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MINIREVIEWS

Potential effects of curcumin on peroxisome proliferator-activated receptor-γ *in vitro* and *in vivo*

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Abstract

Natural peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists are found in food and may be important for health through their anti-inflammatory properties. Curcumin (Cur) is a bright yellow spice, derived from the rhizome of Curcuma longa Linn. It has been shown to have many biological properties that appear to operate through diverse mechanisms. Some of these potentially beneficial effects of Cur are due to activation of the nuclear transcription factor PPAR-γ. It is reported (using *in vitro* and *in vivo* models) that Cur plays a potential role against several diseases. In this review article, we present the current literature on the effects of Cur on the modulation of inflammatory processes that are mediated through PPAR-γ.

Key words: Curcumin; Anti-inflammatory; Peroxisome proliferator-activated receptor-γ

Core tip: In this short review, we highlight the potential antioxidant and anti-inflammatory properties of curcumin (Cur), discussing its impact on peroxisome proliferator-activated receptor-γ (PPAR-γ) receptor function and its effects *in vitro* and *in vivo*. Cur affects the

PPAR-γ gene and prevents cell growth through effects on the cell cycle and induction of apoptosis. It is also well-established that Cur has anti-inflammatory effects *in vivo* through regulation of the PPAR-γ receptor, which leads to the suppression of nuclear factor kappa B, a pro-inflammatory mediator.

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INTRODUCTION

Curcumin

Curcumin (diferuloylmethane) (Cur) is an orange pigment extractable from turmeric. Curcuma is derived from the word "Kourkoum". Due to its color, curcuma is sometimes referred to in Europe as "Indian Saffron". As a result of its chemical and biological properties, Cur is known to contain several potential important phytochemical compounds[1-5]. Cur is a lipophilic polyphenol, is poorly soluble in water and stable at an acidic pH[6]. A critical review of Cur suggests that the compound has potential as a modulator of the activity of many vital bio-macromolecular targets involved in homeostasis of mammalian physiology[7]. Dietary polyphenols have recently received more attention because of their potentially protective characteristics against metabolic diseases[8].

The properties of Cur

Cur has been reported to be safe at dosages of up to 8 g/d in human studies and there is no evidence of resistance. Nevertheless, bioavailability is a major concern as 75% of Cur is excreted in the stool[9,10]. Besides its dietary use, Cur has been considered to have beneficial properties, including anti-inflammatory, antioxidant, antineoplastic, pro and anti-apoptotic, anti-angiogenic, cytotoxic, immune-modulatory and antimicrobial effects, through the modulation of various kinds of targets, including growth factors, enzymes and genes such as *STAT3*, peroxisome proliferator-activated receptor-γ (PPAR-γ) and nuclear factor kappa B (NF-κB)[11,12]. It also has a strong anti-inflammatory effect that inhibits several mediators of the inflammatory response[13-15]. Due to its low solubility in water and therefore poor oral bioavailability, nanoparticles and liposomes have been suggested as potential ways of improving its efficacy[16].

PPARs

PPARs are a class of proteins that are usually activated by their respective ligands and function within the cell nuclei for controlling metabolism, development and homeostasis. PPARs heterodimerize with the retinoid X receptor and bind to PPAR responsive element in the regulatory region of target genes that function in different natural courses, such as adipogenesis, immune response and both cell growth and differentiation[17,18]. There are 3 major isoforms of PPARs in mammals, namely PPARα, PPAR-γ and PPARα/γ. PPAR-α can improve triglyceride concentration and also has some roles in energy homeostasis, whereas activation of PPAR-α/γ improves fatty acid hemostasis[19]. PPAR-γ is involved in lipid anabolism, adipocyte differentiation inflammation and immune response[20]. PPAR-α is triggered by a wide diversity of fatty acids or their metabolites and governs metabolic processes implicated in glucose and lipid metabolism and adipose mass control by modulating the expression of a huge quantity of target genes. Furthermore, PPAR-γ is a molecular target for anti-diabetic thiazolidinedione molecules that selectively bind this nuclear receptor to improve systemic insulin sensitivity and glucose tolerance. Accordingly, the specific position of PPAR-γ in systemic metabolic control is due to its pivotal role in the homeostasis control of glucose and lipid homeostasis, lipid storage and adipogenesis[21]. Lately, PPAR-γ has been recognized to be the major player with a key role in the immune response because of its capability to prevent the production of inflammatory substances[22].

Hepatic stellate cells and liver fibrosis

Hepatic stellate cells (HSCs) are located near to hepatic epithelial cells. In a normal liver, HSCs contain many vitamin A lipid droplets. When the liver is injured, HSCs receive signals from damaged cells in the liver to change into activated myofibroblast-like cells[23,24]. In addition, HSCs secrete growth factors and help in the maintenance of liver cells. In liver disease, extended and frequent activation of HSCs causes liver fibrosis that may eventually result in organ failure and death[25,26]. Activation of hepatic HSCs is a key step in liver collagen production and fibrosis formation[27-31]. Hepatic fibrosis is also a necessary step in the development of hepatic cirrhosis. Thus, treatment of chronic liver diseases depends on the prevention and treatment of fibrosis[32]. Some studies showed that HSC activation significantly reduces the expression of PPAR-γ and that PPAR-γ agonists inhibit HSC activation, resulting in reduced expression of α-SMA and collagen, as well as reduced cell propagation and development of hepatic fibrosis. In normal liver tissues, PPAR-γ is expressed highly in quiescent HSCs. Moreover, increased PPAR-γ expression reduces the synthesis of HSC DNA and results in the diminished expression of collagen and the transforming growth factor (TGF)-1β. At the same time, PPAR-γ is also involved in the apoptosis of HSCs through a variety of mechanisms[33-36]. Some experiments have confirmed that Cur may prevent the proliferation of HSCs whilst also increasing their apoptosis[37]. A further study has shown that Cur increases the expression of PPAR-γ and revives the trans-activating activity in activated

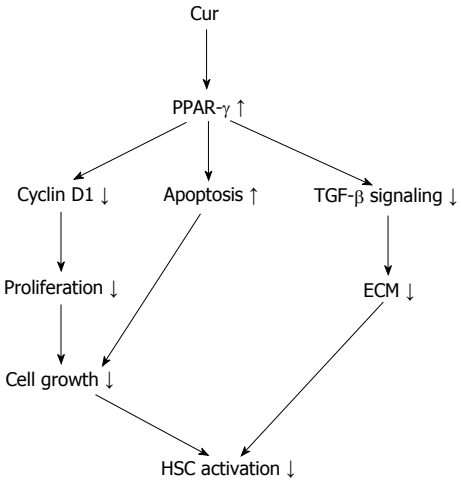

Figure 1 Possible mechanisms, primarily the inhibition of hepatic stellate cell activation by peroxisome proliferator-activated receptor-γ after modulation with curcumin. PPAR-γ: Peroxisome proliferator-activated receptor-γ; HSC: Hepatic stellate cell; TGF: Transforming growth factor; Cur: Curcumin; ECM: Extracellular matrix.

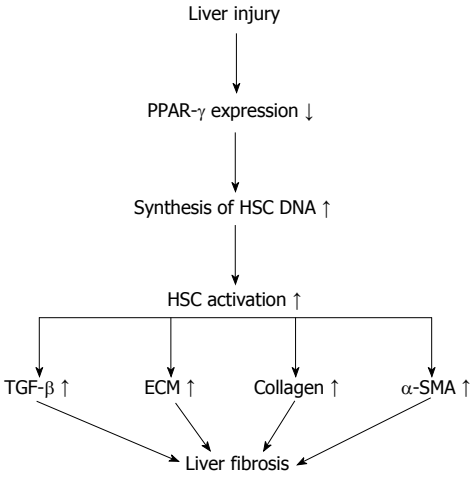

Figure 2 Liver fibrosis creation followed down-regulating of peroxisome proliferator-activated receptor-γ after liver injury. As shown, decrease in PPAR-γ expression after liver injury causes an increase in HSC DNA expression and HSC activation. This regulation also results in increased expression of α-SMA, collagen, ECM and TGF-β and induces liver fibrosis. PPAR-γ: Peroxisome proliferator-activated receptor-γ; HSC: Hepatic stellate cell; TGF: Transforming growth factor; ECM: Extracellular matrix; α-SMA: α-smooth muscle actin.

HSC, which is essential for the anti-inflammatory and antioxidant effects on reserve for HSC propagation and growth[38] (Figure 1).

In this review article, we present the current literature to display the role of Cur on modulation of inflammatory processes that are mediated through PPAR-γ.

EFFECTS OF CUR ON PPAR-γ EXPRESSION IN HSCS AND HEPATIC FIBROSIS

HSCs are activated when gene expression and phenotype changes render the quiescent cells responsive to other cytokines. Kupffer cells provide the potential source of paracrine stimuli for HSCs because they express TGF-β[24,25,39-41]. During HSC activation, regulatory pathways including epigenetic regulation of (NF-κB) and reduction in PPAR-γ expression modulate the expression of many genes, including *TGF-1β* and *MMP-2*[42-46].

Many *in vitro* studies have shown that Cur inhibits cell proliferation and induces apoptosis of stimulated HSC. However, the mechanism and action of Cur on HSC growth *in vitro* is not well defined. Numerous mechanisms have been recognized for the inhibition of TGF-1β signaling *via* Cur, including PPAR-γ activation. Cur inhibits NF-κB, leptin and insulin and mediates HSC activation by stimulating PPAR-γ activity[38,47-51] (Figure 2).

Zheng *et al*[52] confirmed that inhibiting PPAR-γ stimulation abrogated the effects of Cur on the stimulation of apoptosis and prevention of the expression of *ECM* genes in activated HSC *in vitro*. They also showed that Cur repressed the gene expression of TGF-β receptors and disturbed the TGF-β signaling pathway in stimulated HSC, which is facilitated by PPAR-γ stimulation[52]. Zhang *et al*[37] established that Cur improved fibrotic injury and sinusoidal angiogenesis in the rodent liver when fibrosis was initiated by carbon tetrachloride. Cur decreased the expression of a number of angiogenic factors in the fibrotic liver. Moreover, *in vitro* investigation showed that the sustainability and vascularization of rodent liver sinusoidal endothelial cells and angiogenesis in rodents were not diminished by Cur. These findings demonstrated that HSCs could be a possible target for Cur. Moreover, other studies have shown that Cur can inhibit vascular endothelial growth factor expression in HSCs associated with interrupting the mammalian target of rapamycin pathway. PPAR-γ activation was reported to be essential for Cur to prevent the angiogenesis in HSCs. The authors determined that Cur reduced sinusoidal angiogenesis in liver fibrosis probably by HSCs *via* a PPAR-γ activation-dependent pathway. Also, other studies showed that PPAR-γ could be a target molecule for decreasing pathological angiogenesis in liver fibrosis for rodents[37]. These studies offer new perspectives into the mechanisms that underpin prevention of HSC activation by Cur and PPAR-γ ligands and inhibit HSC activation and liver fibrosis. To convert stimulated HSCs to a quiescent state or to induce apoptosis may be a dangerous approach for anti-fibrotic treatment.

EVIDENCE FOR THE PPAR-γ MEDIATED ANTI-INFLAMMATORY EFFECT OF CUR

It appears that the hydroxyl and methoxy residues of Cur are accountable for its antioxidant and anti-inflammatory effects[53,54]. Some of the effects of Cur are through the JAK/STAT pathway, which can decrease pro-inflammatory interleukins and cytokines. Moreover, Cur

Table 1 Molecular targets of curcumin and peroxisome proliferator-activated receptor-γ modulated by curcumin *in vivo* and *in vitro*

Transcription factors	Growth factor/or cytokines	Proteins/or protein kinase pathway	Inflammatory mediators	Enzymes
STAT3 ↓	TGF-β ↓	Cyclin D1 ↓	IL-1 ↓	LOX ↓
NF-κB ↓	TNF-α ↓	Collagen ↓	IL-2 ↓	XO ↓
	MCP-1 ↓	LDL ↓	IL-6 ↓	COX-2 ↓
		Insulin ↓	IL-8 ↓	iNOS ↓
		Leptin ↓	LOX ↓	
		JAK/STAT ↓		

NF-κB: Nuclear factor kappa B; TGF: Transforming growth factor; LDL: Low-density lipoprotein; LOX: Lipoxygenase; COX: Cyclooxygenase; STAT3: Signal transducer and activator of transcription 3; TNF: Tumor necrosis factors; MCP-1: Monocyte chemoattractant protein-1; IL: Interleukin; iNOS: Inducible nitric oxide synthase; XO: Xanthine oxidase.

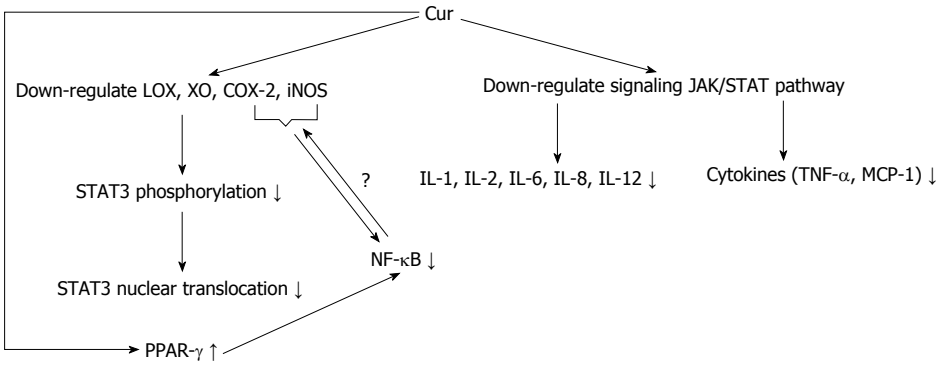

Figure 3 Mechanisms of anti-inflammatory properties of curcumin *in vivo*. Curcumin (Cur) down-regulates some of the factors involved in inflammation, inhibiting NF-κB activation and causing its anti-inflammatory effects. Also, Cur with increasing PPAR-γ expression directly inhibits NF-κB activation. NF-κB: Nuclear factor kappa B; TNF: Tumor necrosis factors; MCP-1: Monocyte chemoattractant protein-1; IL: Interleukins; LOX: Lipoxygenase; COX: Cyclooxygenase; iNOS: Inducible nitric oxide synthase; STAT3: Signal transducer and activator of transcription 3; PPAR-γ: Peroxisome proliferator-activated receptor-γ; XO: Xanthine oxidase.

suppresses the inflammatory response by decreasing the activity of cyclooxygenase-2 (COX-2) and lipoxygenase, resulting in inhibition of STAT3 phosphorylation and consequent STAT3 nuclear translocation[55-58]. Cur suppression of COX-2 and inducible nitric oxide synthase may be *via* the inhibition of the NF-κB activation by this polyphenol group.

Kawamori *et al*[59] have shown that dietary Cur inhibits phospholipase A2 and affects COX and lipoxygenase actions. Cur decreases COX-2 expression at the transcriptional level[13]. Cur is supposed to inhibit NF-κB and pro-inflammatory substances by hindering phosphorylation of inhibitory factor Ⅰ kappa B kinase. The growing incidence of allergic disease, combined with promising outcomes from RCTs, proposes that natural PPAR-γ agonists found in the diet might be helpful by acting as anti-inflammatory factors[59-61].

Cur has been reported to trigger PPAR-γ but whether or not it is a ligand for it is still debated and further experimental work is required in this regard (Figure 3). Moreover, the exact mechanisms by which Cur stimulates PPAR-γ expression are still unknown. Given the important role of Cur, there may be two ways. Cur binds to its own receptor and the complex stimulates the up-regulation of PPAR-γ, or Cur is a ligand of PPAR-γ leading to the stimulation of PPAR-γ[62,63]. A summary of the possible molecular targeting of Cur and PPAR-γ modulated by Cur is shown in Table 1. Investigators have described the *in vitro* anti-inflammatory pathways of Cur and they suggest that it was reached mostly through the down-regulation of NF-κB[4,16]. Most experiments have shown that the anti-inflammatory effect of Cur is attributed to PPAR-γ activation[64]. Recent experimental data have shown that Cur has an antitumor effect in pancreatic cancer by inhibiting propagation and down-regulating NF-κB and its products[65]. Nevertheless, it is reasonable to suggest that Cur prompted an anti-inflammatory effect through the up-regulation of PPAR-γ which is closely related to the NF-κB pathway.

CONCLUSION

In this short review, we have highlighted the potential antioxidant and anti-inflammatory activities of Cur and discussed Cur's significant impact on PPAR-γ receptor function. Cur prompts the expression of the *PPAR-γ* gene, causing its activation in cells to activate HSCs and hepatic fibrosis. This combined action of Cur and PPAR-γ prevents cell growth from the stimulation of the cell cycle and induction of apoptosis. It is also well-established that Cur has anti-inflammatory effects *in vivo* through regulation of the PPAR-γ receptor, which leads to the suppression of NF-κB, a pro-inflammatory mediator.

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