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Exploring the role of the core mechanism of curcumin in the regulation of fat metabolism

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ABSTRACT
Curcumin is a bioactive polyphenol from Curcuma longa which has the potential to regulate fat metabolism. This review explored the mechanisms of curcumin in fat metabolism. Subsequently, the modulation of AMPK and mTORC1-TFEB pathways, lipid oxidation enhancement, inhibition of adipogenesis, and influence on gut microbiota composition were reviewed. However, the major limiting factor is its bioavailability; hence, nanoformulations, liposomes, and synergistic combinations of therapy must be advanced in the future. Curcumin derivatives, delivery technologies, and clinical validation to be used as functional foods or in metabolic disorder treatments should be the focus of future research. As a natural, multi-targeted intervention, curcumin holds significant potential in fat metabolism regulation. Thus it requires further examination and optimization of clinical applications.

KEYWORDS
Fat metabolism; Curcumin; Bioavailability; Lipid oxidation and AMPK-mTORC1 pathway

1 Introduction

Curcumin is a polyphenolic compound found in the rhizome of turmeric (*Curcuma longa*). Currently, curcumin has gained importance because of its anti-inflammatory, antioxidant, and lipid-regulating properties[1]. Its complex chemical structure renders high biocompatibility making it a promising candidate for medical study. Additionally, it modifies metabolic pathways by modulating lipogenesis, enhancing the oxidation of lipids; altering gut microbiota; and inhibiting adipogenesis[2-3, 4]. Thereby, the curcumin has the potential to be used for liver treatment. Understanding curcumin's role in fat metabolism is important because there is an immediate need for safe, natural, and cost-effective interventions for obesity and related metabolic diseases. Currently, WHO has estimated over 1.9 billion overweight adults globally [5]. Thus, the potential of curcumin as a nutraceutical alternative opens the possibility of creating new therapeutic approaches. Thereby, this paper discusses the core mechanism of curcumin in the regulation of fat metabolism, focusing on its specific role in fat metabolism and analyzing its therapeutic potential.

2 Core Mechanisms of Curcumin in Fat Metabolism Regulation

2.1 Enzyme Inhibition and Fat Absorption

Curcumin can be used as a natural inhibitor of pancreatic lipase (PL). Jamai et al. indicated that enzyme inhibition represents a potential obesity and related metabolic syndrome treatment strategy [7]. Ashraf et al. extracted the curcumin using conventional (CSE) and supercritical fluid (SFE) extractions and developed a microcapsule by mixing it with gelatin and maltodextrin [8]. Subsequently, adding it to the supplementary diet showed a reduction in serum cholesterol, low-density lipoprotein (LDL) and triglycerides. Thus, curcumin-enriched formulations had significant reduction of fat absorption and beneficial lipid metabolism in HFD-induced obesity models.

Several studies shed light on the structure-activity relationship (SAR) and inhibitory mechanism. Mu et al. showed that lignans 24-26 of curcuminoids strongly inhibited the activity of PL through mixed-inhibition mechanisms [9]. Additionally, the presence of the 4-hydroxyphenyl substituent in curcumin confers critical inhibitory activity. Furthermore, Jing et al. stated curcumin derivatives aided in improved PL inhibition [8]. The silico and in vitro results showed that some curcumin analogues displayed better inhibitory activity than the natural curcumin, with IC_{50} values, while curcumin had an IC_{50} of 142.24 μM.

Moreover, the molecular docking studies by Jing et al. demonstrated that curcumin binds preferentially to the active site of PL through hydrogen bonding and hydrophobic interactions [8]. A similar study through CADD established that curcumin and its synthetic derivatives exhibited favourable binding scores showing stable binding with csyclooxygenase-2 (COX2), peroxisome proliferator-activated receptor gamma (PPARγ) and fatty acid synthase (FAS) [10]. However, the researchers called for further in-vitro studies for extended scope of inhibition for the treatment of liver diseases.

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2.2 Modulation of Key Signal Pathways

2.2.1 AMPK Pathway in Lipolysis Regulation

Curcumin has been proven to activate AMPK. Since, AMPK plays a significant role in the cellular energy state, it also influences insulin resistance and metabolic syndrome, consideration of curcumin in the AMPK pathway is instrumental. Curcumin downregulates HIF-1α through activation of AMPK and inhibition of mTOR for the mitigation of hypoxia-induced adipose fibrosis [11]. Additionally, a recent study designed on mice showed curcumin could modulate the PI3K/Akt/AMPK/mTOR pathway, enhancing muscle glycogen storage and energy metabolism [12]. Continuous curcumin consumption raised the muscle glycogen (MG), glycogen synthase (GS), and myonectin content in deficient mice's quadriceps muscle while decreasing the LA content and AMP/ATP ratio. At the same time, alterations in these physiological indicators suggest that curcumin, administered intragastrically, greatly decreased exercise exhaustion in mice. Thus, the dual regulation of AMPK and mTOR indicates its role in energy balance and lipolysis.

Furthermore, another study conducted on mice showed curcumin inhibits clozapine-induced dyslipidemia through activation of AMPK[13]. While it also causes inhibition of SREBP-dependent lipid synthesis, thereby indicating a protective role in drug-induced metabolic disturbances [13]. Further the computational docking model revealed that the hydroxyl groups of curcumin may establish three hydrogen bonds with the residues Arg111, Arg83, and Leu115 at the allosteric regulation region of AMPK. Therefore, treatment with curcumin reduces obesity and fat buildup in the periphery while also improving insulin sensitivity.

2.2.2 mTORC1-TFEB Pathway in Autophagy Regulation

Dysregulation of mTORC1 lies at the heart of obesity and metabolic disease. mTORC1 is responsible for controlling cellular metabolic functions, including growth, autophagy, and lipogenesis. Kaur et al. found that IGF-1-mediated stimulation of mTORC1 is repressed by curcumin in Caco-2 cells in colon cancer by blocking the IRS/AKT/PRAS40 signaling pathway [14]. Curcumin suppresses mTORC1 activity through downregulation of IRS1 and activation of AMPK. Subsequently, another study found that curcumin ameliorates NP-induced steatosis through the activation of AMPK and suppression of mTOR in hepatocytes. Consequently, it reduces lipid accumulation and oxidative stress.

Furthermore, Song et al. proved the involvement of curcumin in the regulation of autophagy [15]. In their study, they found that Monocarbonyl analogues of curcumin boosted LC3B-II levels much more when the lysosomal inhibitor chloroquine (CQ) was present. The findings suggest that curcumin analogues promote autophagy rather than inhibit lysosomal breakdown. They identified a curcumin analogue named C1 that activates TFEB and does not inhibit mTOR, thus establishing a new mechanism for autophagy induction. These results suggest that curcumin prevents lipid overload by promoting autophagy and enhancing mitochondrial function. Therefore, curcumin analogues may be considered therapies for non-interference with mTOR.

2.2.3 Adipocyte Differentiation and Gene Regulation

Curcumin also shows regulatory effects on differentiation in adipocytes through the PPARγ and SREBP-1c pathways. Pan et al. in their study investigated the role of curcumin in both C57BL/6 J obese mice and 3T3-L1 adipocytes in vivo and in vitro respectively [16]. It was found that Curcumin regulates glycolipid metabolism in HFD-induced obese C57BL/6J mice. Curcumin boosted glucose absorption and lowered glycerol release in differentiated 3T3-L1 adipocytes, which was consistent with in vivo results. That is, curcumin increases the expression of PPARγ and C/EBPα in mice induced by high-fat diet-related obesity facilitating an increase in lipolysis and insulin sensitivity.

On the other hand, a study conducted on the upregulation of de novo lipogenesis identified curcumin could suppress the expression of key regulators of citrate influx and metabolism, namely SLC13A5 and ACLY, through the AMPK-mTOR pathway [15]. Most importantly, attenuation of lipid accumulation with decreased lipogenesis offers a new target for the treatment of NAFLD. Chen et al. further found that curcumin suppresses adipogenesis through ALKBH5-mediated m6A modification [17]. This modification results in PPARγ degradation and decreased fat accumulation. Curcumin suppresses adipogenesis by lowering the expression of AlkB homolog 5 (ALKHB5), a m6A demethylase, resulting in increased m6A-modified TNF receptor-associated factor 4 (TRAF4) mRNA. This introduces a new epigenetic mechanism through which curcumin regulates adipocyte differentiation requiring further clinical trials.

2.3 Gut Microbiota and the Gut-Liver Axis

2.3.1 Influence on Gut Microbiota

Recent findings have identified gut microbiota as an important player by influencing short-chain fatty acids (SCFAs) and bile acids. Li et al. reported that curcumin lowered the Firmicutes/Bacteroidetes ratio [18]. Since this ratio is an

important indicator of obesity, it enhances the potential application of curcumin. Additionally, Li et al. also found curcumin increased populations of Akkermansia and SCFA-producing bacteria including Bacteroides and Alistipes [18]. Consequently, these increase insulin sensitivity and reduce hepatic steatosis through improved fat metabolism. Thus, curcumin shows prebiotic effects.

Additionally, Islam et al. found that curcumin supplementation could significantly lower obesity-associated inflammation through an interaction with gut microbiota [19]. This occurred through the downregulation of the pro-inflammatory macrophages in white adipose tissue and increased SCFA-producing species, *Clostridium*. A comparative analysis established that curcumin not only boosted gut microbial diversity but also affected gut-liver interactions by boosting beneficial genera [20]. The study reaffirmed that *Oscillibacter*, *Alistipes*, *Pseudoflavonifractor*, *Duncaniella*, and *Flintibacter* are some of the organisms enhanced by curcumin. Thus, such observations imply that curcumin suppresses inflammatory activity and regulates lipids through an alteration of the gut microbiota.

2.3.2 Impact on Bile Acid

Curcumin modulates bile acid homeostasis by interactions with gut microbiota. Hong et al. studied the impact of bile on intestinal microbiota and cholesterol absorption in hamsters [21]. The 12-week study showed that it primarily boosted the microbiota involved with bile acid metabolism and short-chain fatty acid generation. Consequently, it raised the expression of hepatic cholesterol 7-alpha hydroxylase and bile acid synthesis. Furthermore, curcumin dramatically decreased the expression of intestinal Niemann-Pick C1-like protein 1 (NPC1L1) in hamsters and reduced cholesterol absorption in Caco-2 cells [21]. Thus, curcumin increases the lipid breakdown process while preventing hypercholesterolemia.

Another study showed that curcumin changed the metabolism of bile acids to increase thermogenesis, leading to fat loss [2]. Curcumin affected bile acid (BA) metabolism by increasing the percentage of circulating deoxycholic acid (DCA) and lithocholic acid (LCA), the two most active TGR5 ligands. Interestingly, curcumin was also found to influence SCFA profiles and gut barrier function in a Parkinson's disease model [22]. Though the neuroperative mechanism is still unknown, it highlights the broad systemic benefits of curcumin in neurological and immune health as well.

2.3.3 Effect on Oxidative Stress and Inflammation

Curcumin has an antioxidant property. Mokgalaboni et al. showed that curcumin supplementation led to a considerable decrease in oxidative stress biomarkers [23]. This update on the clinical evidence summarized that this impact was associated with the lowering of main indicators of oxidative stress and inflammation, such as tumour necrosis factor-alpha (TNF-α), hs-CRP, malonaldehyde (MDA), and monocyte chemoattractant protein-1 (MCP-1). Subsequently, another study established improvements in oxidative stress parameters through inhibition of lipid peroxidation as well as reduction in NF-κB activation [24]. The reduction in NF-κB activation lowers the IL-6 level and adipose tissue A-FABP-4 expression, markers of systemic inflammation [25]. However, the experiments were conducted on animal models, thus, requiring experiments on humans with subsequent clinical trials.

Curcumin protects against the accumulation of fats and metabolic syndrome due to its anti-inflammatory activity. Curcumin altered gut microbiota, which in turn was followed by reduced adiposity and systemic inflammation in obese mice [19]. Additionally, it decreases inflammation in white adipose tissue increasing thermogenic activity in brown adipose tissue. Additionally, Teich et al. demonstrated curcumin supplementation reduced weight regain and metabolic dysregulation during the recovery from exercise [26]. It indicates that through a decrease in CRP level and insulin resistance, metabolic regulation would be involved. Thus, curcumin acts as a dual agent in reducing fat storage and increasing energy expenditure.

2.4 Combined effect of Curcumin

Curcumin has been observed to have a positive effect when used in combination with other natural compounds. Piperine obtained from black pepper increased the absorption of curcumin increasing its effect on lipid metabolism [27]. Curcumin-piperine supplementation significantly reduced the total cholesterol and LDL-C levels in patients with metabolic syndrome (MS). Similar evidence was drawn from another study conducted on type 2 diabetic patients with hypertriglyceridemia [28]. Thus, curcumin can also be used in combination with other natural products. Curcumin has the potential to be used in combination with pharmaceuticals. Co-administered curcumin in combination with resveratrol leads to effects comparable to those of atorvastatin which is a prescription lipid-lowering medication [29]. Subsequently, curcumin and resveratrol are involved in decreasing hypertension through modulating the renin-angiotensin system and pathways of antioxidants. Thus, such insights open avenues for the therapeutic use of polyphenol combinations for natural cholesterol reduction.

2.5 Current Evidence on Clinical Studies

Some of the clinical trials on its therapeutic application among humans provide further insight into the potential of dosage. Rahmani et al. reported that supplementation of curcumin at a dose of 500 mg daily for 8 weeks caused an improvement in liver fat content by as high as 78.9% [30]. It is accompanied by significant reductions in LDL-C, BMI, triglycerides (TG), and liver transaminases compared to the placebo. However, Nouri-Vaskeh discovered that curcumin improved liver function in cirrhotic individuals but did not substantially affect liver transaminases levels[31]. It indicate that effectiveness varies depending on disease stage and severity. Contrarily, Jarhahzehda et al. demonstrated a significant reduction of liver enzymes ALT, AST, and GGT; LDL-C, and malondialdehyde after turmeric supplementation of 2 g per day for 8 weeks [32]. This indicates the need for further trials especially aligned with liver transaminases.

Despite the high therapeutic potential of curcumin, its poor bioavailability has been a significant problem. The low bioavailability of curcumin is attributed to poor gut absorption thereby, requiring higher concentrations within non-toxic limits to deliver the required bioavailable concentrations [33]. Subsequently, it requires potential formulations for effective delivery. For instance, Jazayeri-Tehrani et al. showed that nano-curcumin formulations substantially improved lipid metabolism and reduced inflammation in NAFLD patients [34]. Thus, clinical and preclinical studies further establish the potential to improve lipid metabolism, reduce hepatic fat buildup, and modulate inflammatory pathways.

3 Conclusion and Future Directions

The core mechanism of curcumin in the regulation of fat metabolism, focusing on its specific role in fat metabolism and analyzing its therapeutic potential in related diseases was explored. Curcumin plays a multifunctional role in the regulation of fat metabolism through modulation of pathways. Current research are consistent in the efficacy of curcumin in reducing liver fat accumulation, and other associated condition. Despite promising results, studies are needed to confirm the efficacy of curcumin and determine optimal dosing strategies. Thus, further research is warranted into synergistic formulations and precision-based therapeutic applications with greater bioactivity and metabolic stability.

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