthritis, and sleep apnea) have been observed. Evidence that phenolic compounds have beneficial effects in fighting obesity is increasingly being reported in the scientific literature. These *in vitro* and *in vivo* effects of phenolic compounds on the induction of pre-adipocytic and adipocytic apoptosis and inhibition of adipocytic lipid accumulation are considered in detail here. This review presents evidence of their inhibitory effects on obesity and their underlying molecular signaling mechanisms.

Keywords: Adipocytes / Anti-obesity / Apoptosis / Molecular mechanism / Phenolic compounds

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1 Introduction

Phenolic compounds constitute a group of substances that are abundant in the plant kingdom, where more than 8000 are known, with different chemical structures and activities. Flavonoids, especially flavones, flavonols, flavanones, flavanols (catechins), anthocyanins, isoflavones, and chalcones, are constituents of fruits, vegetables, nuts and plant-derived beverages such as tea, wine, and traditional Eastern medicines [1]. Phenolic acids, especially hydroxycinnamic acids and hydroxybenzoic acids, are secondary plant products and are commonly found in plant-derived foodstuffs [2]. Many epidemiological studies have indicated that consumption of some foodstuffs and drinks with high phenolic content is associated with the prevention of some diseases [3 – 5]. Phenolic acids and flavonoids have pharmacological properties such as antioxidant, antimutagenic, antithrombotic, anti-inflammatory, anti-HIV-1, and anticancer [6 – 8]. They are widely distributed in higher plants and form part of the human diet [9].

Over the last few decades, obesity has become a global epidemic in both developed and developing countries. The prevalence of obesity has doubled in the past 25 years; today, two-thirds of adults are overweight in the United States [10]. Obesity is characterized at the cell biological level by an increase in the number and size of adipocytes differentiated from fibroblastic pre-adipocytes in adipose tissue [11]. Adipose tissue is vital for maintaining whole body energy homeostasis, and it consists of adipocytes, which store triacylglycerol (TAG) as a fuel for the body. Excessive adipose tissue deposition is attributed to an imbalance between energy intake and energy expenditure [12]. Hausman *et al*. [13] indicated that adipogenesis is a process wherein the pre-adipocytes differentiate into adipocytes. MacDougald and Mandrup [14] also indicated the differentiation program is coordinated by several positive and negative adipogenic molecules, including a variety of growth factors, cytokines, and hormones. Obesity is considered a risk factor associated with the genesis or develop-

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Abbreviations: BMI, body mass index; **EGCG,** epigallocatechin gallate; **ERKs**, extracellular responsive kinases; **JNKs**, c-Jun N-terminal kinases; **MAPK**, mitogen-activated protein kinase

ment of various diseases, including coronary heart disease, hypertension, type 2 diabetes mellitus, cancer, respiratory complications, and osteoarthritis [15]. However, obesity has been shown to be one of the conditions that decrease antioxidant capacity [16, 17], and it seems to accomplish this by lowering the levels of antioxidant enzymes (catalase, glutathione peroxidase, and glutathione reductase) [17]. In animal and human studies, obesity is associated with a decrease in tissue or plasma antioxidant capacity [18, 19]. Phenolic compounds have been considered to play an important antioxidant role as dietary antioxidants for the prevention of oxidative damage in living systems [20]. In recent years, many studies have focused on the role of phenolic compounds in the prevention and treatment of obesity. The current review presents evidence for their effects against obesity and their underlying molecular signaling mechanisms.

2 Obesity and disease risk

Obesity is a term applied to excess body weight with an extremely high ratio of body fat. Body mass index (BMI) is the most widespread tool for measuring overweight and obesity in epidemiological studies. By definition, BMI is the weight in kilograms divided by the square of the height in meters. Table 1 shows the classification of overweight and obesity according to BMI as defined by the CDC (Centers for Disease Control and Prevention). A healthy BMI is considered to be between 18.5 and 24.9 (kg/m^2), whereas an overweight BMI is considered to be between 25.0 and 29.9 (kg/m^2) and obesity is defined as a BMI above 30. Other methods of evaluating body fat include measurements of skinfold thickness and waist circumference, waist-to-hip circumference, ultrasound, and magnetic resonance imaging. Many studies have indicated a relationship between BMI, waist circumference, or waist-to-hip ratio and the risk of some diseases. Obesity and related metabolic abnormalities increase the risk of developing some diseases and are a health risk associated with heart disease, dyslipidemia, hypertension, non-alcoholic fatty liver disease, diabetes, kidney failure, cancer, stroke, osteoarthritis, and sleep apnea [15, 21].

Obesity is associated with an increased risk of coronary heart disease and is strongly associated with dyslipidemia, especially by increasing triglycerides and decreasing the level of high-density lipoprotein (HDL) cholesterol [22]. Obesity has been found to increase the risk of heart failure [23]. Hyson *et al*. [24] indicated that the blood level of low-density lipoprotein (LDL) cholesterol and its oxidation are related to cardiovascular risk, and the LDL cholesterol level of blood is an index of health. The relationship between obesity and type 2 diabetes is so close that around 90% of individuals who develop type 2 diabetes have a BMI higher than 23 kg/m^2 [25]. Excess adipose tissue leads to insulin resistance, thereby increasing the risk of type 2 diabetes mellitus and cardiovascular disease [26]. Obesity is associated with an increased chance of developing non-alcoholic fatty liver disease, with 69–100% of non-alcoholic fatty liver disease patients being obese [27]. They are linked strongly to some diseases, such as insulin resistance, type 2 diabetes, and metabolic syndrome [28]. Obesity-associated glomerulonephropathy is the most accurately described type of renal involvement in obese individuals [29]. The benefits of weight loss should be stressed in obesity-related chronic kidney disease [30]. Obesity-related metabolic abnormalities are associated with increased risk of cancers, such as colon, prostate, and pancreatic cancers [31]. Relationships between BMI, waist circumference, or waist-to-hip ratio and cancer risk (colon and prostate) have been observed [32–36]. Obesity is associated with a significantly increased risk of stroke, consistent with the evidence that insulin resistance is associated with stroke in subjects without diabetes [37]. Obesity seems to be an important risk factor for osteoarthritis of the knee and hip [38, 39]. Relationships between BMI and hip osteoarthritis have been observed, especially in adults 30–59 years old [38]. Epidemiological studies indicated that 2% of women and 4% of men are affected by obstructive sleep apnea syndrome [40]. Obstructive sleep apnea syndrome is strongly and independently correlated with insulin resistance and visceral obesity [41].

Table 1. Classification of overweight and obesity according to BMI

BMI[a)] [kg/m^2]	Considered	Height [cm]	Weight range [kg]
< 18.5	Underweight	172	< 55
18.5–24.9	Healthy weight		55–74
25.0–29.9	Overweight		74–89
> 30	Obese		> 89

a) BMI is the weight in kilograms divided by the square of the height in meters. Derived from Centers for Disease Control and Prevention (CDC).

3 Antiobesity effects of phenolic compounds

Obesity is characterized at the cell biological level by an increase in the number and size of adipocytes differentiated from fibroblastic pre-adipocytes in adipose tissues [11]. The adipocyte is the primary site of energy storage and it accumulates triglycerides during nutritional excess. Recent reports have outlined the mechanisms of proposed antiobesity including decreased energy intake and increased energy expenditure, decreased pre-adipocyte differentiation and proliferation, decreased lipogenesis and increased lipolysis, and fat oxidation [42]. In this review, we focus on the effects

Table 2. Effect of phenolic compounds on 3T3-L1 pre-adipocytes

Compounds	Dose (Duration)	Results	Reference
Chlorogenic acid	0–250 μM (72 h)	Caused cell cycle arrest in the G_1 phase	[46]
o-Coumaric acid	0–250 μM (72 h)	Caused cell cycle arrest in the G_1 phase	[46]
p-Coumaric acid	0–250 μM (72 h)	Caused cell cycle arrest in the G_1 phase	[46]
EGCG	0–400 μM (48 h)	Induction of cell apoptosis	[50]
EGCG	0–100 μM (24–48 h)	Caused cell cycle arrest in the G_1 phase	[47]
Esculetin	200 μM (48 h)	Induction of cell apoptosis	[51]
Gallic acid	0–250 μM (0–72 h)	Induction of cell apoptosis	[46]
Gallic acid	0–50 μM (0–12 h)	Induces apoptosis *via* Fas- and mitochondria-mediated pathway	[53]
Quercetin	0–250 μM (0–72 h)	Induction of cell apoptosis	[52]
Naringenin	0–100 μM (0–48 h)	Inhibition of cell proliferation	[49]

of phenolic compounds on induction of pre-adipocytic and adipocytic apoptosis and inhibition of adipocytic lipid accumulation. Many studies have indicated that phenolic compounds have been used in cell culture and animal models for the treatment of obesity. The current review presents evidence of the antiobesity effects of phenolic compounds. These *in vitro* and *in vivo* effects on phenolic compounds are considered in detail in the sections that follow.

3.1 *In vitro*

Adipocytes are the primary site of energy storage and accumulated triacylglycerol that results from an energy imbalance. It has been reported that adipocyte dysfunction plays an important role in the development of obesity and related diseases [43]. Obesity is a condition in which adipocytes accumulate a large amount of fat and become enlarged. It is characterized at the cellular level by an increase in the number and size of adipocytes differentiated from pre-adipocytes in adipose tissue [11]. The 3T3-L1 pre-adipocytes are not cancer cells, but the pre-adipocytes could be differentiated into mature adipocytes. Reports have outlined the mechanisms of proposed anti-obesity [42]. Among them, pre-adipocytes play a key role in differentiation into mature adipocytes and increased fat mass. The murine 3T3-L1 cell line, which is widely used as a cell model, has been a mainstay for adipose cell biology research over several decades [44–46]. Therefore, the inhibition of cell growth and induction of apoptosis by phenolic compounds may prove to be a pivotal mechanism for antiobesity. The effects of phenolic compounds on 3T3-L1 pre-adipocytes are summarized in Table 2.

The cell cycle is a critical regulator of the processes of cell growth and proliferation. Hsu *et al.* [47] established that some phenolic acids (such as chlorogenic acid, *o*-coumaric acid, and *p*-coumaric acid) could lead to cell cycle arrest at the G_1 phase in 3T3-L1 pre-adipocytes. Hung *et al.* [48] indicated that epigallocatechin gallate (EGCG) arrested 3T3-L1 pre-adipocytes in the G_1 phase of the cell cycle. EGCG could lead to cell cycle arrest through decreased levels of phospho-ERK 1/2, Cdk2, and cyclin D_1, and through increased levels of p21 and p27. Moreover, apoptosis is characterized by the activation of the caspase family of cysteine proteases followed by caspase-mediated specific morphological changes including cell shrinkage, chromatin condensation, unclear DNA fragmentation, membrane blebbing, and breakdown of the cell into apoptotic bodies [49]. Many reports have indicated that some phenolic compounds (such as EGCG, esculetin, gallic acid, quercetin, and naringenin) efficiently induce apoptosis in 3T3-L1 pre-adipocytes [47, 50–54]. Recent reports have shown that some phenolic compounds (such as EGCG, esculetin, and genistein) efficiently induce apoptosis in 3T3-L1 adipocytes [52, 55–57]. The effects of phenolic compounds on 3T3-L1 adipocytes are summarized in Table 3. These results indicate that EGCG and genistein suppress the adipocyte differentiation process and induce apoptosis in 3T3-L1 adipocytes through activation of AMP-activated protein kinase [55, 56]. Esculetin inhibits adipocyte differentiation, including the early, intermediate, and late stages of the differentiation process [52].

During adipocyte differentiation, transcriptional factors such as peroxisome proliferator-activated receptor (PPAR)γ and CCAAT/enhancer-binding proteins (C/EBPs) are involved in the sequential expression of adipocyte-specific proteins [58]. Wang and Jones [42] reported that decreased adipocytic lipogenesis is one of the mechanisms of proposed antiobesity. In this section, we focus on the effects of phenolic compounds on the inhibition of adipogenesis in 3T3-L1 adipocytes (Table 3). Many studies indicated that some phenolic compounds (such as *o*-coumaric acid, EGCG, esculetin, genistein, procyanidin, pycnogenol, rutin, and tea catechin) cause an inhibition of intracellular triglyceride and glycerol-3-phosphate dehydrogenase (GPDH) in 3T3-L1 adipocytes [11, 55, 59–65]. The cytosolic enzyme GPDH appears to have an important role in the conversion of glycerol into triglyceride [66]. A recent report indicated that (–)-catechin efficiently inhibits the expression of Kruppel-like factor 7 protein and increases expression and secretion of adiponectin protein in 3T3-L1 adipocytes [67]. Adiponectin is an adipocytokine that has been shown to have antiatherogenic, anti-inflammatory,

Table 3. Effect of phenolic compounds on 3T3-L1 adipocytes

Compounds	Dose (Duration)	Results	Reference
(−)-catechin	50 μM (24 h)	Suppresses expression of Kruppel-like factor 7 and induce the production of adiponectin	[66]
o-Coumaric acid	250 μM (72 h)	Inhibition of intracellular triglyceride and glycerol-3-phosphate dehydrogenase	[64]
EGCG	0–100 μM (3 h)	Inhibition of resistin expression	[63]
EGCG	0–200 μM (24 h)	Induction of cell apoptosis	[54]
EGCG	0–200 μM (6 days)	Inhibition of adipogenesis	[54]
EGCG	0.02 mg/mL (14 days)	Inhibition of intracellular triglyceride and glycerol-3-phosphate dehydrogenase	[61]
Esculetin	0–800 μM (6 h)	Induction of cell apoptosis	[51]
Genistein	0–400 μM (12–48 h)	Induction of cell apoptosis	[56]
Genistein	100 μM (8 days)	Inhibition of adipocyte differentiation and induction of cell apoptosis	[55]
Genistein	100 μM (72 h)	Inhibits the expression of adipogenic transcription	[60]
Procyanidin	150 μM (0.5–24 h)	Inhibition of intracellular triglyceride and glycerol-3-phosphate dehydrogenase	[58]
Pycnogenol	50 μg/mL (24 h)	Inhibition of glycerol-3-phosphate dehydrogenase	[59]
Rutin	250 mM (72 h)	Inhibition of intracellular triglyceride and glycerol-3-phosphate dehydrogenase	[64]
Rutin	1 mg/mL (6 days)	Inhibition of adipocyte differentiation and glycerol-3-phosphate dehydrogenase	[62]
Tea catechin (CG, EGC and EGCG)	30 μM (0–10 days)	Inhibition of intracellular triglyceride and glycerol-3-phosphate dehydrogenase	[11]

and antidiabetic roles [68]. Yamauchi *et al*. [69] reported that adiponectin has emerged most recently as an important adipocytokine with insulin-sensitizing effects and represents a novel treatment target for insulin resistance and type 2 diabetes. These results suggest that (−)-catechin may have some beneficial effects on the treatment of obesity-related disease.

3.2 *In vivo*

Dietary fat is one of the most important environmental factors associated with the occurrence of cardiovascular disease; high levels of cholesterol and saturated fat diets have been shown to promote atherosclerosis [70]. Lavie and Milani [71] indicated that obesity adversely affects plasma lipids, especially by increasing triacylglycerol levels and decreasing the level of HDL-cholesterol. Muller *et al*. [72] indicated that the high dietary intake of saturated fat is associated with a high level of serum cholesterol and strongly correlates with coronary death rates. Many studies have reported that obesity is induced in mice and rats by feeding them a high-energy diet, such as lard, coconut oil, corn oil, soybean oil, beef tallow, and shortening [57, 63, 73–86]. Some reports have demonstrated that antioxidants may act as regulators of obesity in mice or rats fed with high fat-diets [76, 87]. The effects of phenolic compounds on body weight in mice and rats are summarized in Table 4. The addition of polyphenol fractions of *Salix matsudana* leaves to the diet decreases body weight gain, plasma triacylglycerol levels, and hepatic steatosis in male Wistar rats [76]. Choi *et al*. [85] showed that the oral administration of germinated buckwheat caused significant reduction in body weight, serum parameters, and hepatic steatosis in male C57BL/6 mice. Chan *et al*. [74] indicated that the consumption of tea catechin showed a reduction in body weight, serum parameters, and hepatic lipid levels in hamsters. Aoki *et al*. [84] reported that the consumption of licorice flavonoid oil caused a significant reduction in body weight, adipose tissue weight, and serum parameters in female C57BL/6J mice. Hsu and Yen [86] indicated that addition of gallic acid to the diet decreased dyslipidemia, hepatosteatosis, and oxidative stress in male Wistar rats. Phenolic compounds (such as anthocyanins, flavonoids, and phenolic acids) have been considered to play an important role in the treatment of obesity and thus the possibility is raised of a new application as a health supplement [63, 74–77, 79–86, 88–92]. These results showed that the body weights of subjects in the high-fat diet with phenolic compounds groups were significantly decreased as compared with the high-fat diet group. Moreover, some studies have demonstrated that phenolic compounds (such as genistein, daidzein, tannic acid, tea catechin, and naringin) may act as regulators of plasma lipids in mice, hamsters, or rats fed with high-fat diets [73, 74, 78, 81, 93]. Hyperlipidemia is known to enhance the risk of coronary heart disease, fatty liver disease, and carcinogenesis, which is associated with reactive oxygen species formation [94]. Recent studies concerning the bioavailability of phenolic compounds verify their potential therapeutic effects. Bioavailability is the extent to which a nutrient in a food constituent can be absorbed and used by the body after ingestion. These health-promoting effects have been mainly attributed to the content of poly-

Table 4. Effect of phenolic compounds on body weight in animals

Compound	Species	Fat intake [%]	Fat source	Dose (*per* kg body weight)	Duration [wk]	Body weight	Reference
Anthocyanins	Male C57BL/6 mice	24.5	Lard	1 g/kg diet	8	↓	[79]
Cyanidin 3-*O*-b-D-glucoside	Male C57BL/6J mice	30	Lard	2 g/kg diet	12	↓	[76]
EGCG	Female Wistar rat	0.5 wt% cholesterol, 2.5 wt% coconut oil, 2.5 wt% corn oil		0.7 g	4	Plasma lipids ↓	[77]
Flavonoid of Germinated buckwheat	Male C57BL/6 mice	7 wt% soybean oil, 33 wt% shortening		100 and 200 mg	8	↓	[84]
Gallic acid	Male Wistar rat	40	Beef tallow	50 and 100 mg	10	↓	[85]
Genistein	Female C57BL/6 mice	7	Corn oil	1.5 g/kg diet	3	↓	[56]
Genistein	Male C57BL/6J mice	25	Soybean oil	2 g/kg diet	12	↓	[82]
Genistein	Male C57BL/6J mice	18	Fat	2 g/kg diet	12	↓	[88]
Genistein + daidzein	Female C57BL/6J mice	15	Cocoa butter	270 + 90 mg/kg diet	6	Plasma lipids ↓	[92]
Green tea	Male New Zealand black mice	15	Fat	10 g/kg diet	4	↓	[89]
Licorice flavonoid oil	Female C57BL/6J mice	20	Soybean oil	0–20 g/kg diet	8	↓	[83]
Licorice flavonoid oil	Female KK-A^y/Ta mice	28	Lard + beef tallow	0–20 g/kg diet	4	↓	[78]
Polyphenol fractions of *Salix matsudana* leaves	Male Wistar rat	40	Beef tallow	570 mg	9	↓	[75]
Phenolic from the roots of *Salacia reticulata*	Female Zucker fatty rat Male Wistar rat	58	Lard	125 mg	27 days	↓	[74]
Resveratrol	Male C57BL/6NIA mice	60% of calories from fat		22.4 mg	110	↓	[90]
Rutin	Male C57BL/6 mice	40	Shortening + soybean oil	25 and 50 mg	4	↓	[62]
Tannic acid	Male Wistar rat	16	Lard	100 mg	10	Plasma lipids ↓	[72]
Tea catechin	Male C57BL/6 mice	30	Fat	5 g/kg diet	15	↓	[91]
Tea catechin	Male C57BL/6J mice	30	Fat	5 g/kg diet	11 months	↓	[87]
Tea catechin	Male Syrian golden hamsters	20	Lard	5.7 g/kg diet	4	Plasma lipids ↓	[73]
Naringin	Sprague-Dawley rat	15	Lard	200 mg/kg diet	6	Plasma lipids ↓	[80]
Quercetin	Male Sprague-Dawley rat	15	Lard	5 g/kg diet	4	↓	[81]

phenols and plant secondary metabolites [95–97]. Plasma concentrations reached after polyphenol consumption vary highly according to the nature of the food source. They are on the order of 0.3–0.75 μmol/L after consumption of 80–100 mg quercetin equivalent administered in plant-derived foodstuffs [98–100]. Some authors claim that phenolic compounds have a no-observed-adverse-effect level (NOAEL). Niho *et al*. [101] reported that intake of gallic acid (119 mg/kg/day) for 13 wk is determined to be a NOAEL in male rats. Hasumura *et al*. [102] reported that intake of rutin for 13 wk is determined to be a NOAEL and the no-observed-effect levels (NOEL) in male and female Wistar rats are 539 and 3227 mg/kg/day, respectively. Thus, phenolic compounds have an anti-obesity effect through suppression of dyslipidemia, hepatosteatosis, and oxidative stress in obese rats. Therefore, these results provide direct evidence that phenolic compounds may be useful for the treatment of obesity. Prevention and treatment of obesity are relevant to health promotion.

4 Molecular mechanism of antiobesity by phenolic compounds

Phenolic compounds have demonstrated a chemopreventive potential in a variety of bioassay systems and animal models. They have pharmacological properties such as antioxidant, antithrombotic, anti-inflammatory, anti-HIV-1, and anticancer [6–8]. They also affect cell functions such as growth, differentiation, and apoptosis [103–105]. Many reports have indicated that phenolic compounds efficiently induce apoptosis in 3T3-L1 adipocytes [52, 55–57]. In this section, we focus on the molecular mechanism of phenolic compounds on the apoptosis pathway in 3T3-L1 pre-adipocytes.

Apoptotic cells are characterized by distinct morphological features such as cell shrinkage, chromatin condensation, membrane blebbing, and the formation of apoptotic bodies. In cells responsive to apoptotic stimuli, there are two major apoptotic pathways, ultimately classified into the mito-

chondria-dependent pathway (intrinsic pathway) and the death receptor-dependent pathway (extrinsic pathway) [106]. The mitochondria-dependent pathway and the death receptor-dependent pathway are both regulated by Bcl-2 family proteins. Bcl-2 family proteins involved in apoptosis have been identified, including the pro-apoptotic proteins Bax, Bak, Bad, and Bcl-X_S, and the anti-apoptotic proteins Bcl-2, Bcl-X_L, and Mcl-1. Moreover, apoptosis may be initiated through the regulation of death receptors located on the cell surface or through an intrinsic pathway including the release of apoptotic signals from the mitochondria [107]. Fas and its receptor Fas ligand (FasL) are part of an important cellular pathway regulating the induction of apoptosis in diverse cell types and tissues [108]. Recent reports have determined the signaling pathway of gallic acid-induced apoptosis in 3T3-L1 pre-adipocytes [54]. Hsu and Yen [53] indicated that treatment of 3T3-L1 pre-adipocytes with quercetin resulted in a marked loss of the mitochondrial transmembrane potential ($\Delta\Psi$m), down-regulation of the Bcl-2 protein, and activation of Bax, Bak, and caspase-3 proteins, followed by the cleavage of PARP. Phenolic compounds can mediate the apoptotic pathway through the induction of stress proteins. They lead to death receptor (Fas and FasL) and p53 signaling, loss of the mitochondrial transmembrane potential ($\Delta\Psi$m), release of cytochrome *c* from the mitochondria into the cytosol, and the subsequent activation of caspase-9 and caspase-3, followed by the cleavage of PARP. The ratio of expression levels of pro- and anti-apoptotic Bcl-2 family members was changed by phenolic compound treatment.

The mitogen-activated protein kinase (MAPK) family is ubiquitously expressed and regulates the survival, proliferation, and death of the cell [109]. Three subfamilies of MAPKs have been identified, including extracellular responsive kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38-MAPKs. Cross *et al*. [110] reported that many signaling molecules such as ERK, JNK, and p38 kinase are involved in the apoptotic process. Chen and Tan [111] indicated that JNK pathway activation is required for apoptosis induced by pro-inflammatory cytokines, ultraviolet light, γ-irradiation, and DNA-damaging agents. The activation of JNK and p38 MAP kinases is generally associated with induction of apoptosis, while ERK activity inhibits apoptosis. Various reports have shown that the anti-mitogenic effect of phenolic compounds (such as EGCG) on 3T3-L1 pre-adipocytes is dependent on the ERK and Cdk2 pathways [48, 51]. These results have indicated that the treatment of 3T3-L1 pre-adipocytes with EGCG causes a cell cycle arrest in the G_1 phase. It inhibits 3T3-L1 pre-adipocyte proliferation and cell cycle progression through a transient activation of p21 and p27.

Many studies have shown that phenolic compounds efficiently induce cell apoptosis in 3T3-L1 pre-adipocytes. However, the inhibition of phenolic compounds on the adipogenesis in 3T3-L1 adipocytes and their molecular mechanisms remains unclear. Hsu and Yen [65] indicated that phenolic compounds (rutin and *o*-coumaric acid) efficiently suppress adipogenesis in 3T3-L1 adipocytes. It appears to be mediated through the down-regulated expression of adipogenic transcription factors (PPARγ and C/EBPα) and adipocyte-specific proteins (leptin), and then through the up-regulated expression of adiponectin.

5 Conclusion

In summary, the information available in the literature is increasingly supportive of the antiobesity action of phenolic compounds. *In vitro* studies have shown that phenolic compounds efficiently induce apoptosis in 3T3-L1 pre-adipocytes and adipocytes. A possible molecular mechanism for the antiobesity action of phenolic compounds in 3T3 pre-adipocytes was proposed to involve the mitochondria and MAPK pathway with subsequent induction of apoptosis. Phenolic compounds also caused an inhibition of intracellular triglyceride and GPDH in 3T3-L1 adipocytes. *In vivo* studies have indicated that intake of phenolic compounds can be beneficial for the inhibition of a high fat diet-induced obesity in mice, hamsters, or rats. Results from such studies may be related to the mechanism by which phenolic compounds prevent obesity in humans. These studies also provide initial evidence for phenolic compounds possibly being useful in the treatment of obesity and raise the possibility of a new application of phenolic compounds as a health supplement. Nonetheless, a greater understanding is needed of the molecular interactions of the pre-adipocytic and adipocytic genes responsible for the ability of phenolic compounds to prevent obesity.

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