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Curcumin as a novel agent targeting adipose tissue, lipid metabolism,and inflammatory pathways in obesity: a narrative review

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ABSTRACT

Abstract: Obesity is considered a major public health concern that is increasing around the world. It is characterized by chronic low-grade inflammation contributing to metabolic dysfunction. Compelling evidence shows potential protective and anti-inflammatory effects of curcumin in obesity and metabolic disorder. Curcumin, the active component of turmeric, interacts with white adipose tissue and suppresses inflammatory responses through multiple biochemical and cellular mechanisms. It also can inhibit adipocyte differentiation, enhance fatty acid oxidation, improve lipid profile, and has a role in increased basal metabolic rate and weight control. Hence, curcumin may be helpful as an adjuvant therapy for obesity and inflammatory process. The present review will focus on all recent studies on potential anti-inflammatory roles of curcumin in obesity. The review is presented in several parts. The first part explains the inflammatory pathogenesis of obesity; the second reviews the role of curcumin in inflammatory pathways; the third summarized the mechanisms of action of curcumin in adipose tissue; and, finally, there is a review of evidence from animal and human studies on the potentially beneficial effects of curcumin in obesity.

Introduction

Obesity is a worldwide health concern that is increasing rapidly and has gained considerable attention because of its effects on the economy, morbidity, and mortality [1]. Obesity is regarded as an important risk factor for many chronic diseases such as diabetes mellitus, heart disease, stroke, osteoarthritis, and hypertension [2]. Obesity is a condition characterized by chronic low-grade inflammation and likely to be regulated by differentiation control of preadipocytes [3]. Based on the evidence, obesity is accompanied by white adipose tissue (WAT) expansion, marked changes in the cellular makeup of adipose tissue as well as the secretion of factors derived from this tissue [4]. Adipose tissue macrophages become activated and more abundant in obesity, leading to cytokine secretion pattern changing as enhancing of proinflammatory mediators and suppression of protective anti-inflammatory factors such as adiponectin production and secretion [5]. These

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changes contribute to the pathological obesity-related health consequences such as type 2 diabetes [4,5].

Previous studies confirm that some dietary factors such as curcumin may have anti-inflammatory activities as well as effects on cellular oxidation and preadipocyte differentiation [6]. Moreover, curcumin exerts potent anti-inflammatory activities by interacting with multiple transcription factors and modulating multiple molecular targets, and thus, may play a helpful role in obesity and metabolic diseases [7].

In this context, the present study attempts to provide new insights into the molecular pathways of curcumin in obesity and review the mechanisms of curcumin's anti-inflammatory role in the prevention and treatment of obesity. On this base, we performed a comprehensive review of the evidence using MEDLINE and PubMed, with the following keywords: "curcumin" OR "curcuminoid" AND "obesity" OR "overweight" OR "adiposity" AND "inflammation." All papers from inception to May 2016 fulfilling these criteria were considered.

Inflammatory pathogenesis of obesity

The chronic and low-grade inflammation observed in obesity contributes to the development of atherosclerosis and generally inflammatory disease [2]. WAT is an endocrine organ composed of multiple cell types such as adipocytes (the predominant type), preadipocytes, fibroblasts, stem cells, mesenchymal precursor cells, tissue macrophages, and lymphocytes [8]. WAT also secretes a wide variety of cytokines called adipocytokines, including leptin, adiponectin, visfatin, resistin, plasminogen activator inhibitor type-1 (PAI-1) as well as inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, monocyte chemotactic protein (MCP)-1, and IL-6. These adipocytokines and chemokines are involved in chronic inflammation and insulin resistance [9]. Adipokines play crucial roles in the regulation of metabolic pathways, immune homeostasis, vascular function, and, particularly, inflammation [10,11]. The low-grade inflammation accompanying obesity is associated with macrophage infiltration in WAT, which results in an altered adipokine secretion pattern leading to increased circulating levels of proinflammatory cytokines and reduced levels of anti-inflammatory adipokines such as adiponectin. Moreover, the changes in the secretion of adipokines and fatty acids from WAT can cause lipotoxicity, insulin resistance, and mitochondrial dysfunction [12].

Risk factors associated with obesity are attributed to obesity-associated chronic, low-grade inflammation [13]. Based on the evidence, acute-phase reactants and levels of inflammatory mediators, including proinflammatory adipokines, are increased significantly in obesity and obesity-related metabolic diseases such as type 2 diabetes [14]. For example, the proinflammatory cytokine TNF-α can induce insulin resistance [15]. It has also been shown that Adipose tissue–derived TNF-α is overproduced both in human and animal models [16,17].

Emerging evidence suggests that TNF-α is a key mediator of inflammation in obesity and, particularly, insulin resistance. Laboratory studies have shown that adipocytes express TNF receptors, and in vivo studies have reported TNF-α overexpression in adipose tissues from obese mice [18,19]. In addition, it has been demonstrated that TNF-α expression is elevated in obesity but reduced following weight loss. An inverse relationship has also been reported between TNF-α and lipoprotein lipase [20]. In obese subjects, TNF-α levels are correlated with C-reactive protein (CRP) levels, which is considered a systemic inflammation marker [21]. TNF-α neutralization can enhance peripheral insulin sensitivity [15]. Similarly, TNF-α was found to induce suppressor of cytokine signaling (SOCS)-3 expression, which is enhanced in obesity and which can suppress insulin signaling [22]. It has been reported that a high-fat diet can promote TNF-α activity in adipose tissue [23], and TNF-α can induce leptin secretion through a post-transcriptional mechanism in adipocytes [24]. Suppression of TNF receptor-1 can reverse diet-induced obesity and insulin resistance [25].

Evidence indicates that there is an inverse relationship between obesity and plasma fibrinolytic activity, which is another factor contributing to low-grade inflammation [26]. The reduced activity of plasminogen activator leads to low blood fibrinolytic activity in obesity. The reduction of plasminogen activator and fibrinolytic activity in obesity, which increases the risk of thromboembolism, is associated with increased levels of PAI-1. The elevated PAI-1 levels may be caused by the secretion of proinflammatory cytokines such as TNF-α in adipose tissue [27].

NF-κB is a transcription factor contributing to the expression of genes, most of which involve in the inflammatory process. Compelling evidence shows that inflammation mediated by NF-κB is closely associated with obesity and insulin resistance. The TNF-α expression is regulated by NF-κB and considered as one of the most potent activators of NF-κB, which is a transcription factor [28,29].

Adiponectin, which has anti-inflammatory features, is known to suppress NF-κB activation [30,31]. It should be noted that increased plasma levels of different chemokines such as MCP-1 and MCP-4 in overweight subjects are mediated by NF-κB [32-34].

As mentioned above, the PAI-1 level, which is correlated with visceral fat in obesity, can be also regulated by NF-κB [35]. In addition, NF-κB regulates levels of IL-6 in adipose tissue and correlates with serum CRP levels [36,37]. Zhang and colleagues found that overnutrition can activate hypothalamic NF-κB by enhancing endoplasmic reticulum stress, resulting in central insulin/leptin signaling dysfunction [38]. It is necessary to mention that many genes contributing to the regulation of inflammatory mediators and macrophage-specific genes are downregulated in WAT in obesity [39]. Additionally, high glucose intake can lead to reactive oxygen species (ROS) production by macrophages and, thus, to NF-κB pathway activation [40]. Another mechanism involved in the induction of NF-κB is the release of saturated fatty acids following macrophage-induced lipolysis in adipocyte, which activates TLR4 and, consequently, NF-κB [41]. Generally, these studies conclusively demonstrate that inflammation plays a key role in obesity and related diseases.

Effects of curcumin on inflammatory pathways

Curcumin (diferuloylmethane) is a bright yellow compound found in turmeric. It is a water-insoluble lipophilic polyphenol [42]. Mounting evidence from cellular, animal, and human studies indicates that curcumin can suppress the inflammatory response through regulating a wide range of inflammatory pathways [43]. In vitro and in vivo studies provide strong evidence for the beneficial effects of curcumin on conditions linked to inflammation [44]. Curcumin has been shown to attenuate inflammatory responses in LPS-, IFN-γ–, or TNF-α–stimulated macrophages and natural killer cells by inhibiting cyclooxygenase-2 (COX-2), lipoxygenase, inducible nitric oxide synthase (iNOS), nitrite oxide (NO), and NF-kB production [42,45]. NF-kB is suppressed by inhibitor Kappa B (IkB) in cells [42]. Curcumin can suppress NF-kB activation through the inhabitation of the phosphorylation and degradation of IkB [46]. Curcumin can also contribute to cell proliferation and survival and attenuate NF-kB activation by inhibiting protein kinase C (PKC) [47]. Another anti-inflammatory mechanism of curcumin is attributed to its ability to inhibit activator protein (AP)-1 [48]. In addition, curcumin can inhibit the expression of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-12, and IFN-γ [49,50]. It has been indicated that cell adhesion molecules that promote adhesion of T cells to endothelial and antigen-presenting cells play a major role in the inflammatory response. Pretreatment with curcumin leads to downregulation of intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and endothelial leukocyte adhesion molecule (ELAM)-1 expression and blocks the adhesion of monocytes to endothelial cells through interfering with NF-kB activation [42,44].

Furthermore, curcumin has shown promising effects in terms of inflammatory condition. Belcaro et al found that curcumin can significantly reduce a variety of proinflammatory markers such as IL-1β, IL-6, and the erythrocyte sedimentation rate (ESR) in osteoarthritic patients [51]. Additionally, it has been reported that curcumin decreases ESR levels in a similar manner to nonsteroidal anti-inflammatory drug diclofenac sodium in patients with rheumatoid arthritis [52]. Khajehdehi et al showed that administration of curcumin decreased serum levels of TGF-β and IL-8 and urine level of IL-8 in patients with type 2 diabetes [53]. Curcumin also significantly reduced TNF-α and IL-6 in comparison with placebo in type 2 diabetic patients [54].

Curcumin mechanisms of action in cellular pathways in adipose tissue

Effect of curcumin on adipocytes

A number of in vitro studies have examined curcumin's effects on adipocytes. The majority of them used 3T3-L1 mouse embryonic fibroblasts that differentiate into adipocytes. It has been reported that curcumin inhibits the differentiation of preadipocytes into adipocytes and induces apoptosis. Curcumin is also able to suppress adipocytokine-induced angiogenesis by blocking vascular endothelial growth factor (VEGF)-α expression in human endothelial cells. In addition, adipocyte treatment with curcumin promotes fatty acid oxidation and leads to increased AMPK activation through phosphorylating the α subunit of AMPK in adipocytes [55]. AMPK activation leads to the downregulation of PPAR-γ and, consequently, the suppression of adipocytes differentiation [56].

It has been shown that curcumin inhibits adipocyte differentiation through the activation of Wnt/β-catenin signaling. Additionally, curcumin can suppress CCAAT/enhancer-binding protein-α (C/EBP-α), sterol regulatory element–binding protein (SREBP)-1, PPAR-γ, and fatty acid synthase (FAS) in adipocytes [57]. Curcumin can also block the expression of other markers of adipocyte differentiation, such as Wnt 10β and Ap2 [56]. In contrast to this evidence, some studies reported that curcumin can enhance the differentiation of preadipocytes into adipocytes through binding PPAR-γ [58,59]. Wang et al found that curcumin can stimulate insulin-induced glucose uptake in 3T3-L1 adipocytes and reduce the expression and secretion of IL-6 and TNF-α induced by palmitate through suppression of NF-κB pathway. Curcumin, can also reduce JNK, ERK1/2, and p38 MAPK signaling and

exerts its effects via inhibition of JNK pathway in adipocytes [60]. It has been observed that curcumin treatment suppresses NF-κB activation, leading to reduced COX-2, TNF-α, IL-1β, and IL-6 gene expression and decreased IL-6 and prostaglandin release in adipocytes [61]. Curcumin can enhance adiponectin expression in adipocytes [62], which in turn can inhibit NF-κB activation through cyclic adenosine monophosphate (cAMP)-dependent pathway in endothelial cells, which is considered another potential mechanism of curcumin activity in adipocytes [31]. Curcumin-induced adiponectin has vasoprotective and anti-inflammatory effects and can suppress TNF-α–induced adhesion of monocytes to vascular endothelial cells through promoting nitric oxide production and reducing the expression of ICAM-1, VCAM-1, and ELAM-1 in endothelial cells [63,64].

Another mechanism of curcumin action in adipocytes acts through blocking proinflammatory cytokine MCP-1 release. According to Woo et al, curcumin inhibits the secretion of MCP-1 from 3T3-L1 adipocytes. Curcumin inhibits obesity-related inflammatory responses by preventing macrophage accumulation in adipose tissue and suppressing the expression of adipokines such as MCP-1 and TNF-α, two key inflammatory mediators in obesity [65].

Overall, evidence suggests that curcumin can modulate adipocytes metabolism directly.

Effect of curcumin on lipid metabolism

Recently, in vivo studies suggest that curcumin has hypolipidemic effects and can reduce plasma levels of triglycerides (TG) and free fatty acids in high-fat-fed animals [66]. It has been shown that curcumin supplementation can effectively decrease the elevated TG levels in serum and liver of high-fat–fed rats [67]. Likewise, curcumin can significantly reduce hepatic TG concentration in mice, suggesting that curcumin may be beneficial in treating fatty liver disease–induced hyperlipidemia and obesity [55]. Curcumin can also act as a PPAR-γ ligand, which explains its hypolipidemic effects. Moreover, curcumin can reduce hepatic cholesterol, total cholesterol, LDL, and VLDL levels through blockage of the hepatic enzymes HMG-CoA reductase and Acyl CoA cholesterol acyltransferase (ACAT) [66]. The evidence demonstrated that curcumin supplementation can enhance hepatic beta-oxidation of fatty acids and suppress FAS activity.

Curcumin can also downregulate FAS significantly, resulting in an effective reduction of fat storage [68]. In addition, it has been shown that curcumin prevents lipid accumulation in adipocytes through reducing glycerol-3-phosphate acyltransferase-1 mRNA expression in a dose-dependent manner and, on the contrary, promotes fatty acid oxidation via enhancing mRNA expression of the carnitine palmitoyltransferase-1 [55]. Curcumin can lead to acetyl CoA carboxylase phosphorylation by increasing AMPK activation, resulting in decreased acetyl CoA availability —which is necessary to synthesize malonyl CoA, the key precursor for fatty acid synthesis [55].

Jang et al showed that curcumin supplementation is able to increase HDL particles, Apo-A1, and paraoxonase (PON) plasma levels significantly in high-fat–fed hamsters [66,69]. PON has multiple isoforms two of which, PON1 and PON3, are associated with HDL-C and can inhibit the oxidized LDL formation [69].

In addition, dietary curcumin supplementation led to increases in the lean tissue mass and significant weight loss in ob/ob mice [70]. Curcumin could also reduce serum CRP and inflammatory cytokine levels accompanied by weight loss [71]. Based on the experimental and human studies, curcumin can enhance energy expenditure and basal metabolic rate, resulting in decreased adverse consequences of obesity-induced inflammation, including insulin resistance and cardiovascular disease [55,70]. Additionally, curcumin supplementation can improve lipid profile and blood glucose, and also significantly reduce BMI and waist circumference in type 2 diabetic patients.

To summarize, evidence suggests that curcumin can suppress lipid synthesis, storage, and accumulation and, at the same time, promote fatty acid degradation through modulating key enzymes and transcription factors involved in lipid metabolism. Curcumin may also reduce body weight and increase the basal metabolic rate [71].

Curcumin and inflammation-induced obesity

Curcumin exerts its anti-inflammatory effects in obesity at multiple levels of gene expression and molecular pathways [19,70]. Curcumin downregulates the transcriptional activity and DNA binding of inflammatory transcription factors such as NF-kB and AP-1 in adipocytes, plays a protective role against ROS, and inhibits mitogen-activated protein kinase production following inflammatory response [7,72]. In vitro and in vivo studies demonstrated that curcumin can suppress the secretion of proinflammatory cytokines such as TNF-α and MCP-1 in mesenteric adipose tissue. Furthermore, pretreatment with curcumin can suppress proinflammatory cytokines in a dose-dependent manner [65]. Additionally, pretreatment with curcumin analogs can block LPS-stimulated mRNA and TNF-α, IL-1β, and IL-6 serum levels in a dose-dependent manner in a mouse macrophage cell line [73]. In addition, curcumin can suppress DNA binding and nuclear translocation of NF-κB. It has

been shown that curcumin supplementation can significantly reduce macrophage infiltration into WAT in obese mice consuming high-fat diets and genetically obese ob/ob mice. Similarly, an enhanced production of adiponectin, increased total circulating adiponectin, and a reduced hepatic NF-kB activity were observed in curcumin-fed mice. Taken as a whole, curcumin supplementation can reduce inflammation and improve glycemic status in experimental studies [70].

The laboratory studies demonstrated that curcumin can inhibit NF-κB activation through the suppression of IκBα degradation [46]. In addition, in vitro inhibition by curcumin of IKK has been demonstrated. The IKK signaling is linked to NF-κB activation, and IKK inhibition leads to the suppression of inflammatory markers expression including COX-2 and VEGF [19]. It has been observed that curcumin downregulates the expression of the NF-κB-regulated inflammatory adipocytokines including MCP-1, MCP-4, and eotaxin [65] as well as IL-1, IL-6, and IL-8 [60]. Curcumin can also inhibit the plasminogen activator inhibitor type-1 expression through the suppression of the transcription factor early growth response (Egr)-1 gene product, which is closely associated with obesity and insulin resistance [74]. It has been reported that curcumin downregulates c-Jun NH2 terminal kinase (JNK) activation and inhibits the Wnt/β-catenin pathway, both closely related to obesity [28,65]. Studies have been shown that curcumin is able to suppress Wnt signaling through downregulating of the transcription coactivator p300 [75]. Another potential anti-inflammatory mechanism of curcumin can be inhibiting β-catenin signaling through glycogen synthase kinase (GSK)-3β suppression, which directly phosphorylates β-catenin and leads to the inhabitation of β-catenin [75]. Curcumin can also induce heme oxygenase (HO)-1 expression through the Nrf2 signaling activation, leading to the increased pancreatic cell survival [76,77]. Finally, curcumin can interrupt leptin signaling by reducing the phosphorylation of the leptin receptor and its downstream targets while enhancing adiponectin expression, which has a negative relation with obesity [70,78].

Evidence of anti-inflammatory effects of curcumin in obesity in animal studies

Recently, a number of animal studies have focused on the anti-inflammatory role of curcumin obesity. In this context, Xu et al recently reported that fructose feeding induces hippocampal microglia activation and neuroinflammation via enhancing the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway, leading to neurogenesis defection in mice. In this condition, curcumin can protect against neuronal damage .due to obesity-associated inflammation through suppression of microglia activation [79]. Another study found that dietary curcumin significantly suppressed the expression of TNF-α, IL-6, and COX-2, enhanced AMPK, and inhibited NF-κB in colonic premalignant lesions in a mouse model of obesity-related colorectal cancer.

Curcumin also enhanced serum levels of adiponectin, while reduced serum levels of leptin and the fat weight [80]. Similarly, Kuo et al showed that curcumin leads to weight loss and significantly decreases serum TG levels and adipose TNF-α, IL-6, and MCP-1 levels in obese mice. In addition, the induction of signal transducer and activator of transcription (STAT) 3 phosphorylation by curcumin can lead to suppressor of cytokine signaling 3 downregulation in the liver of these obese mice. Curcumin also reduces hepatic TG by downregulating the gene expression of sterol regulatory element–binding protein-1c in the liver and reducing hepatic NF-κB activity [81]. In this regard, Zeng et al reported that curcumin suppressed high-fat diet–induced inflammation, oxidative stress, fibrosis, apoptosis, hypertrophy, and tissue remodeling through its ability to increase Nrf2 expression and inhibit NF-κB in mice [82]. In the same line with this study, Qian et al recently showed that Y20, a new monocarbonyl curcumin analog, may have a therapeutic potential for treating obesity-related disorders through targeting Nrf2 and NF-κB pathways [83]. However, curcumin, alone or in combination with citrus polyphenol, had no effect on the production of cytokines IL-4, IL-10, IFN-γ, and IL-17, or the proportion of different CD4+ T cell subsets [84]. Similarly, Leray et al indicated that, although curcumin could improve obesity-related inflammation in PBMC of obese cats via reducing IL-2 mRNA levels and acute-phase protein α1-acid glycoprotein (AGP) plasma levels, mRNA levels of IL-1β, IL-4, IL-5, IL-10, IL-12, IL-18, TNF-α, and TGF-β remained unaffected by curcumin supplementation [85]. Curcumin significantly decreases the effect of high-fat diet on body weight or fat gain. It can block the lipogenic gene expression in the liver and suppress macrophage infiltration and the inflammatory response in the adipose tissue [86]. There is evidence that co-supplementation of curcumin and white pepper leads to decreased high-fat–induced proinflammatory cytokine expression in the subcutaneous adipose tissue of mice [87]. Moreover, curcumin had protective properties against obesity-induced inflammation in obese male C57BL/6 mice. GSH and the GSH:GSSG ratio were enhanced via curcumin treatment, suggesting that aside from its effects on adiposity, curcumin has also positive effects on frontal cortical functions, which is linked to anti-inflammatory or antioxidant actions [88].

Table 1. Evidence of anti-inflammatory effects of curcumin in obesity

Reference	Target population	Main finding
Animal studies		
Weisberg et al 2008 [70]	high-fat diet–fed obese, leptin-deficient ob/ob male C57BL/6J mice	•Significantly reduced macrophage infiltration into white adipose tissue •Significantly increased adipose tissue adiponectin production •Significantly decreased hepatic NF-kB activity and markers of hepatic inflammation •Significant reductions in the expression of hepatic TNF-α, suppressor of cytokine signaling-3, MCP-1, and chemokine •Significant reduction of food intake
Leray et al. 2011 [85]	Obese cats	•Lower plasma AGP concentration •No effect on TNF-α, IL-1β, IL-4, IL-5, IL-10, IL-12, IL-18, and TGF-β mRNA levels •Reduction of IL-2 mRNA levels
Kubota et al. 2012[80]	C57BL/KsJ-db/db (db/db) obese mice	•Significant reduction in the total number of colonic premalignant lesions •Significant decrease in the expression levels of TNF-α, IL-6, and COX-2 mRNAs • Markedly activated AMP-activated kinase •Significant inhabitation of NF-κB activity •Increases in the serum levels of adiponectin •Decreasing the serum levels of leptin
Kuo et al. 2012[81]	Obese mice with hepatic steatosis	•Significant decreases in the number of F4/80-positive macrophages in epididymal adipose and liver tissue •Downregulation of the suppressor of cytokine signaling 3 in the liver •Decreased expression of sterol regulatory element–binding protein-1c in the liver •Decreased hepatic TG •Reduced hepatic NF-κb activity
Shao et al. 2012 [86]	C57BL/6J mice fed a high-fat diet	•Significant reduction in the effects of high-fat diet on glucose disposal and body weight/fat gain •No stimulatory effect on Wnt activation in the mature fat tissue • No stimulatory effect on Wnt signaling in vitro in primary rat adipocytes •Inhibition of lipogenic gene expression in the liver •Blocking the effects of high-fat diet on macrophage infiltration and inflammation in the adipose tissue
Neyrinck et al. 2013 [87]	Mice fed a high-fat diet	•Cosupplementation of curcumin and white pepper decreased high-fat diet–induced proinflammatory cytokines expression in the subcutaneous adipose tissue •No significant changes in body weight gain, glycemia, insulinemia, serum lipids, and intestinal inflammatory factors
Wang et al. 2013 [84]	Mice fed a high-fat diet	•Caloric restriction alone or in combination with curcumin had no effect on the production of cytokines IL-4, IL-10, IFN-γ, and IL-17, or the proportion of different CD4+ T cell subsets
Zeng et al. 2013 [82]	Mice fed a high-fat diet	•Significant increases in Nrf2 expression and inhibition of NF-κB activation •Suppressed high-fat diet–induced inflammation and oxidative stress
Öner-İyidoğan et al.2013[89]	Male Sprague-Dawley rats fed a high-fat diet	•Reducing the liver TG and serum fetuin-A levels
Sarker et al. 2015 [97]	Male C57BL/6 mice	•Significant increases in GSH and the GSH:GSSG ratio •No reduction of adiposity •Significant reduction of CRP
Qian et al. 2015 [83]	High-fat diet–fed rats	•Y20, a new monocarbonyl curcumin significantly decreased the cardiac inflammation and oxidative stress •Significant increases in Nrf2 expression and inhibition of NF-κB activation
Human studies		
Mohammadi et al. 2013 [92]	Obese individuals (1 g/day for 30 days)	•No significant effects on anthropometric parameters including weight, BMI, waist circumference, hip circumference, arm circumference, and body fat •No effect on serum levels of total cholesterol, LDL-C, HDL-C, and hs-CRP •Significant reduction of serum TG
Chuengsamarn et al. 2014[91]	Type 2 diabetic patients (250 mg/day for 6 month)	•Significant reduction of pulse wave velocity, increase in serum adiponectin, and decrease in plasma leptin levels •Reduced levels of TG, uric acid, visceral fat, and total body fat
Ganjali et al. 2014[90]	Obese individuals 1g/day for 4 weeks (Following a 2-week wash-out period, each group was assigned to the alternate treatment regimen for another 4 weeks)	•Significant reduction of serum IL-1β, IL-4, and VEGF •No significant effect on IL-2, IL-6, IL-8, IL-10, IFN-γ, EGF, and MCP-1 levels

To summarize, it seems that curcumin treatment can be effective in reducing serum fetuin-A levels and liver TG content. Fetuin-A synthesized in the liver is involved in the pathogenesis of metabolic disorders such as visceral obesity. These findings suggest a beneficial role of curcumin in the pathogenesis of obesity [89].

Evidence for anti-inflammatory effects of curcumin in obesity from human studies

Despite relatively extensive experimental/animal studies in obesity, evidence for anti-inflammatory impacts of curcumin in human studies is limited. Ganjali et al found that curcumin therapy significantly reduced serum cytokines (IL-1β, IL-4, and VEGF) in obese individuals; however, no significant difference was seen in the levels of IFN-γ, IL-2, IL-6, IL-8, IL-10, MCP-1, and EGF [90]. Additionally, Chuengsamarn et al investigated the effects of curcumin on risk factors of atherosclerosis in type 2 diabetic patients. The authors reported that curcumin treatment significantly enhanced serum levels of adiponectin, decreased leptin levels, and pulse wave velocity. Curcumin also reduced visceral fat and total body fat [91]. Another study reported that curcuminoid supplementation (1 g/day for 30 days) led to a significant reduction in serum TG levels but had no significant influence on other lipid profile parameters, body mass index, or body fat [92]. The findings from reviewed papers are summarized in Table 1.

Conclusion

In the past decade, curcumin has been studied intensively in obesity and obesity-related metabolic disorders because of its potential anti-inflammatory and therapeutic properties. Curcumin can suppress inflammatory response and differentiation of preadipocytes into mature adipocytes through multiple mechanisms. It is clear that obesity is accompanied by a chronic, low-grade inflammation leading to the development of metabolic dysfunctions such as insulin resistance and cardiovascular disease. Curcumin interacts with adipose tissue and can inhibit inflammation both directly and indirectly. Generally, curcumin can suppress macrophage infiltration, downregulate proinflammatory adipocytokines including TNF-α, MCP-1, PAI-1 and NF-kB pathway activation, while it induces the expression of adiponectin with anti-inflammatory features released by adipocytes. In the adipose tissue, curcumin exerts its anti-inflammatory effects by targeting a variety of molecules including differentiation factors like Wnt10b, transcription factors such as NF-kB, proinflammatory interleukins (TNF-α, IL-1β, and IL-6), and other regulatory mediators. In addition to suppressing the systemic inflammation at diverse biochemical and cellular levels, curcumin can also improve lipid profile and weight loss. It is worth mentioning that, although numerous studies confirm curcumin's potential effects as a promising anti-inflammatory agent, the clinical studies are limited. Further studies are required to confirm the beneficial function of curcumin in obesity and metabolic disorders.

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Conflicts of interest

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