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REVIEW

New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases

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Abstract
Purpose A metabolic abnormality such as obesity is a major obstacle in the maintenance of the human health system and causes various chronic diseases including type 2 diabetes, hypertension, cardiovascular diseases, as well as various cancers. This study was designed to summarize the recent scientific knowledge regarding the anti-obesity role of curcumin (diferuloylmethane), which is isolated from the herb *curcuma longa*, known to possess anti-inflammatory activities. However, little is known about its exact underlying molecular mechanisms in the treatment of obesity and metabolic diseases. Furthermore, cell cultures, animal models of obesity, and few human clinical and epidemiological studies have added the promise for future therapeutic interventions of this dietary compound.
Methods An electronic search was performed using Science finder, Medline, Scopus, Google scholar and collected English language articles from 2000 to 2010, relating to the role of curcumin in obesity and metabolic diseases.
Results Obesity has been classified as a growing epidemic and its associated metabolic disorders are considered a major risk to the health system. Curcumin interacts with specific proteins in adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells, where it suppresses several cellular proteins such as transcription factor NF-kB, STAT-3, Wnt/β-catenin and activates PPAR-γ, Nrf2 cell signaling pathway. In addition, curcumin downregulates the inflammatory cytokines, resistin and leptin, and upregulates adiponectin as well as other associated proteins. The interactions of curcumin with several signal transduction pathways reverse insulin resistance, hyperglycemia, hyperlipidemia, and other inflammatory symptoms associated with obesity and metabolic diseases.
Conclusion The modulation of several cellular transduction pathways by curcumin has recently been extended to elucidate the molecular basis for obesity and obesity-related metabolic diseases. These findings might enable novel phytochemical treatment strategies as well as curcumin translation to the clinical practice for the treatment and prevention of obesity-related chronic diseases. Furthermore, the relatively low cost of curcumin, safety and proven efficacy make it advisable to include curcumin as part of healthy diet.

Keywords Curcumin · Obesity · Inflammation · Adipocytes · Adiponectin

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Introduction

The worldwide incidence of obesity has been rapidly increasing in the last two decades. According to a W.H.O report, obesity has been classified as a growing epidemic, and if immediate action was not taken, millions will suffer from an array of serious weight-related disorders. Obesity

counts a major health problem and common chronic disease, affecting more than 1 in 4 of all Americans, including children, and its incidence has been steadily increasing in the last two decades. In health surveys conducted in the United States in 2005, 24.2% of men and 23.5% of women or over one-fifth of the respondents were classified as obese [1]. Similarly, in the United Kingdom, a survey conducted in 2007 found that 21.9% of men and 24.4% of women were obese [2]. According to German government statistics report, two-thirds of all German men between the ages of 18 and 80 are overweight; almost half of all women have weight problems, and more than 1 million of their youth show symptoms of eating disorders [http://EzineArticles.com/?expert=Vreel_Mistee]. Several studies have shown that obesity is associated with an increase in mortality rates. Those persons who suffer from obesity have a 10–50% increased risk of death from natural causes compared with those of normal healthy weight individuals. This increased risk of death is due to the obesity-induced cardiovascular diseases, which accounts for about 112,000 deaths per year in the United States population, compared with healthy weight individuals [http://www.cdc.gov/obesity/index.html].

Obesity arises when there is an imbalance between energy intake, principally stored as triglycerides (food consumption), and energy expenditure (basal metabolic rate and biochemical processes). The excess energy is primarily stored in adipose tissue in the form of triglycerides. When adipose tissue function is compromised during obesity, the excessive fat accumulation in adipose tissue, liver, and other organs predisposes the individual to the development of metabolic changes that increase overall morbidity risks [3, 4]. Obesity is a complex trait influenced by diet, developmental stage, age, physical activity, and genes [5]. Obesity is also a significant risk factor for major diseases including Type 2 diabetes, coronary heart disease, hypertension, and certain forms of cancer including gastrointestinal, ovary, breast, uterus, cervical, pancreatic, hepatic, kidney, multiple myeloma, and lymphoma [6–8]. In addition, international Agency for Research on Cancer (IARC) used obesity prevalence data from Europe and relative risks from a meta-analysis of published studies, had shown that obesity was a cause of 11% of colon cancer, 9% of postmenopausal breast cancer, 39% of endometrial cancer, 25% of kidney cancer, and 37% of esophageal cancer cases [9].

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5dione], the active constituent of turmeric, has been used as a treatment for a wide variety of inflammatory ailments, including obesity and other metabolic diseases. Curcumin interacts directly with cyclooxygenase-2 (COX-2), DNA polymerase, lipoxygenase (LOX), glycogen synthase kinase-3β (GSK-3β), and cytokines (TNF-α) [10]. It interacts indirectly with several transcription factors, including nuclear factor-kappa B (NF-kB), activator protein 1 (AP-1), β-catenin, signal transducer and activator of transcription (STAT) proteins, and peroxisome proliferator–activated receptor γ (PPARγ) [11]. Curcumin modulates multiple molecular targets and has potent anti-inflammatory activities, which might contribute to its therapeutic role in obesity and obesity-related metabolic diseases.

After summarizing the background epidemiological observations, this review details the evidence behind these various, often overlapping, mechanisms and briefly mentions curcumin's anti-inflammatory role in the prevention and treatment of obesity and obesity-related metabolic diseases. It is hoped that this study will add new insights into the molecular pathways that are mediated by curcumin in obesity and may hold promise for future therapeutic intervention.

Inflammation and obesity-related metabolic diseases

Inflammation is a major component of obesity that is associated with insulin resistance (Fig. 1). Pharmacological or genetic inhibition of pathways that underlie inflammatory responses has been found to protect experimental animals and human subjects from diet-induced insulin resistance [12]. The subclinical or chronic inflammation has been recognized, as being involved in the development of obesity, type 2 diabetes, and obesity-related atherosclerosis [13]. An important initiator of the inflammatory response to obesity is adipose tissue, which is involved in energy regulation and homeostasis. It is now understood that adipose tissue is not simply a storage depot for excess calories but that it also actively secretes fatty acids and a variety of polypeptides, which can function in an endocrine or paracrine fashion as well as sensitive to insulin. Thus, the mixture of adipokines secreted by adipose tissue in a given path physiological state is commonly associated with obesity. The adipose tissue consists of a variety of cell types, including adipocytes, immune cells (macrophages and lymphocytes), pre-adipocytes, and endothelial cells. Adipocytes uniquely secrete adipokines, such as leptin, adiponectin, resistin as well as inflammatory cytokines such as TNF and interleukins 1, 6 (IL-1, IL-6) [14–16]. These factors are critically involved in obesity-induced insulin resistance and chronic inflammation. Hajri et al. proposed that TNF-α and IL-6 expression and secretion increased significantly in the adipose tissue of obese subjects and were negatively associated with those of adiponectin. In 3T3-L1 and human adipocyte cultures, insulin strongly enhanced adiponectin expression (twofold) and secretion (threefold). It is believed that insulin upregulates adiponectin expression and that TNF-α opposes the

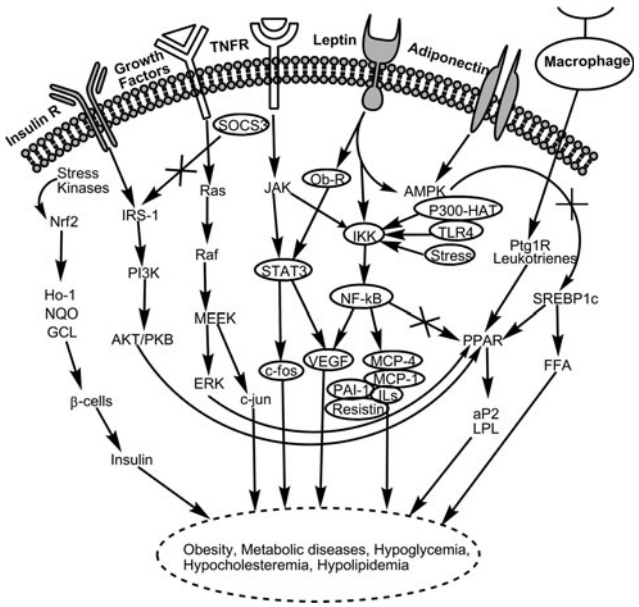

Fig. 1 A model illustrating the multiple inflammatory molecular targets and cell signaling complexes in obesity and insulin resistance. Cell signaling intermediates indicated in *circles* are downregulated, without *circles* are upregulated, and *cross lines* indicate inhibition

stimulatory effects of insulin [17]. Studies have demonstrated the elevated levels of adipose IL-6 and TNF-α mRNA in obese subjects and a decrease was observed in IL-6 and TNF-α with weight loss [18]. High TNF secretion from human adipose tissue was associated with decreased [3H] glucose incorporation into lipids [19]. TNF phosphorylates S6K1 (p70S6K) known to impair insulin resistance through serine phosphorylation of insulin receptor substrate (IRS-1), which then inhibits the tyrosine kinase activity of the insulin receptor in adipocytes and hepatocytes [20]. In addition, dephosphorylation of serine in IRS-1 was also associated with the overexpression of the dual-specificity phosphatase MKP-4/DUSP-9 that found to protect against stress-induced insulin resistance [21]. TNF also induces protein tyrosine phosphatase (PTP)-1B, which acts as a negative regulator of TNF signaling, and mice lacking PTP-1B are protected from TNF-induced insulin resistance [22]. Numerous studies have shown that a blockade of TNF receptor type 1–mediated TNF-α signaling protected Wistar rats from diet-induced obesity and insulin resistance [23]. Moreover, circulating concentrations of inflammatory cytokines are considered to be the most important factor in causing and maintaining insulin resistance, although the normal mode of cytokine-mediated insulin resistance involves local paracrine effects, elevated levels of the inflammatory cytokines such as TNF-α, IL-6, and IL-1β have been reported in obesity, insulin-resistant states, raising the possibility that tissue cytokines can leak into the circulation and impair insulin sensitivity in distal tissues through endocrine effects [24, 25].

NF-kB is a transcription factor that widely acts as a regulator of genes that control cell proliferation and cell survival, as well as promote insulin resistance through inflammation and cytokine production. In adipocytes, inflammatory signals including TNF-α lead to an activation of IKK, which then phosphorylates the inhibitor of NF-kB (IkB). In the resting state, IkB forms a complex with NF-kB, restricting NF-kB to a cytoplasmic location. After phosphorylation, IkB dissociates from NF-kB and undergoes degradation. The released NF-kB translocates to the nucleus, where it binds to its specific DNA response elements, leading to transactivation of inflammatory pathway genes. Several studies have shown that lipid accumulation in the liver leads to hepatic inflammation through NF-kB activation and downstream cytokine production, which leads to insulin resistance hepatically as well as systemically [26, 27]. Several studies have also demonstrated that Toll-like pattern recognition receptors play an important roles in mediating pro-inflammatory effects of saturated fatty acids, particularly Toll-like receptor 4 (TLR4), which induces insulin resistance through activation of NF-kB. TLR4 expression is increased in obesity, and when this receptor is deleted, saturated fatty acid induced inflammation, which is impaired in adipocytes and skeletal muscle cells [28, 29]. Similarly, the other major intracellular pro-inflammatory pathway involved in obesity is c-Jun N-terminal protein kinase 1/AP-1 (JNK1/AP1) system [30]. In this pathway, external inflammatory signals lead to the phosphorylation and activation of JNK, which then phosphorylates the N terminus of c-Jun on target genes. This induces an exchange of c-Jun dimers for c-Jun/c-Fos heterodimers, transactivating a set of inflammatory pathway genes, which substantially overlap with the set of genes transactivated by NF-kB [31, 32].

PPARs belong to the superfamily of nuclear hormone receptors, which antagonize the activities of NF-kB and have potential role in inflammatory conditions such as obesity. Among PPARs, PPAR-γ is a known molecular target in the treatment of type 2 diabetes, for all insulin-sensitizing drugs [33]. It has been observed that insulin resistance may be linked with downregulation of PPAR-γ by TNF. In addition, TNF induced NF-kB that blocks the PPAR-γ binding to DNA, by forming complex with PPAR-γ and its AF-1-specific co-activator PGC-2 [34].

A lot of compelling evidence has suggested that increased infiltration of macrophages in white adipose tissue (WAT) is also an important source of inflammation in obesity. Histological studies indicated that these macrophages are primarily localized to the intramuscular adipose depots, which accumulate within skeletal muscle in obesity. Many inflammatory and macrophage-specific genes are

considerably upregulated in WAT in mouse models of genetic and high-fat diet-induced obesity (DIO). The upregulation is progressively increased in WAT of mice with DIO by macrophage-related inflammatory activities and contributes to the pathogenesis of obesity-induced insulin resistance [35]. In summary, inflammation represents a major role in the progression of obesity toward insulin resistance.

Curcumin molecular targets in obesity and metabolic diseases

In the last two decades, a huge amount of research has been published on curcumin, which revealed that it modulates many regulatory proteins, including those of transcription factors, enzymes, cytokines, and growth factors (Table 1). Studies have shown that curcumin inhibits a number of signaling pathways and molecular targets involved in inflammation and obesity-related metabolic diseases [36]. Curcumin can inhibit the IKK signaling complex that is responsible for the phosphorylation of IkB, thereby blocking improper activation of NF-kB induced by various inflammatory agents [37]. Anti-obesity effects of curcumin are also linked with the inhibition of inflammatory and angiogenic biomarkers such as COX-2 and vascular endothelial growth factor (VEGF). Curcumin downregulates the expression of various pro-inflammatory cytokines including TNF-α, VEGF, interleukins 1, 2, 6, 8, 12 (IL-1, IL-2, IL-6, IL-8, IL-12) by inactivation of the NF-kB. Studies have shown that curcumin treatment reduced the tumor-induced overexpression of COX-2 and serum VEGF in HepG2 groups significantly ($p < 0.001$), indicating that curcumin has potential role in angiogenesis [38]. In addition, curcumin has been shown to downregulate the expression of various NF-kB-regulated proinflammatory adipocytokines including chemokines (such as monocyte chemotactic protein 1, 4 (MCP-1, MCP-4), and eotaxin) [39]. Curcumin was reported as excellent inhibitors of β-catenin/TCF-LEF and hence reduced the β-catenin/TCF signaling, which is closely linked to obesity. This effect is mediated through the inhibition of the GSK-3β, which is responsible for the β-catenin phosphorylation [40]. Recent studies have shown that curcumin-induced suppression of adipogenic differentiation in 3T3-L1 cells is accompanied by activation of Wnt/β-catenin signaling. During differentiation, curcumin restored nuclear translocation of the integral Wnt signaling component beta-catenin in a dose-dependent manner. In parallel, curcumin reduced differentiation-stimulated expression of CK1α, GSK-3β, and Axin, components of the destruction complex targeting β-catenin [41]. Several studies have also demonstrated the antioxidant role of curcumin in obesity. Transcription factors such as AP-1 are

Table 1 Molecular targets of curcumin in obesity and metabolic diseases

Transcription factors	References
Activator protein-1	57
β-catenin	40
GATA binding protein 4	62
Nuclear factor-kappa B	39
Nuclear factor E2–related factor	45
Peroxisome proliferator–activated receptor γ	50
Signal transducers and activator of transcription	51
Sterol regulatory element binding protein-2	53
Adipokines	
Tumor necrosis factor α	51
Interleukins	38
Leptin	47
Adiponectin	49
Resistin	36
Monocyte chemotactic proteins	39
Enzymes	
Arylamine *N*-acetyltransferases-1	67
Cyclooxygenase-2	38
Inducible nitric oxide synthase	65
Lipoxygenase	10
Matrix metalloproteinases	54
NADPH:quinine oxidoreductase	58
Phospholipase D	10
Haem oxygenase-1	54
Growth factors	
Connective tissue growth factor	54
Epidermal growth factor	46
Hepatocyte growth factor	53
Platelet-derived growth factor	70
Transforming growth factor-β	54
Vascular endothelial growth factor	38
Kinases	
AMP-activated protein kinase	50
Focal adhesion kinase	54
Glycerol-3-phosphate acyltransferase 1	67
Protein kinases	49
Protein tyrosine kinase	57
Receptors	
Insulin receptors	67
Chemokine receptor 4	39
Epidermal growth factor receptor	46
Histamine 2-receptor	36
Integrin receptor	65
Low-density lipoprotein receptor	67
Others	
Urokinase-type plasminogen activator	46
Triglycerides	71
Plasma free fatty acids	67
Iron regulatory protein	71
Antioxidant-responsive element	58

activated in response to stress, growth factors, and inflammatory cytokines. Curcumin can inhibit the stress-stimulated activation of AP-1 and has been shown to ameliorate oxidative stress–induced renal injury in mice [42]. Curcumin in the dose of 10 μM prevented the protein glycosylation and lipid peroxidation caused by high glucose levels in erythrocyte cell model. Curcumin inhibited oxygen free radical production caused by high glucose concentrations in a cell-free system and increased glucose utilization in erythrocytes [43]. Numerous studies have indicated that curcumin reduces serum cholesterol concentrations by increasing the expression of hepatic low-density lipoprotein (LDL) receptors, blocks the oxidation of LDL, increased bile acid secretion and metabolic excretion of cholesterol, represses the expression of genes involved in cholesterol biosynthesis, and protects against liver injury and fibrogenesis in animal models [36]. The hypocholesterolemic effect of curcumin was correlated with increase in LDL-receptor mRNA, whereas mRNAs of the genes encoding the sterol biosynthetic enzymes HMG CoA reductase and farnesyl diphosphate synthase were only slightly increased in human hepatoma cell line (HepG2). Although curcumin strongly inhibited alkaline phosphatase activity, an activation of a retinoic acid response element reporter employing alkaline phosphatase secretion was observed [44]. Moreover, curcumin has been identified as a potent inducer of hem oxygenase-1 (HO-1), a redox-sensitive inducible protein via regulation of nuclear factor E2-related factor 2 (Nrf2) and the antioxidant-responsive element (ARE), which provides protection against various forms of stress. Curcumin stimulates HO-1 gene activity through inactivation of the Nrf2–Keap1 complex, leading to increased Nrf2 binding to the resident HO-1 and AREs [45]. The early growth response (Egr-1) gene is a transcription factor that modulates the activity of plasminogen activator inhibitor type-1 that has been associated with insulin resistance and obesity. Curcumin inhibits the expression of the plasminogen activator inhibitor type-1 by reducing the activity of Egr-1 in obesity-related diseases [46]. Several studies have shown that curcumin blocks the leptin signaling by reducing the phosphorylation levels of the leptin receptor (Ob-R) and increases the induction of adiponectin, which improves obesity-associated inflammation [47, 48]. These finding support the existence of direct and indirect molecular mechanisms by which curcumin inhibits several inflammatory pathways that are responsible for obesity and obesity-related metabolic diseases.

Curcumin role in adipocytes

Several studies have shown the potential role of curcumin in angiogenesis, adipogenesis, differentiation, and apoptosis in adipocytes. Research evidence narrated that curcumin inhibits the differentiation of pre-adipocytes to adipocytes and inhibited adipokine-induced angiogenesis of human endothelial cell through suppression of VEGF-α. Curcumin treatment in C57/BL mice increased the fatty acid oxidation in adipocytes and also increased the activity of AMP-activated protein kinase (AMPK) by phosphorylating the α-subunit of AMPK, as well as suppressed the expression of amino-cyclopropane carboxylic acid by phosphorylation [49]. Lee et al. investigated the effect of curcumin on cancer and obesity and suggested that activation of AMPK by curcumin was crucial for the inhibition of differentiation or growth in both adipocytes and cancer cells. Curcumin-stimulated AMPK resulted in the down-regulation of PPAR-γ in 3T3-L1 adipocytes and decreased the COX-2 expression. Application of a synthetic AMPK activator also supported evidence that AMPK acts as an upstream signal of PPAR-γ in 3T3-L1 adipocytes. It is suggested that regulation of AMPK and its downstream targets such as PPAR-γ, mitogen activated protein kinase (MAPK), and COX-2 by curcumin appears to be important in controlling adipocytes and cancerous cells [50]. Curcumin increased the insulin-stimulated glucose uptake in 3T3-L1 cells and suppressed the transcriptional secretion of TNF-α and IL-6 induced by palmitate in a concentration-dependent manner through the inhibition of NF-kB. It is concluded that curcumin reverses palmitate-induced insulin resistance state in 3T3-L1 adipocytes through the inhibition of NF-kB and JNK [51]. In addition, curcumin enhances the expression of adiponectin in adipocytes, which inhibits NF-kB activation and negatively controls obesity [48]. Studies have also shown that curcumin significantly inhibited the cellular production of proinflammatory mediators such as TNF-α and nitric oxide and significantly inhibited the release of MCP-1 from 3T3-L1 adipocytes. Curcumin dose dependently inhibited phorbol myristate acetate (PMA)-induced MCP-1 expression by inhibiting ERK and NF-kB transcriptional activity in U937 cells [52]. These studies suggest that curcumin can suppress obesity-induced inflammatory responses and modulate adipose tissue macrophage accumulation or activation [39].

Curcumin role in hepatic stellate cells

Curcumin inhibited hepatic stellate cells (HSC) activation and intervened in liver fibrogenesis associated with hyperleptinemia in nonalcoholic steatohepatitis (NASH) patients. HSCs are the major effector cells during liver fibrogenesis and could be activated by leptin. Curcumin abrogated the stimulatory effect of leptin on HSC activation in vitro by reducing the phosphorylation level of Ob-R,

stimulating PPAR-γ activity, and attenuating oxidative stress, which leads to the suppression of Ob-R gene expression and elimination of leptin signaling [47]. In the same cells, Woo HM and his coworkers have shown that curcumin inhibited LDL-induced HSC activation in vitro by repressing gene expression of the transcription factor sterol regulatory element binding protein-2 (SREBP-2) by activating PPAR-γ, thus reducing the specificity protein-1 (SP-1) activity, which leads to the repression of ldlr expression. Activation of PPAR-γ has been linked to the reduction in the level of intracellular cholesterol in HSCs and to the attenuation of the stimulatory effects of LDL on HSCs activation [53]. In vitro studies have also shown that activation of PPAR-γ is required for curcumin to induce apoptosis and to inhibit the expression of extracellular matrix genes in HSC. Curcumin suppressed the expression of gene products regulated by PPAR-γ including α1 collagen, α-smooth muscle actin (α-SMA), connective tissue growth factor (CTGF), and receptors for TGF-β, platelet-derived growth factor beta (PDGF-β), and epidermal growth factor (EGF) [54]. Recently, it has been shown that curcumin protected HSCs against leptin-induced activation by accumulating intracellular lipids. Curcumin eliminated the stimulatory effects of leptin on HSCs activation and increased AMPK activity, leading to induced expression of genes relevant to lipid accumulation and elevated levels of intracellular lipids [55]. The same research group also reported that curcumin prevents leptin raising glucose levels in hepatic stellate cells by blocking translocation of glucose transporter-4 (GLUT4) and increasing glucokinase. Curcumin prevented leptin from elevating levels of intracellular glucose in rat HSCs and immortalized human hepatocytes by inhibiting the membrane translocation of GLUT4 and inducing the conversion of glucose to glucose-6-phosphate (G-6-P), leading to the inhibition of HSC activation [56]. These observations suggest a novel insight into mechanism of curcumin that mediates its effects on HSCs through direct and indirect activation of PPAR-γ as well as by inhibiting leptin-induced HSCs activation.

Curcumin role in pancreatic cells

Activated pancreatic stellate cells (PSCs) play a pivotal role in the pathogenesis of pancreatic fibrosis and inflammation. Curcumin decreased the pancreatic beta cell volume, which could be associated with hypoglycemic/antidiabetic effects of this agent. Curcumin inhibited PDGF-induced proliferation, α-SMA gene expression, interleukin-1β- and TNF-α-induced MCP-1 production, type I collagen production, and activation of AP-1 in activated PSCs. Curcumin also inhibited PDGF-BB-induced cyclin D1 expression and activation of ERK [57]. Curcumin has been reported as potent inducers of phase 2 enzyme HO-1, via regulation of nuclear factor Nrf2 and the ARE in mouse beta cells. Curcumin stimulates HO-1 gene activity, which is correlated with the increase in the expression of glutamyl cysteine ligase (GCL) needed for glutathione (GSH) biosynthesis and NADPH2:quinone reductase, which detoxifies quinines [45, 58]. In addition, curcumin protected beta cells from oxidative stress through increased GSH islet content and basal insulin secretions. It has also been observed that curcumin protected islets from cytokine-induced islet death in vitro by scavenging ROS and normalized cytokine-induced NF-kB translocation by inhibiting phosphorylation of the inhibitor of kappa B alpha (IkBα). In vivo, this group observed that curcumin also prevented the progression of diabetes induced by streptozotocin (STZ), which is associated with the suppression of pro-inflammatory cytokine (TNF-α and IL-1β). Inflammatory cytokine concentrations in the serum and pancreas were raised in STZ-treated animals, but not in animals pretreated with curcumin before STZ [59]. Currently, Karthikesan et al. have shown that combined treatment of tetrahydrocurcumin and chlorogenic acid exerts potential antihyperglycemic effect on streptozotocin/nicotinamide-induced diabetic rats [60].

Curcumin role in obesity-related diseases

Curcumin effects in animals

Until recently, the relation between obesity and coronary heart disease was viewed as indirect, that is, through covariates related to both obesity and coronary heart disease risk, including hypertension, dyslipidemia, particularly reductions in high-density lipoprotein (HDL) cholesterol, and impaired glucose tolerance or type 2 diabetes, although most of the comorbidities relating obesity to coronary artery diseases increase as body mass index (BMI) and related to body fat distribution. Pongchaidecha et al. and his coworkers have shown that curcumin ameliorated cardiac sympathovagal disturbance in high-fat-induced obese rats. In one study, male Wistar rats were fed with curcumin 30, 60, and 90 mg/kg body weight every day for 12 weeks. The researcher observed an elevated plasma FFA level in high-fat-induced obese rats, which is associated with an increased low-frequency/high-frequency (LF/HF) ratio, an expression of sympathovagal disturbance. Curcumin supplementation ameliorated cardiac autonomic imbalance in high-fat-fed rats, by lowering the FFA plasma concentration [61]. In addition, Morimoto et al. found that curcumin inhibited the hypertrophy-induced acetylating and DNA-binding abilities of GATA binding protein 4 (GATA4), a hypertrophy-responsive

transcription factor, in rat cardiomyocytes. Curcumin also disrupted the p300/GATA4 complex and repressed p300-induced hypertrophic responses in these cells. In addition, the effects of curcumin were examined in vivo in 2 different heart failure models, hypertensive heart disease in salt-sensitive Dahl rats and in surgically induced myocardial infarction rats. In both models, curcumin prevented the deterioration of systolic function and heart failure-induced increase in myocardial wall thickness and diameter [62]. LDL oxidation plays an important role in the development of atherosclerosis (a disease characterized by oxidative damage) and inhibition of LDL oxidation can reduce the risk of atherosclerosis. Curcumin effects were evaluated based on the development of experimental atherosclerosis in rabbits and its interaction with other plasmatic antioxidants. Rabbits were fed an atherogenic diet for 30 days, and histological results for the fatty streak lesions revealed damage in the thoracic and abdominal aorta that was significantly lower in the curcumin fed group than in the control group after 30 days [63].

Diabetes is also the most common cause of kidney failure, and nearly 180,000 people in the USA are living with kidney failure as a result of diabetes [64]. Diabetic nephropathy is characterized by increased production of extracellular matrix (ECM) proteins including fibronectin and extradomain B containing fibronectin that are regulated by TGF-β1, NF-kB and p300 in the kidneys. Curcumin treatment inhibited p300, suppressed the activation of NF-kB, and decreased TGF-β, vasoactive factors (endothelial nitric oxide synthase and endothelin-1), and ECM [65]. A decrease in the blood glucose level in diabetic models has been reported in obesity studies regarding the curcumin. Diabetic albino rats were fed with curcumin (0.08 g/kg body weight) and a decrease was observed in blood sugar levels when compared with the control group [66]. In another study, Seo et al. investigated the effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis-related enzyme activities in diabetic db/db mice, which were fed with curcumin (0.02%, wt/wt) for 6 weeks. In db/db mice, curcumin significantly lowered the hepatic activities of fatty acid synthase, beta-oxidation, 3-hydroxy-3-methylglutaryl coenzyme reductase, and ratio of acyl-CoA to cholesterol acyltransferase. Curcumin lowered plasma FFA, cholesterol, triglyceride concentrations and increased the hepatic glycogen and skeletal muscle lipoprotein lipase in db/db mice [67]. Epidemiological data indicated that diabetes is a potential predisposing factor for neuropsychiatric deficits such as stroke, cerebrovascular diseases, diabetic encephalopathy, depression, and anxiety. Diabetic encephalopathy is characterized by impaired cognitive functions and neurochemical structural abnormalities, which involves directly in neuronal damage caused by intracellular glucose. Curcumin (60 mg/kg) treatment significantly attenuated cognitive deficit, cholinergic dysfunction, oxidative stress, and inflammation in diabetic rats [68].

Curcumin effects in humans

Numerous studies have been carried out in human subjects with curcumin to examine its effect on obesity-related parameters. Cardiovascular complications are common in patients with obesity and to some extent are related with increased FFA level. Curcumin has been observed to lower blood sugar levels in diabetic patients. Curcumin administration also reduced the serum levels of cholesterol and lipid peroxides in 10 healthy human volunteers receiving 500 mg of curcumin daily for 7 days. A significant decrease in the level of serum lipid peroxides (33%), an increase in high-density lipoproteins (HDL) cholesterol (29%), and a decrease in total serum cholesterol (12%) were noted. Ramirez Bosca et al. found that administration of 10 mg of curcumin per day for 30 days to 8 human subjects increased HDL cholesterol and decreased LDL cholesterol. The same research group also investigated the effect of curcumin in human subjects with atherosclerosis, in which 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 [69, 70]. Idrus et al. conducted an interventional, randomized, double-blind, controlled trial to investigate the effects of curcumin administration at escalating doses (low dose 3 times 15 mg/day, moderate dose 3 times 30 mg/day, and high dose 3 times 60 mg/day) on total cholesterol level, LDL cholesterol level, HDL cholesterol level, and triglyceride level in 75 acute coronary syndrome (ACS) patients. Based on 63 patient's results, it is concluded that the administration of low-dose curcumin showed a trend of reduction in total cholesterol level and LDL cholesterol level in ACS patients [71]. However, Baum et al. and his coworkers reported that curcumin consumption does not appear to have a significant effect on the serum lipid profile in 6 months' human study, contrary to the previous reported studies. A 6-month placebo, randomized, double-blinded trial investigated the effects of consuming curcumin (4 and 1 g/day) on the serum lipid profile in both elder genders ($n = 36$). Plasma curcumin and its metabolites were measured at 1 month, and the serum lipid profile was measured at baseline, 1, and 6 months. The plasma curcumin concentration reached a mean of 490 nmol/L but did not significantly affect triacylglycerols or total, LDL, and HDL cholesterol over 1 or 6 months. Moreover, curcumin in physiological concentration of 2 μmol/L was reported to induce the expression of ABCG1 in the human hepatoma cell line HepG2, thus increasing HDL-dependent lipid efflux and plasma HDL cholesterol levels [72]. In addition,

hyperglycemia leads to increased oxidative stress resulting in endothelial dysfunction. A randomized, parallel-group, placebo-controlled, 8-week study was performed to evaluate the effects of NCB-02 (a standardized preparation of curcuminoids), atorvastatin, and placebo on endothelial function and its biomarkers in patients with type 2 diabetes mellitus. In this study, 72 patients with type 2 diabetes were randomized to receive NCB-02 (two capsules containing curcumin 150 mg twice daily), atorvastatin 10 mg once daily, or placebo for 8 weeks. NCB-02 had a favorable effect, comparable with that of atorvastatin, on endothelial dysfunction in association with reductions in inflammatory cytokines and markers of oxidative stress. Patients receiving NCB-02 showed significant reductions in the levels of malondialdehyde, endothelin-1 (ET-1), IL-6, and TNFα [73]. Recently, the effect of curcumin has been investigated in the activities of drug-metabolizing enzymes such as CYP1A2, CYP2A6, *N*-acetyltransferase (NAT2), and xanthine oxidase (XO) in 16 healthy male Chinese volunteers, using caffeine as a probe drug. After 14 days, in the curcumin-treated (1,000 mg/day) group, CYP1A2 activity was decreased by 28.6%, while CYP2A6 activity was increased by 48.9% [74]. Curcumin–phosphatidylcholine complex (Meriva®) was evaluated in 50 patients with osteoarthritis at dosages corresponding to 200 mg of curcumin per diem. After three months of treatment, C-reactive protein (CRP) levels decreased from 168 ± 18 to 11.3 ± 4.1 mg/L in the subpopulation with high CRP, while control group experienced only a modest improvement in these parameters (175 ± 12.3 to 112 ± 22.2 mg/L) in the CRP plasma concentration. It has been suggested that Meriva® is clinically effective in the treatment of osteoarthritis and could be taken into consideration for clinical use [75]. In addition, the same curcumin–phosphatidylcholine complex has been investigated among inflammatory conditions such as chronic anterior uveitis relapses in a 12-month follow-up clinical trial. Curcumin–phosphatidylcholine complex, Meriva (Norflo), administered twice a day in 106 patients of recurrent anterior uveitis of different etiologies. The results showed that Norflo was well tolerated and could reduce eye discomfort symptoms and visible effects after a few weeks of treatment in more than 80% of patients [76]. Curcumin's ability to lower blood glucose and cholesterol and its antioxidant nature make it a potential therapeutic for the treatment of obesity-related diseases. Recent evidence has shown that curcumin plays a key role in the protection against various obesity-related cancers including pancreatic cancer. Curcumin (8,000 mg/day) in concomitant administration with gemcitibine intravenously (1,000 mg/m/week) was observed in 17 patients of advanced pancreatic cancer for 4 weeks. Curcumin has a proven efficacy in patients, with the exception of a few patients (29%) who discontinued curcumin after a few days to 2 weeks due to intractable abdominal fullness or pain, and the dose of curcumin was reduced to 4,000 mg/day because of abdominal complaints in 2 other patients [77].

According to a joint report of the Food and Agriculture Organization and the World Health Organization on food additives, the recommended maximum daily intake of curcumin is 0–1 mg/kg body weight, but several clinical studies dealing with its efficacy suggested that it is safe and well tolerated even when intake is as high as 12 g/day [10, 78]. However, apparent side effects have been reported thus far. Gastrointestinal upset, chest tightness, inflamed skin, and skin rashes are said to occur with high doses. A few cases of allergic contact dermatitis from curcumin have also been reported [79]. The chronic use of curcumin can cause liver toxicity, and individuals with hepatic disease, persons misusing alcohol, and those who take prescription medications that are metabolized by liver should probably avoid curcumin. Curcumin is not recommended for persons with biliary tract obstruction, because it stimulates bile secretion [80]. Nevertheless, the multifaceted pharmacological nature of curcumin and its pharmacokinetics in obesity remains unknown and additional research is needed in this field.

Future prospects

In recent decades, a rapid increase in the costs of health care has increased the importance of naturally occurring phytochemicals in plants for the prevention and treatment of human diseases, including obesity. The modulation of several cellular transduction pathways by curcumin has recently been extended to elucidate the molecular basis for obesity and obesity-related metabolic diseases. Current knowledge suggests that the potential complementary effect of curcumin may occur through several mechanisms including suppression of inflammatory proteins, uptake of glucose, stimulation of catabolic pathways in adipose tissues, liver, and other tissues, inhibition of angiogenesis in adipose tissues, inhibition of differentiation of adipocytes, stimulation of apoptosis of mature adipocytes, and reduction in chronic inflammation associated with adiposity. Numerous studies confirm its potential role in vitro and in animals, yet further human studies, in particular clinical trials, are required to confirm the therapeutic nature of curcumin in obesity and insulin resistance. Expanded use of molecular technologies such as DNA microarrays and proteomics will help to identify newly molecular targets of curcumin and individuals at high risk of obesity-related metabolic diseases. Future trials should also include suitably planned pharmacodynamic studies, because the effective dose required for modulating these metabolic

responses is unclear at the present. It is important to note that high doses of curcumin in supplement form may have adverse effects. At present, there is not sufficient data to support recommending long-term, safe usage for the prevention and treatment of obesity. Future translational and clinical research overlapping metabolism with the aim to unravel the role of curcumin in obesity-related comorbidities is highly warranted. On behalf of such studies, one might be able to gain insights into curcumin mechanisms at a clinical level and assess, within a short period, the potential success or failure of long-term interventions.

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