NIH-PA Author Manuscript

# Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals

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## Abstract

Extensive research within the past two decades has revealed that obesity, a major risk factor for type 2 diabetes, atherosclerosis, cancer, and other chronic diseases, is a proinflammatory disease. Several spices have been shown to exhibit activity against obesity through antioxidant and anti-inflammatory mechanisms. Among them, curcumin, a yellow pigment derived from the spice turmeric (an essential component of curry powder), has been investigated most extensively as a treatment for obesity and obesity-related metabolic diseases. Curcumin directly interacts with adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells. There, it suppresses the proinflammatory transcription factors nuclear factor-kappa B, signal transducer and activators of transcription-3, and Wnt/β-catenin, and it activates peroxisome proliferator-activated receptor-γ and Nrf2 cell-signaling pathways, thus leading to the downregulation of adipokines, including tumor necrosis factor, interleukin-6, resistin, leptin, and monocyte chemotactic protein-1, and the upregulation of adiponectin and other gene products. These curcumin-induced alterations reverse insulin resistance, hyperglycemia, hyperlipidemia, and other symptoms linked to obesity. Other structurally homologous nutraceuticals, derived from red chili, cinnamon, cloves, black pepper, and ginger, also exhibit effects against obesity and insulin resistance.

## Keywords

inflammation; obesity; diabetes; insulin; cancer; NF-κB; curcumin; nutraceuticals

## INTRODUCTION

According to Centers for Disease Control and Prevention (CDC), America is a home to the largest population of obese people in the world (http://www.cdc.gov/obesity/index.html). Thirty-three percent of adult Americans are obese, obesity has increased 60% within the past 20 years, 66% of American adults are overweight, one in six children are obese (http://www.cdc.gov/obesity/data/index.html), and obesity-related deaths have climbed to more than 300,000 a year, second only to tobacco-related deaths (191).The CDC indicated that American society has become obesogenic, characterized by environments that promote increased food intake, nonhealthful foods, and physical inactivity. According to the National Institute of Diabetes and Digestive and Kidney Diseases, approximately two-thirds of U.S. adults—nearly 167 million—are overweight, and nearly one-third (31.4%) are obese

(http://www2.niddk.nih.gov/AboutNIDDK/OfficeofObesityResearch). In 2008, the nation spent $147 billion on obesity-related diseases. The list of morbidities associated with obesity is extensive. Obesity is a risk factor for heart disease, diabetes, stroke, and cancer. As many as 18 million Americans are currently diabetic, and the global incidence approaches 221 million cases. It is a leading cause of blindness, renal failure, and limb amputation for nontraumatic reasons. The total cost of this disease is approaching $130 billion per year in the United States alone (http://www.cdc.gov/obesity/index.html). Additionally, obesity may account for 14% of all cancer deaths in men and 20% in women (12). Some of the most common obesity-associated cancers include cancer of the colon, stomach, esophagus, gall bladder, ovary, breast, liver, endometrium, uterus, rectum, pancreas, cervix, and kidney, as well as non-Hodgkin's lymphoma and multiple myeloma.

Obesity and metabolic syndrome are considered to be major public health crises not only in the United States but also globally. An expert panel convened by the National Institutes of Health has defined overweight as a body mass index (BMI) of 25 to 29.9 kg/m$^2$ and obesity as a BMI of 30 kg/m$^2$ or greater. According to the World Health Organization (WHO), as of 2005 there were approximately 1.6 billion overweight adults globally, of whom at least 300 million were clinically obese. The prevalence of overweight and obese American adults has steadily increased over the years in both genders, at all ages, in all racial and ethnic groups, at all educational levels, and for all smoking levels. Most studies show an increase in mortality rates associated with obesity. Individuals who are obese have a 10%–50% increased risk of death from all causes, compared with healthy-weight individuals. Most of the increased risk is due to cardiovascular causes. Obesity is associated with about 112,000 excess deaths per year in the U.S. population relative to healthy-weight individuals (http://www.cdc.gov/obesity/index.html).

A condition related to obesity, metabolic syndrome is marked by a collection of unhealthy body measurements and abnormal laboratory test results that identify persons at high risk for developing cardiovascular disease and/or type 2 diabetes. Aggressive lifestyle modification and possible use of medications to treat the conditions that make up metabolic syndrome may reduce a person's chances of developing heart disease or stroke. According to the CDC, an estimated 47 million Americans—nearly one-fourth of U.S. adults—have metabolic syndrome. These data illustrate the seriousness of the problem that most believe is preventable (22).

Although caloric intake is one of the major contributors to obesity, people have known for centuries the role that diet plays in obesity. Certain kinds of diet (proinflammatory) can promote obesity, whereas other kinds (anti-inflammatory) can reduce it (3, 53, 93, 115, 142). A high-calorie, high-fat, and low-fiber diet usually promotes obesity; caloric restriction, exercise, and wholesome foods have been shown to reverse it (51, 151, 192). It is generally believed that highly processed, packaged, and refined foods loaded with sugar and hydrogenated oils are likely to promote obesity.

Knowledge of traditional medicine has allowed us to identify foods, food supplements, herbs, and spices believed to exhibit antiobesity effects. Some of these can be considered components of the complementary and alternative medicine (CAM) pharmacopoeia. According to findings released in July 2009 from the National Health Interview Survey (NHIS), Americans spent as much as $34 billion out of pocket on CAM in 2007. Whether CAM treatments are safe and effective, however, is unclear. The current review examines the role of inflammatory pathways in the pathogenesis of obesity and the modulation of obesity by various spice-derived nutraceuticals, with particular emphasis on curcumin.

## ROLE OF INFLAMMATION IN OBESITY AND METABOLIC DISEASES

In obesity, as in most other chronic diseases, inflammation appears to play a major role. Obesity, type 2 diabetes, hypertension, and dyslipidemia are closely linked to insulin resistance, and this cluster of diseases is called metabolic syndrome. The chronic inflammation observed in obesity has been reported in the development of atherosclerosis, another proinflammatory disease (153). Pluripotent mesenchymal stem cells in bone marrow differentiate into adipocytes, osteoblasts, and other cells. Adipocytes play a major role in the development of metabolic syndrome. These cells are involved in energy regulation and homeostasis. Energy metabolism is primarily controlled by insulin, a hormone that promotes the synthesis and storage of proteins, carbohydrates, and lipids. Thus, insulin resistance is commonly associated with obesity.

Fat tissue is not a simple energy storage organ but rather exerts important endocrine and immune functions. These functions are achieved primarily through the release of adipocytokines by white adipose tissues (WAT), which include leptin, resistin, plasminogen activator inhibitor type-1 (PAI-1), and adiponectin (or visfatin), as well as such inflammatory cytokines as tumor necrosis factor (TNF), interluekin (IL)-6, monocyte chemotactic protein (MCP)-1, and IL-1. These cytokines and chemokines are critically involved in insulin resistance and chronic inflammation. Numerous lines of evidence suggest that TNF-α, which was discovered as a result of its anticancer activities (2), is a major mediator of inflammation in general and of obesity and insulin resistance in particular. First, our laboratory showed that adipocytes express TNF receptors and mediate catabolic effects (129). Second, adipose tissue of genetically obese mice is known to overexpress TNF-α. Third, TNF-α expressed in human adipocytes is elevated in most obese subjects and is decreased by weight loss. An inverse relationship exists between TNF and lipoprotein lipase (LPL) (87). Furthermore, neutralization of TNF-α levels leads to an increase in peripheral insulin sensitivity (63), and TNF levels in obese subjects correlated with C-reactive protein levels, a marker of systemic inflammation (31). Fourth, TNF was found to induce insulin resistance through serine phosphorylation of insulin receptor substrate (IRS)-1, which then inhibits the tyrosine kinase activity of the insulin receptor in adipocytes (62). Later, it was shown that TNF induces the expression of suppressor of cytokine signaling (SOCS)-3, which is elevated during obesity and can inhibit insulin signaling (50). Overexpression of the dual-specificity phosphatase MKP-4 was similarly found to protect against insulin resistance, possibly through the dephosphorylation of serine in insulin receptor substrate 1 (49). Also, protein tyrosine phosphatase (PTP)-1B, which acts as a negative regulator of insulin signaling, is induced by TNF, and mice that lack PTP-1B are protected from insulin resistance induced by TNF (116). In contrast to soluble secreted TNF, transmembrane TNF in adipose tissue causes local but not systemic insulin resistance (203). Fifth, antidiabetic drugs such as thialidinedione (beta-2 adrenoreceptor agonist) block TNF-induced inhibition of insulin signaling through the activation of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-γ (133). Sixth, high-fat diet can elevate TNF activity in adipose tissue but not the secreted TNF levels (109). Seventh, TNF can induce the secretion of leptin, a fat-specific energy balance hormone, through posttranscriptional mechanism in adipocytes (90). Eighth, TNF-α gene polymorphism (G-308A) has been linked with insulin resistance, increases % body fat, and serum leptin levels (66). Ninth, blockade of the TNF receptor-1 has been shown to reverse diet-induced obesity and insulin resistance (96). Finally, mice lacking TNF-α are protected from obesity-induced insulin resistance (190). Thus, all these studies indicate that regulation of adipocytokines such as TNF is directly linked to obesity-induced insulin resistance, and targeting this pathway may allow us to treat metabolic diseases such as obesity. Interestingly, in contrast to white adipose tissue, brown adipose tissue that mediates thermoregulation responds to TNF by apoptosis (118).

NF-κB is a transcription factor that regulates the expression of more than 400 different genes, most of which control the expression of inflammatory gene products (http://www.nf-kb.org). Much compelling evidence suggests that inflammation mediated by this transcription factor is also closely linked to obesity and insulin resistance. First, TNF-α, expressed in adipocytes, is one of the most potent activators of NF-κB, and the expression of TNF-α itself is regulated by NF-κB (7, 155). Second, NF-κB activation can induce insulin resistance (55), and antidiabetic drugs are known to suppress NF-κB activation through upregulation of inhibitor of NF-κB (10, 67, 121, 156). Third, adiponectin, an adipocyte-derived plasma protein, is known to inhibit NF-κB activation (8, 125). Fourth, insulin is known to inhibit NF-κB and stimulate IκBα synthesis in obese patients (43); mixed meal increases NF-κB and decreases IκBα synthesis (11, 45, 127). Fifth, mice lacking the IκBα kinase (IKK)-β needed for NF-κB activation in hepatocytes or myeloid cells develop insulin resistance in response to high-fat diet, obesity, or aging (16, 208). These mice exhibited a type 2 diabetes phenotype, characterized by hyperglycemia and profound hepatic insulin resistance (33). Investigators in these studies concluded that lipid accumulation in the liver leads to subacute hepatic inflammation through NF-κB activation and downstream cytokine production, which causes insulin resistance both locally in liver and systemically. Sixth, resistin, an adiopokine, exhibits proinflammatory activities (29). Seventh, palmitate and high glucose can activate NF-κB and induce TNF and IL-6 in adipocytes (8, 46, 60, 68, 127, 196, 206, 207). Eighth, activation of TOLL-like receptor (TLR)-4 by saturated fatty acids induces insulin resistance through activation of NF-κB (152, 167, 175, 181). TLR4 deficiency protects against the development of insulin resistance linked to obesity induced by diet rich in saturated fatty acids (44). Ninth, deletion of a hepatic NEMO gene, required for NF-κB activation, prevents obesity-induced insulin resistance (200). Elevated serum levels of various chemokines, including MCP-4, MCP-1, and eotaxin, encountered in overweight subjects, are regulated by NF-κB (39, 59, 159). Plasma plasminogen activator inhibitor type-1 levels that have been correlated with visceral fat during the development of obesity (168) are also regulated by NF-κB. Additionally, NF-κBregulated IL-6 levels in adipose tissue correlate well with insulin resistance (24) and with serum C-reactive protein levels (97). Taken together, this evidence suggests that WAT is a major source of chronic inflammation in obese subjects and that NF-κB is another important target for management of obesity.

Zhang and colleagues (211) examined whether metabolic inflammation compromises the neural regulatory systems and therefore promotes overnutrition-associated obesity. They found that overnutrition activates hypothalamic NF-κB in part through elevated endoplasmic reticulum stress, which interrupts central insulin/leptin signaling and actions. Thus, suppressing hypothalamic NF-κB may be another strategy to combat obesity and related diseases.

Another factor in obesity, adipocyte differentiation, is a tightly controlled process regulated by PPAR-γ and CCAA/enhancer binding protein-alpha. PPAR belong to the super family of nuclear receptors. Among all the PPARs, PPAR-γ is a major molecular target for all insulin-sensitizing drugs, such as troglitazone, pioglitazone, and rosiglitazone, approved for the treatment of patients with type 2 diabetes (107). It has been shown that TNF downmodulates the expression of the PPAR-γ gene, which may also lead to insulin resistance (187, 209). It was found that TNF-induced NF-κB blocks the PPAR-γ binding to DNA by forming a complex with PPAR-γ and its AF-1-specific coactivator, PPAR-γ coactivator -2 (PGC-2) (187). Another report, however, indicated that TNF-α inhibits PPAR-γ trans activity in cultured hepatic stellate cells (HSCs) by diminished PPAR-γ-PPRE (peroxisome proliferator response element) DNA binding and extracellular signal-related protein kinase (ERK)1/2-mediated phosphorylation of Ser (88) of PPAR-γ1 but not via the NF-κB pathway (182).

Another important source of inflammation is increased infiltration of macrophages in WAT of obese subjects (198). Many inflammation-related and macrophage-specific genes are unregulated in WAT (202). High glucose intake can cause the generation of reactive oxygen species (ROS) by macrophages, leading to the activation of NF-κB (11). Saturated fatty acids released by adipocytes through macrophage-induced lipolysis activate TLR4 for induction of NF-κB (181). Circulating mononuclear cells in obese individuals are in a proinflammatory state (52). Overall, these studies conclusively demonstrate that inflammation plays a major role in obesity and insulin resistance.

### Targeting Inflammatory Pathways by Curcumin in Obesity and Metabolic Diseases

Spices that are primarily used in India and surrounding countries were sought for centuries by such great explorers as Marco Polo, Vasco de Gama, and Christopher Columbus. The spices are primarily herbs, including leaves (as in mint and cilantro), seeds (e.g., fenugreek), barks (e.g., cinnamon), fruit (e.g., black pepper, red chili, cardamon, mango, and pomegranate), and roots (e.g., turmeric and licorice) of plants that have been used for centuries to preserve food, enhance its color, make it more aromatic, and improve its taste; perhaps more importantly, the spices were used to improve the digestive qualities and medicinal value of the food. Several of these spices have been shown to modulate inflammatory pathways (5).Turmeric (*Curcuma longa*), for example, has been described in the literature of Ayurveda ("science of long life"), dating from about 3000 BC, for a wide variety of ailments including obesity. The name turmeric derives from the French word *terre-merite* (meritorious earth), referring to the color of ground turmeric, which resembles a mineral pigment. It is known as "*Safaran des Indes*" in French and simply as "yellow root" in many languages. In many cultures, its name is based on the Latin "curcuma." In Sanskrit, turmeric has at least 53 different names, including jawarantika, which destroys fever; mehagni, killer of fat; rabhangavasa, which dissolve fat; and ratrimanika, which glows in night (referring to its fluorescent property).

More than 100 components have been isolated from turmeric (114, 122, 149). The main component is a volatile oil, containing turmerone, and other coloring agents called curcuminoids. Curcumin is the yellow pigment present in the spice turmeric and is a diferuloylmethane (Figure 1). Curcuminoids consist of curcumin demethoxycurcumin, 5′-methoxycurcumin, and dihydrocurcumin, which are natural antioxidants (103). In a standard preparation, turmeric contains moisture (>9%), curcumin (5%–6.6%), extraneous matter (<0.5% by weight), mold (<3%), and volatile oils (<3.5%). There are also reports of omega-3 fatty acid in turmeric. The volatile oils include d-α-phellandrene, ᴅ-sabinene, cinol, borneol, zingiberene, and sesquiterpenes. Turmeric contains a variety of sesquiterpenes, including germacrone, termerone, ar-(+)-, α- and β- termerones, β-bisabolene, a-curcumene, zingiberenel, β-sesquiphellanderene, bisacurone, curcumenone, dehydrocurdione, procurcumadiol, bis-acumol, curcumenol, isoprocurcumenol, epiprocurcumenol, procurcumenol, zedaoronediol, and curlone, many of which are specific for species. The responsible components for the aroma of turmeric are turmerone, arturmerone, and zingiberene. The rhizomes are also reported to contain four new polysaccharides-ukonans along with stigmasterole, β-sitosterole, cholesterole, and 2-hydroxymethyl anthraquinone. Nutritional analysis showed that 100 grams of turmeric contains 354 kilocalories, 10 g of total fat, 3 g of saturated fat, 38 mg of sodium, 2525 mg of potassium, 65 g of total carbohydrates, 21 g of dietary fiber, 3 g of sugars, and 8 g of protein. It may also contain omega-3 fatty acid. It lacks cholesterol.

Since the report in 1972 that curcumin could lower blood glucose levels in human diabetic subjects (178, 179), more than 3000 reports have been published on curcumin, with more than 300 on its effects on obesity and obesity-associated complications (Table 1).

## Curcumin Can Modulate Various Targets Involved in Obesity and Metabolic Diseases

Several reports suggest that curcumin has potential in the prevention and treatment of obesity, diabetes, atherosclerosis, and metabolic syndrome. Curcumin has been reported to modulate numerous targets that have been linked to obesity and insulin resistance (Figure 2). First, curcumin has been shown to downregulate the expression of TNF in various tissues (35). Second, our laboratory was the first to demonstrate that curcumin can suppress NF-κB activation induced by a wide variety of inflammatory agents through inhibition of degradation of IκBα (170) (Figure 3). Third, our laboratory has also demonstrated that curcumin can inhibit the activation of IKK linked to the activation of NF-κB, and this leads to the suppression of expression of inflammatory biomarkers such as cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (4). Fourth, the spice has been shown to downregulate the expression of various NF-κB-regulated proinflammatory adipocytokines including chemokines (such as MCP-1, MCP-4, and eotaxin) (199) and interleukins (IL-1, IL-6, and IL-8) (195). Curcumin also suppressed the expression of plasminogen activator inhibitor type-1 through the inhibition of the transcription factor early growth response (Egr)-1 gene product (131) that has been closely linked with insulin resistance and obesity. Fifth, it has been reported to mimic most antidiabetic drugs in that it activates PPAR-γ in hepatic stellate cells (204). Sixth, this nutraceutical has been shown to downregulate activation of c-Jun NH2 terminal kinase ( JNK) (195). Seventh, curcumin has been shown to inhibit the Wnt/β-catenin pathway, which is closely linked to obesity (70). Later studies have indicated that curcumin inhibits Wnt pathway signaling through downregulation of the transcription coactivator p300 (157). Another potential mechanism by which curcumin could inhibit β-catenin signaling is through inhibition of glycogen synthase kinase (GSK)-3β, which directly causes the phosphorylation of β-catenin. Curcumin was found to inhibit GSK-3β with as little as 66 nM IC50 (32). Eighth, the spice has been shown to induce the expression of hemeoxygenase (HO)-1 through the activation of Nrf2 in pancreatic cells and thus mediate the survival of these cells (14, 111). Ninth, curcumin downregulates the secretion of insulin-like growth factor-1 but induces the expression of insulin-like growth factor binding protein-3 (201). Tenth, this nutraceutical interrupts leptin signaling by reducing phosphorylation levels of the leptin receptor (Ob-R) and its downstream targets (189). In addition, curcumin suppresses gene expression of Ob-R in HSCs. Finally, curcumin has been reported to increase the expression of adiponectin, which negatively controls obesity (197).

## Effect of Curcumin on Adipocytes

Several studies have been done in vitro to examine the effect of curcumin on adipocytes, in most cases using 3T3-L1 mouse embryonic fibroblasts, which differentiate into adipocytes. Ejaz et al. (48) examined the effect of curcumin on angiogenesis, adipogenesis, differentiation, and apoptosis in these cells. They found that curcumin suppressed the differentiation of preadipocytes to adipocytes and induced apoptosis; it also inhibited adipokine-induced angiogenesis of human endothelial cells through suppression of expression of vascular endothelial growth factor-α. Curcumin increased the activation of AMP-activated protein kinase (AMPK) in adipocytes by phosphorylating the α-subunit of AMPK and suppressed the expression of aminocyclopropane carboxylic acid by phosphorylation. Treatment of cells with curcumin increased the fatty acid oxidation in adipocytes (48).

Recently, curcumin was shown to suppress differentiation of adipocytes through activation of the Wnt/β-catenin pathway. Ahn's group (6) showed that curcumin inhibited the expression of CCAAT/enhancer binding protein-α (C/EBP-α), PPAR-γ, downstream genes, sterol regulatory element-binding protein (SREBP)-1, and fatty acid synthase (FAS) in adipocytes. This was accompanied by inhibition of phosphorylation of ERK1/2, JNK, and

p38 by curcumin. Curcumin induced the nuclear localization of β-catenin and inhibited the expression of GSK-3β, CK-1α, and axin, which led to an increase in expression of c-myc and cyclin D1. In addition to Wnt signaling, curcumin inhibited the expression of other markers of adipocyte differentiation, including Ap2 and Wnt 10β, but it induced Lrp 5. In sum, curcumin could affect adipocytes through the Wnt/β-catenin pathway. Lee and colleagues (94) also showed that curcumin stimulates AMPK in 3T3 L1 adipocytes, which leads to downregulation of PPAR-γ and thus inhibition of differentiation. In contrast to these studies, Kuroda et al. (92) used human adipocytes and showed that ethanolic extracts of turmeric can stimulate the differentiation of human preadipocytes to adipocytes in a dose-dependent manner, an activity also mimicked by PPAR-γ agonists such as troglitazone. Kuroda's group showed that besides curcumin, demethoxycurcumin, bis-demethoxycurcumin, and ar-turmerone also exhibited PPAR-γ binding activity. These results are in agreement with those reported by Nishiyame et al. (117), who showed that curcumin binds PPAR-γ and stimulates differentiation of human adipocytes.

Wang et al. (195) also examined the effect of curcumin on 3T3-L1 adipocytes. They showed that curcumin increased insulin-stimulated glucose uptake in the cells and suppressed the transcription and secretion of TNF-α and IL-6 induced by palmitate through the inhibition of activation of NF-κB. Curcumin decreased the activities of JNK, ERK1/2, and p38MAPK. Because JNK inhibitors blocked the upregulation of palmitate-induced TNF-α expression, it was concluded that curcumin mediates its effects in adipocytes through inhibition of JNK. Gonzales & Orlando (54) examined the effect of curcumin on NF-κB and on expression of NF-κB-regulated gene products in adipocytes. They demonstrated that both preadipocytes and differentiated adipocytes express the genes for TNF-α, IL-6, and COX-2. Preadipocytes were also found to express IL-1β, but differentiated adipocytes did not. TNF-α treatment activated NF-κB signaling in differentiated adipocytes and increased IL-6 and COX-2 mRNA levels. TNF-α also activated IL-1β gene expression in differentiated adipocytes, but it had no effect on endogenous TNF-α mRNA levels. No detectable TNF-α or IL-1β was secreted by adipocytes. Curcumin treatment inhibited NF-κB activation and resulted in a reduction of TNF-α, IL-1β, IL-6, and COX-2 gene expression and of secreted IL-6 and prostaglandin.

Another potential mechanism of suppression of NF-κB in adipocytes is through induction of adiponectin (Figure 3). Curcumin can enhance the expression of adiponectin in adipocytes (120). Furthermore, adiponectin has been shown to inhibit NF-κB activation in endothelial cells through a cyclic adenosine monophosphate-dependent pathway (125). This 30-kDa plasma protein is made almost exclusively by adipose tissue, can bind to collagens, circulates in high (μg/ml) concentration in plasma, has anti-inflammatory and vasoprotective activities, is involved in metabolic disorders such as obesity and diabetes, and enhances insulin sensitivity (26, 205). Adiponectin can block TNF-α-induced adherence of monocytes to endothelial cells by decreasing the surface expression of VCAM-1, ICAM-1, and ELAM-1 (124) and stimulating production of nitric oxide in vascular endothelial cells (36). The role of the inflammatory cytokine MCP-1 in obesity is known from several studies in which MCP-1-deficient or MCP-1 receptor-deficient mice were resistant to atherosclerosis (56, 57) and to insulin resistance (77, 198). Woo et al. (199) showed that curcumin inhibits the release of MCP-1 from 3T3-L1 adipocytes. They also showed that curcumin suppresses obesity-induced inflammatory responses by suppressing macrophage accumulation in adipose tissue and by suppressing expression of adipocytokines including TNF-α, MCP-1, and nitrite. Suppression of MCP-1 expression from adipocytes by curcumin should thus have beneficial effects on obesity-related pathologies such as insulin resistance and atherosclerosis. All these studies suggest that curcumin directly modulates the metabolism of adipocytes.

## Effect of Curcumin on Hepatic Stellate Cells

Nonalcoholic steatohepatitis (NASH) is an advanced form of nonalcoholic fatty acid liver disease, characterized by fat accumulation and inflammation in the liver (9, 75, 102). NASH is commonly found in obese people and is usually accompanied by abnormally elevated levels of plasma leptin (hyperleptinimia). NASH patients usually develop hepatic fibrosis and even cirrhosis. Leptin and its receptor are known to stimulate HSC activation and play an essential role in hepatic fibrosis in patients with NASH. Hepatic stellate cells are the major effector cells during liver fibrogenesis and could be activated by leptin. Curcumin has been shown to suppress hepatic fibrosis (119). This nutraceutical has also been shown to inhibit HSC activation (204). Activation of PPAR-γ inhibits the proliferation of nonadipocytes. The level of PPAR-γ is dramatically diminished along with activation of HSC. Curcumin, the yellow pigment in curry, is a potent antioxidant. Xu et al. (204) showed that curcumin significantly inhibited the proliferation of activated HSC and induced apoptosis in vitro. This was mediated through induction of the gene expression of PPAR-γ and activated PPAR-γ. Blocking its transactivating activity by a PPAR-γ antagonist markedly reduced the effects of curcumin on inhibition of cell proliferation. Curcumin was also found to block the expression of gene products regulated by PPAR-γ including α1 (1) collagen, α-SMA, connective tissue growth factor (CTGF), and receptors for TGF-β, platelet-derived growth factor (PDGF)- β, and EGF (212, 213). These results provide a novel insight into mechanisms underlying the inhibition of activated HSC growth by curcumin. Tang et al. (189) more recently showed that curcumin eliminates the stimulatory effect of leptin on HSC by interrupting leptin signaling and attenuating leptin-induced oxidative stress. Curcumin inhibits phosphorylation of Ob-R and its downstream signaling. Curcumin also suppresses gene expression of Ob-R in HSCs, which requires the activation of PPAR-γ and de novo synthesis of glutathione (GSH). Thus, curcumin abrogates the effects of leptin on the activation of HSC by blocking leptin signaling. In another report, Kang & Chen (79) showed that curcumin suppressed low-density lipoprotein (LDL)-receptor gene expression in activated HSC in vitro by activating PPAR-γ and differentially regulating gene expression of SREBPs, which reduces cellular cholesterol and attenuates the stimulatory effect of LDL on HSC activation. These reports all indicate that curcumin mediates its effects on HSC through multiple mechanisms.

## Effect of Curcumin on Pancreatic Cells

Curcumin has direct effects on pancreatic beta cells, which could contribute to the hypoglycemic/antidiabetic effects of this agent. Best et al. (27) reported that curcumin induces electrical activity in rat pancreatic beta cells by activating volume-regulated anion channel. This effect led to depolarization of cell membrane potential, generation of electrical activity, and enhanced insulin release. Curcumin also decreased the beta cell volume, suggested that this is another novel target for curcumin.

Another report indicated that curcumin induces the expression of phase 2 enzyme HO-1 through activation of Nrf2, which binds to antioxidant response element in mouse beta cells (137). This enzyme is known to have cytoprotective effects on pancreatic beta cells. Induction of HO-1 correlated with the increase in expression of glutamyl cysteine ligase (GCL) needed for GSH biosynthesis and NADPH:quinone oxidoreductase, which detoxifies quinines. Interestingly, demethoxycurcumin and bis-demethoxycurcumin were more active than curcumin in inducing these phase 2 enzymes. The same group later showed that curcumin induced the expression of HO-1; modulatory subunit of γ-GCL; and NADPH:quinone oxidoreductase-1 at the mRNA and at the protein levels in human islets (23). Increased expression of antioxidant enzymes was seen in beta cells of islets. Curcumin also increased the islet content of GSH (a product of the modulatory subunit of γ-GCL) and the basal insulin secretion and protected them from oxidative stress.

Curcumin has also been shown to protect islets against streptozotocin (STZ)-induced oxidative stress by scavenging free radicals (104). Meghana et al. (104) showed that islet viability and secreted insulin in curcumin-pretreated islets were significantly higher than in islets exposed to STZ alone. Curcumin retarded the generation of islet ROS along with the inhibition of poly ADP-ribose polymerase-1 activation. Kanitkar et al. (81) also showed curcumin can protect islets from cytokine-induced cell death in vitro by scavenging ROS. In vivo, they showed that curcumin when given intraperitoneally prevents the progression of diabetes induced by STZ, and this correlated with suppression of inflammatory cytokine (TNF-α and IL-1β) in the serum and pancreas induced by STZ and maintained the insulin-production capacity (81). Curcumin was also found to protect islets during cryopreservation of the islets (80).

## EFFECT OF CURCUMIN ON OBESITY AND METABOLIC DISORDERS IN ANIMALS

Numerous studies have been done on the effect of dietary curcumin in metabolic disorders in rodents. An early study examined the effect of curcumin on fatty acid metabolism; it showed that curcumin can lower serum and liver cholesterol levels in rats (147). Patil & Srinivasan (128) used hypercholesteremic rats to demonstrate that curcumin induces hypocholesteremia. Babu & Srinivasan (21) showed that dietary curcumin lowered blood cholesterol significantly in these diabetic animals. The cholesterol decrease was exclusively from the LDL-VLDL fraction. A significant decrease in blood triglycerides and phospholipids was also brought about by dietary curcumin in diabetic rats. In a parallel study, diabetic animals maintained on a high-cholesterol diet had greater extents of hypercholesterolemia and phospholipidemia than did those maintained on a control diet. Curcumin lowered cholesterol and phospholipid levels in these animals also. Liver cholesterol, triglyceride, and phospholipid contents were elevated under diabetic conditions. Dietary curcumin showed a distinct tendency to counter these changes in lipid fractions of liver. This effect of curcumin was also seen in diabetic animals maintained on a high-cholesterol diet, countering the elevations in renal cholesterol and triglycerides. Babu & Srinivasan (21) found that hepatic cholesterol-7a-hydroxylase activity was markedly higher in curcumin-fed diabetic animals, suggesting curcumin induced a higher rate of cholesterol catabolism.

In another study by Babu & Srinivasan (20), albino rats rendered diabetic with STZ injection were fed a 0.5% curcumin diet or a 1% cholesterol diet. Diabetic rats maintained on curcumin for eight weeks had a lowered relative liver weight at the end of the study in comparison with the other diabetic groups and had lowered lipid peroxidation in plasma and urine. Babu & Srinivasan (21) concluded that curcumin feeding improves the metabolic status in diabetic conditions. Similarly, Quiles and colleagues demonstrated that oral administration of ethanolic extracts of turmeric (which primarily contain curcumin) to atherosclerotic rabbits inhibited lipid peroxidation in liver microsomes and mitochondria (139), inhibited LDL oxidation, and lowered plasma cholesterol, triglyceride, and phospholipid levels (144).

Curcumin also mediates its effects through a potential antioxidant mechanism. Dietary supplementation of curcumin in mice suppressed Fe/ascorbic acid–induced lipid peroxidation in liver (19). This correlated with the decrease in plasma triacylglycerol levels. In another study, Asai & Miyazawa (18) showed that dietary curcumin (0.2–1 g/100 g diet) prevents high-fat (15% soybean oil)-induced lipid accumulation in rat liver and epididymal adipose tissue; this correlated with induction of hepatic acyl-CoA oxidase. Kempaiah & Srinivasan (83) showed that a cholesterol-enriched diet for eight weeks increased the cholesterol contents of the red blood cell membrane (resulting in increased fragility), and

supplementation with dietary curcumin restored levels to normal. These effects, however, were not unique to curcumin; they were also noted with other spices including capsaicin and garlic. The same investigators also reported a reduction of oxidative stress in red blood cell membrane and liver tissue by curcumin (0.2%) in rats rendered hyperlipidemic by maintaining them on high-fat (30%) diet for eight weeks (84). Kempaiah & Srinivasan (85, 86) later showed that hypercholesteremia in mice reduced the activity of $Ca^{2+}$, $Mg^{2+}$ ATPase in erythrocyte membranes and diet with curcumin (0.2%) or capsaicin (0.015%) reversed. Mesa et al. (105) also demonstrated that oral administration of hydroalcoholic extracts of turmeric (1.66 mg/kg body weight) prevented the oxidation of red blood cell membranes and oxidative stress in rabbits fed an atherogenic diet. Curcumin was found to abolish oxidative stress (lipid peroxidation and protein carbonyls) and induce antioxidant enzymes in STZ-induced diabetic rats but had no effect on the hyperglycemic state in most tissues (186).

The C57BL/Ks-db/db diabetic mouse is considered to be a good model for type 2 diabetes. It displays many features of human disease including hyperphagia, hyperglycemia, insulin resistance, and progressive obesity. Seo et al. (162) used this model to examine the effect of curcumin on insulin resistance, glucose homeostasis, and oxidative damage in C57BL/Ks-db/db diabetic mice and their age-matched lean nondiabetic db/+ mice. They fed curcumin (0.02% wt/wt) for six weeks. Curcumin lowered the blood glucose and glycosylated hemoglobin levels and suppressed body weight loss in db/db mice. Curcumin also increased the plasma insulin levels and increased hepatic glucokinase activity. However, it lowered the activities of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase and the hepatic activities of FAS, β-oxidation, 3-hydroxy-3-methylglutaryl coenzyme (HMG-Co) reductase, and acyl-CoA: cholesterol acyltransferase. In addition, curcumin lowered plasma free fatty acid, cholesterol, and triglyceride levels and increased hepatic glycogen and skeletal muscle LPL. Moreover, polyphenol antioxidant activities [superoxide dismutase (SOD), catalase, and glutathione peroxidase] in erythrocytes and liver led to a reduction in lipid peroxidation. These changes were not observed in control db/+ mice. Overall, Seo's group concluded that curcumin has the potential to lower blood glucose levels.

Because the lipoprotein profiles of hamsters are more similar to humans than are those of mice or rats, Jang et al. (71) examined the effect of curcumin on insulin resistance in hamsters fed a high-fat and high-cholesterol diet. They found that curcumin (50 mg/100 g diet) lowered the levels of free fatty acids (FFAs), total cholesterol, triglycerides, and leptin levels and suppressed insulin resistance. It also elevated the levels of HDL and apolipoprotein A-1 and paraoxonase activity in plasma and lowered hepatic cholesterol and triglyceride levels. Fatty acid-β-oxidation in the liver was enhanced, but FAS, 3HMG-CoA reductase, and acyl-CoA: cholesterol acyltransferase were significantly lowered. Overall, curcumin exhibited hypolipidemic effects in hamsters fed a high-fat diet.

In another study, it was shown that dietary curcumin (3% by wt) ameliorated diabetes in obese and leptin-deficient ob/ob C57 BL/6J mice fed a high-fat diet as indicated by glucose and insulin-tolerance testing and percentage glycosylated hemoglobin (197). Curcumin also reduced macrophage infiltration of WAT, increased adipose tissue adiponectin production, and decreased hepatic NF-κB activity, hepatomegaly, and markers of hepatic inflammation such as TNF-α, IL-1β, suppressor of cytokine signaling 3, MCP-1, and C-C motif receptor-2. Jain et al. (69) reported that curcumin supplementation lowers the production of inflammatory cytokines including TNFα, IL-6, IL-8, and MCP-1 from monocytes induced by high glucose. They also showed that the blood levels of TNF-α, IL-6, MCP-1, and glucose and glycosylated hemoglobin are decreased in diabetic rats on a curcumin diet (69).

Among the endogenous cannabinoid (CB) receptors,CB-1, which is expressed in the brain, smooth muscle cells, and colon cells, has been linked with food intake and body weight in mice (130). CB-1 antagonists are known to reduce food intake and body weight. Recent studies indicated that curcumin selectively binds to CB-1 with nanomolar affinity and acts as an antagonist. When administered to mice repeatedly (2–10 mg/kg; twice daily; IP $\times$ 3 days), curcumin significantly reduced body weight in a dose-dependent manner (160).Thus, curcumin could work against obesity by reducing food intake and body weight.

## EFFECT OF CURCUMIN ON OBESITY-RELATED DISEASES

### Heart

The incidence of coronary syndrome and other cardiovascular complications increases as a result of obesity. Premature ventricular contractions causing arrhythmia and sudden death also frequently occur in obese people. Sudden cardiac death, associated with sympathetic activation, in obesity is frequently associated with hyperlipidemia connected with increased plasma FFA levels. Pongchaidecha et al. (135) examined the effect of curcumin on cardiac sympathovagal disturbance in high-fat-induced obese rats. Along with high-fat diet, they fed the animals 30, 60, or 90 mg/kg body weight curcumin for 12 weeks. They found that elevated plasma FFA in high-fat-induced obese rats is associated with an increased low-frequency/high-frequency ratio, an expression of sympathovagal disturbance; curcumin supplementation ameliorated cardiac autonomic imbalance in high-fat-fed rats by decreasing the plasma FFA concentration. Quiles et al. (140) induced atherosclerosis in rabbits by feeding them an atherogenic diet, which caused higher levels of plasma lipid peroxide, lowered α-tocopherol and coenzyme Q levels, and damaged the thoracic and abdominal aorta. All these conditions were reversed by curcumin supplementation of the diet.

In humans, plasma LDL is the major transport protein for cholesterol, and its elevation is a major risk factor for the development of atherosclerosis. A large amount of cholesterol in LDL fractions is atherogenic, whereas that in high-density lipoprotein is protective. Oxidation of LDL plays an important role in the development of atherosclerosis, and inhibition of LDL oxidation can reduce the risk of atherosclerosis. Curcumin has been shown to inhibit LDL oxidation in vitro (144). Recently, two independent groups demonstrated that administration of curcumin for two weeks to rats or mice can prevent hypertrophy of the heart (95, 108). Both groups showed that these effects were mediated through the ability of curcumin to inhibit p300, a histone acetyltransferase.

### Kidney

Diabetic nephropathy that leads to end-stage renal failure is a major cause of morbidity in diabetic patients. A structural hallmark of this disease is thickening of the glomerular basement membrane and mesangial matrix expansion, characterized by increased production of extracellular matrix (ECM) proteins, which are regulated by TGF-β1, NF-κB, and p300 in the kidneys. Hyperglycemia is the key initiating factor that mediates increased oxidative stress, leading to increased production of vasoactive factors (endothelial nitric oxide synthase and endothelin-1) and ECM proteins. Chiu et al. (38) examined the effect of curcumin on diabetic nephropathy in rats and showed that STZ-induced diabetes caused hyperglycemia, which led to the upregulation of endothelin-1, TGF-β, and ECM (fibronectin and extradomain B-containing fibronectin) in the kidney. These changes were accompanied by oxidative stress (as indicated by a decrease in 8-OHdG), mesangial expansion, induction of p300, and activation of NF-κB. Curcumin treatment inhibited p300, suppressed the activation of NF-κB, and decreased TGF-β, endothelial nitric oxide synthase, vasoactive factors, and ECM. Thus, curcumin seems to prevent diabetes-induced abnormalities in the kidney.

One of the earliest known effects of turmeric and its active component curcumin was on blood sugar levels. The beneficial effects of curcumin on blood sugar levels in diabetic rabbits were reported nearly half a century ago (112). A decrease in blood sugar levels has also been reported in diabetic rats given oral curcumin (0.08 g/kg body weight) or turmeric (1 g/kg), and this correlated with the decrease in oxidative stress (17). This effect was linked with a decrease in the enzyme sorbitol dehydrogenase, which converts sorbitol to fructose. In these studies, curcumin was more effective than turmeric, which contains only 2%–5% curcumin. Using genetically modified diabetic KK-A mice, Kuroda et al. (92) also showed that turmeric (0.2–1 g/100 g diet for four weeks) has hypoglycemic effects. These results are in agreement with those reported by Nishiyama et al. (117).

Chronic hyperglycemia associated with diabetes can lead to secondary complications including diabetic cataracts, as characterized by cloudiness or opacification of the crystalline eye lens, leading to blindness (41, 74, 98). Turmeric (0.5%) and curcumin (0.01%) were found to delay the progression and maturation of cataract in rats with STZ-induced diabetes (185). Interestingly, turmeric was found to be more effective than curcumin. This is consistent with another study in which attenuation of galactose-induced cataracts by curcumin in rats was reported (126). The mechanism of galactose-induced cataract, however, differs from that of STZ-induced diabetic cataract.

Diabetes is a major risk factor for neuropsychiatric deficits such as stroke, cerebrovascular diseases, diabetic encephalopathy, depression, and anxiety. Diabetic encephalopathy is characterized by impaired cognitive functions due to direct neuronal damage caused by intracellular glucose. Chronic treatment with curcumin (60 mg/kg; p.o.) significantly attenuated cognitive deficit, cholinergic dysfunctions, oxidative stress, and inflammation in diabetic rats (91, 165).

## EFFECT OF OTHER SPICE-DERIVED NUTRACEUTICALS ON OBESITY

In addition to curcumin, there are reports that other spice nutraceuticals may also affect obesity and insulin resistance, in part through the modulation of inflammatory pathways (30, 188). This may be because a significant structural homology exists between curcumin, capsaicin derived from red chili, piperine derived from black pepper, eugenol derived from cloves, and gingerol derived from ginger (Figure 1). In addition to turmeric, several other spices, e.g., garlic, onions, red pepper, and fenugreek, have been shown to have beneficial hypolipidemic or hypocholesterolemic effects (82, 164, 177). In another study, dietary supplementation with capsicum pigment but not rosemary suppressed Fe/ascorbic acid–induced lipid peroxidation in liver (19). Several spice-derived nutraceuticals have been identified that can inhibit oxidation of LDL in vitro, including curcumin, capsaicin, eugenol, piperine, zingerone (ginger), and cuminaldehyde (cumin) (113, 150). Manjunatha & Srinivasan (100) showed that dietary curcumin and capsaicin inhibited the oxidation of LDL in rats.

Most of these spices also exhibit potent antioxidant activity (1, 163). For instance, various spice-derived nutraceuticals suppress arachidonic acid–induced platelet aggregation in vitro in the following order of potency: eugenol>capsaicin>curcumin>cinnamaldehyde>piperine (141). The antiinflammatory activity of these spices is also indicated by their ability to directly inhibit 5-lipooxygenase, an enzyme responsible for leukotriene production (136). Based on IC50, their ability to suppress 5-lipooxygenase was found to be eugenol>curcumin>cinnamaldehyde>piperine>capsaicin. How other spice-derived nutraceuticals affect obesity and obesity-related diseases is elaborated below.

### Capsaicin

Capsaicin is an active component of red chili. Numerous studies suggest that capsaicin has a potential against obesity and insulin resistance (for review, see 184). We have shown that capsaicin can suppress both NF-κB and signal transducer and activators of transcription-3 pathways (28, 171). Capsaicin has been shown to induce apoptosis and inhibit adipogenesis (64). This nutraceutical was found to modulate adipokine gene expression and protein release from adipocytes derived from obese mouse (78). These investigators (78) showed that capsaicin can also suppress the inflammatory response of macrophages derived from adipose tissue. Capsaicin-desensitized rats exhibit a long-term decrease in body fat and in brown adipose tissue (42).

Capsaicin mediates its effects against adipogenesis and obesity through numerous mechanisms. One of the mechanisms is the activation of its receptor, transient receptor potential vanilloid type 1 (TRPV-1) channels, in adipocytes (184, 210). In agreement, TRPV-1-null mice are protected from diet-induced obesity (110). All these studies suggest the potential role of red chili in preventing obesity.

### Gingerol

Gingerol is one of the most active compounds in ginger (*Zingiber officinale*). Methanolic extracts of dried ginger have been shown to prevent fructose-induced elevation of serum cholesterol, triglycerides, glucose, insulin, and gain in body weight in rats (76). Ginger extracts containing gingerol were found to enhance adipocyte differentiation (161) and insulin-sensitive glucose uptake, thus suggesting its potential for treating diabetes. Zingerone, another component of ginger, was found to suppress the inflammatory responses of adipose tissue in obesity by suppressing the inflammatory action of macrophages and release of MCP-1 from adipocytes (199). Thus, these studies also suggest that ginger has potential in preventing obesity and obesity-linked metabolic effects.

### Piperine

Piperine is an active component of black pepper that can effectively suppress lipid peroxidation (58, 176) and enhance the bioavailability of curcumin and other drugs through the inhibition of drug-metabolizing enzymes in the liver (169). The effect of piperine was examined in STZ-induced diabetic Sprague-Dawley rats (148). Treatment with piperine reversed the diabetic effects on GSSG concentration in brain, on renal glutathione peroxidase (GPO) and SOD activities, and on cardiac glutathione reductase activity and lipid peroxidation. Piperine treatment did not, however, reverse the effects of diabetes on hepatic GSH concentrations, lipid peroxidation, or GPO or catalase activities; on renal SOD activity; or on cardiac GPO or catalase activities. These data indicate that subacute treatment with piperine is only partially effective as an antioxidant therapy in diabetes.

### Cinnamaldehyde

Cinnamaldehyde is one of the active components of cinnamon. The essential oil of cinnamon bark is about 90% cinnamaldehyde. There are numerous reports about the role of cinnamon in obesity and diabetic conditions (13, 72, 123, 180, 193). Antidiabetic effects of cinnamon extracts have been demonstrated in db/db mice (89). In vitro studies have shown that cinnamon can increase the expression of PPAR-γ/α and their target genes such as LPL, CD 36, GLUT 4, and ACO in 3T3-L1 adipocyte (166). The transactivities of both full-length and ligand-binding domain of PPAR-γ/α were activated by cinnamon. Furthermore, this spice in vivo was found to activate PPARγ and α, resulting in improved insulin resistance and reduced fasting glucose, FFA, LDL-cholesterol, and aspartate aminotransferase levels in high-caloric-diet-induced obesity and db/db mice in its water extract form (166). Another

study showed that water extracts of cinnamon reverse TNF-induced overproduction of intestinal apoB48-containing lipoprotein in vivo by modulation of expression of inflammatory cytokines, insulin, and lipoprotein-signaling pathways (138). Similar to insulin, cinnamon has been shown to regulate protein phosphorylation and dephosphorylation of insulin receptor through inhibition of PTP-1 (65). Cao et al. (34) showed that cinnamon-derived nutraceuticals can increase the insulin receptor–β levels and that water-soluble extracts and these nutraceuticals together can increase the glucose-transporting protein 4 and tristetraprolin levels in the adipocytes. Tristetraprolin mRNA levels in the adipocytes increased by almost sixfold.

The antidiabetic activity of cinnamon appears to be due to multiple constituents including cinnamaldehyde, hydrocinnamic acid, polyphenol type A polymer, dihydroxyhydrocinnamic acid, and proanthocyanidines (13, 88, 132, 180).

### Fenugreek

Fenugreek (*Trigonella foenum-graecum*) seed, used as a condiment, is documented for amelioration of abnormalities in lipid homeostasis due to its hypolipidemic properties. The hypolipidemic effect of a novel thermostable extract of fenugreek seeds has been examined on differentiating and differentiated 3T3-L1 cells and HepG2 cells cultured in normal or sterol-enriched conditions (194). These extracts inhibited accumulation of fat in differentiating and differentiated 3T3-L1 cells via decreased expression of adipogenic factors such a PPAR-γ, sterol SREBP-1, and C/EBP-α. Cellular triglycerides and cholesterol concentrations were decreased in HepG2 cells via reduced expression of SREBP-1. These extracts also upregulated LDL-receptor expression, resulting in enhanced LDL uptake. Treating fat-supplement-fed C57BL6/J mice with extracts for 15 days resulted in decreases of serum triglyceride, LDL-cholesterol, and body weight. Thus, these studies suggest that fenugreek has potential application in the management of dyslipidemia and its associated metabolic disorders.

## HUMAN STUDIES

Several pilot studies have been done in human subjects with curcumin to examine its effect on obesity-related parameters. One of the first studies showed that curcumin lowered blood sugar levels in diabetic patients (178).Another study examined the effect of curcumin in humans on the levels of HDL- and LDL-cholesterol (146). Administration of 10 mg curcumin per day for 30 days to eight human subjects increased HDL-cholesterol, decreased LDL-cholesterol, and increased APO A but decreased APO B and APO A/B. The same group reported another study with curcumin in human subjects with atherosclerosis (143). In this study, 10 mg curcumin was administered twice a day for 15 days to 16 men and 14 women. Curcumin significantly lowered the levels of plasma fibrinogen in both men and women.

A placebo-controlled double-blind clinical trial of capsaicin in obese subjects has been carried out. Body fat decreased in this eight-week intervention trial (P < 0.05) (25). A 12-week, placebo-controlled, double-blind, randomized study examined the effect of a novel capsinoid on fatness and energy metabolism in humans (172). These investigators explored the safety and efficacy of capsinoids taken orally (6 mg/d) for weight loss, fat loss, and change in metabolism. Treatment appeared to be safe and was associated with abdominal fat loss. Capsinoid ingestion was associated with an increase in fat oxidation. No significant difference in total change in adiposity was noted, but abdominal adiposity decreased more in the capsinoid group than in the placebo group, and this change correlated with the change in body weight. The authors identified two common genetic variants that may be predictors of

therapeutic response. These included TRPV-1 Val585Ile and UCP2 -866 G/A, and they correlated with change in abdominal adiposity.

Most of the studies in humans involving the effects of spices on obesity and diabetes have tested cinnamon (40, 47, 61, 73, 88, 99, 154, 158, 173, 174, 216). All these studies suggested that cinnamon modulated the levels of various biomarkers linked with insulin resistance and obesity favorably. For instance, Crawford (40) showed that taking cinnamon could lower serum HbA1C in type 2 diabetes with HbA1C >7. The difference between the groups was found to be statistically significant. In another study, cinnamon was also found to affect postprandial blood glucose levels, gastric emptying, and satiety in human subjects (61). All these studies provide evidence that cinnamon can affect the metabolic syndrome.

## CONCLUSION

This review delineates the role of various spice-derived nutraceuticals, turmeric in particular, in obesity and insulin resistance. Whether preclinical or clinical, most studies suggest that curcumin and the other spices have favorable effects against obesity and insulin resistance as well as against various complications resulting from these diseases. The relatively low cost of these spices, their safety, and the evidence of their efficacy make it essential to include them as a part of the daily diet. Adding spices, especially turmeric, everyday is likely to help most people in the prevention of obesity, diabetes, and associated complications. More research, in particular clinical trials, is needed to further strengthen the link between spices and chronic diseases such as obesity and insulin resistance. Most human studies have been pilot studies with a small number of human subjects. Although curcumin and other spices are safe, the effective dose required to modulate these metabolic responses is unclear at present.

## Glossary

| | |
|---|---|
| **CAM** | complementary and alternative medicine |
| **NHIS** | National Health Interview Survey |
| **PAI-1** | plasminogen activator inhibitor type -1 |
| **MCP-1** | monocyte chemotactic protein-1 |
| **PTP** | protein tyrosine phosphatase |
| **PPAR** | peroxisome proliferator-activated receptor |
| **PGC-2** | PPAR gamma coactivator-2 |
| **PPRE** | peroxisome proliferator response element |
| **C/EBP-α** | CCAAT/enhancer binding protein-alpha |
| **SREBP** | sterol regulatory element-binding protein |
| **NASH** | nonalcoholic steatohepatitis |
| **TRPV-1** | transient receptor potential vanilloid type 1 |

## Acknowledgments

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**Figure 1.**
Similarity in chemical structure of curcumin and other nutraceuticals derived from different spices.
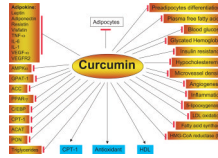
**Figure 2.**
Modulation by curcumin of various targets linked to obesity. Orange/yellow boxes indicate downregulation, and blue boxes indicate upregulation.
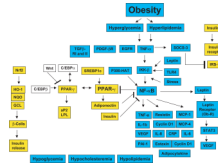
**Figure 3.**
Inflammatory cell signaling network implicated in obesity and insulin resistance. Cell-signaling intermediates indicated in blue boxes are downregulated, yellow are upregulated, and white could go up or down based on the cell type.

**Table 1**

A list of the metabolic effects of curcumin

| | |
|---|---|
| Can lower blood sugar levels in rabbits | (109) |
| Decreases blood sugar levels in diabetic subjects | (175) |
| Increases fecal excretion | (144) |
| Suppresses the serum and liver cholesterol levels in rats | (144) |
| Can reverse the retinol deficiency in rats | (79, 80) |
| Induces hypocholesterolemia in induced hypercholesterolemic rats | (128) |
| Reverses progression of experimentally induced diabetes in albino rats | (20) |
| Decreases renal lesions associated with STZ-induced diabetic rats | (183) |
| Induces hypolipidemia (blood triglycerides and PL) associated with STZ-induced diabetic rats | (21) |
| Reduces oxidative stress in high-fat-diet-fed atherosclerotic rabbits | (139) |
| Inhibits LDL oxidation and lowers cholesterol levels in rabbits with experimental atherosclerosis | (145) |
| Prevents deposition of triglycerides in the liver of mice | (19) |
| Prevents the high-fat-diet-induced lipid accumulation in liver and epididymal adipose tissue of rat | (18) |
| Reverses structural integrity of erythrocytes from cholesterol (0.5%)-fed rats | (83) |
| Reduces the oxidative stress and blood sugar levels of diabetic rats | (17) |
| Delays STZ-induced diabetic cataracts in rats | (185) |
| Inhibits galactose-induced cataract | (126) |
| Suppresses blood glucose levels via activation of PPAR-γ in type 2 diabetic KK-A mice | (92, 117) |
| Inhibits liver microsome membrane oxidation in rabbits fed with an atherogenic diet | (105) |
| Reduces the oxidative stress (total thiols, LPO, and GSH) in high-fat-fed (30%) rats | (84) |
| Reverses the deformity and fragility of erythrocytes from cholesterol-fed (0.5%) rats | (85) |
| Reduces the hepatic triglyceride levels in high-fat-fed (30%) rats | (86) |
| Inhibits oxidative stress in streptozotocin-induced diabetic rats | (186) |
| Suppresses the expression of LDL receptor by activating PPAR-γ and inactivating SREBPs | (79) |
| Attenuates diet-induced hypercholesterolemia | (15) |
| Induces changes in gene expression involved in cholesterol homeostasis | (134) |
| Inhibits the activation of HSC or fat cells by inhibiting proliferation and inducing apoptosis | (212) |
| Induces gene expression of PPAR-γ | (204) |
| Blocks PDGF signaling cascade | (215) |
| Blocks EGF signaling cascade | (215) |
| Blocks TGF-β signaling cascade | (213) |
| Attenuates oxidative stress in fat cells | (214) |
| Reduces leptin receptor (OB-R) expression through PPAR-γ and inhibits phosphorylation of OB-R in HSC | (189) |
| Decreases high glucose–induced inflammatory cytokine (IL-6, IL-8, MCP-1, TNF-α) production in rats | (69) |
| Reduces oxidative stress and attenuates fatty acid streak development in rabbits | (140) |
| Induces apoptosis in vascular smooth muscle cells | (37) |
| Ameliorates cardiac autonomic imbalance in high-fat-fed rats by decreasing plasma FFA | (135) |
| Inhibits diabetic nephropathy by inhibiting p300 and NF-κB in rats | (38) |
| Inhibits diabetic nephropathy in rats | (165) |
| Inhibits differentiation of adipocytes through modulation of AMPK and PPAR-γ | (94) |

| | |
|---|---|
| Cardioprotective in myocardial reperfusion-injury model in mice | (106) |
| Reverses obesity-associated inflammation and diabetes in mouse model of insulin-resistant obesity | (197) |
| Inhibits adipogenesis in adipocytes and angiogenesis and obesity in mice | (48) |
| Inhibits induced oxidation of LDL in experimental rats | (100) |
| Reduces the lipid peroxide levels in high-fat-fed (30%) rats | (101) |
| Lowers serum levels of FFA, total cholesterol, triglycerides, and leptin but elevates HDL and apoA in hamsters | (71) |
| Lowers the hepatic activity of FAS, β-oxidation, and HMG-CoA reductase in diabetic db/db mice | (162) |
| Prevents cytokine-induced islet death and diabetogenesis in STZ-induced diabetic rats | (81) |
| Prevents diabetes-induced encephalopathy in rats | (91) |
| Enhances beta cell survival by upregulating HO-1 through induction of Nrf2 | (137) |
| Directly stimulates the beta cell function (VRAC) leading to release of insulin and hypoglycemia | (27) |
| Inhibits the production of proinflammatory cytokines such as TNFα, MCP-1, and NO from adipocytes | (199) |
| Induces hypolipidemia in high-fat-fed rats | (101) |
| Suppresses adipogenic differentiation through activation of Wnt/b-catenin signaling | (6) |

AMPK-activated protein kinase; EGF, endothelial growth factor; FAS, fatty acid synthase; FFA, free fatty acid; GSH, glutathione; HDL, high-density lipoprotein; HMG, 3-hydroxy-3-methylglutryl; HO-1, hemeoxygenase-1; HSC, hepatic stellate cells (also called fat cells); LDL, low-density lipoprotein; LPO, lipid peroxide; NF-κB, nuclear factor-kappa B; PDGF, platelet-derived growth factor; PL, phospholipids; PPAR-γ, peroxisome proliferator-activated receptor-gamma; SREBP, sterol regulatory element–binding protein; STZ, streptozotocin; TGF, tissue growth factor; TNFα, tumor necrosis factor alpha; VRAC, volume-regulated anion channel.