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

Mazidi M *et al.* Curcumin and PPAR-γ

**Mohsen Mazidi, Ehsan Karimi, Mohsen Meydani, Majid Ghayour-Mobarhan, Gordon A Ferns**

**Mohsen Mazidi,** Key State Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China

**Mohsen Mazidi,** Institute of Genetics and Developmental Biology, International College, University of Chinese Academy of Science, Beijing 100101, China

**Ehsan Karaimi, Majid Ghayour-Mobarhan,** Biochemistry of Nutrition Research Center, School of Medicine, Mashhad University of Medical Science, Mashhad 9138813944, Iran

**Mohsen Meydani,** Vascular Biology Laboratory, Jean Mayer USDA-Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA

**Majid Ghayour-Mobarhan,** Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Science, Mashhad 9138813944, Iran

**Gordon A Ferns,** Division of Medical Education, Brighton and Sussex Medical School, Rm 342, Mayfield House, University of Brighton, Brighton BN1 9PH, United Kingdom

**Author contributions:** Mazidi M, Meydani M and Ghayour-Mobarhan M designed research; Mazidi M and Ghayour-Mobarhan M wrote the first draft; Karaimi E and Mazidi M performed research; Ferns GA and Meydani M revising the paper.

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**Correspondence to:** **Majid Ghayour-Mobarhan,MD, MSc, PhD,** Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Science, Paradise Daneshghah, Azadi Square, Mashhad 9138813944, Iran. [ghayourm@mums.ac.ir](mailto:ghayourm@mums.ac.ir)

**Telephone:** +98-915-5171478

**Fax:** +98-511-7112596

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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:** Peroxisome proliferator-activated receptor-γ; Curcumin; Anti-inflammatory

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**Core tip:** In this short review, we have highlighted the potential anti-oxidant 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 *PPAR-γ*gene and prevents cell growth through effects on the cell cycle and induction of apoptosis. It was 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 derivative from the word “Kourkoum.” Because of its color, curcuma is sometimes referred to in Europe as “Indian Saffron”. Because of its chemical and biological properties, Cur is knows to contain several potential important phytochemical compounds[1-5]. Cur is a lipophilic polyphenol and is poorly soluble in water, and is stable at an acidic pH[6]. A critical review on Cur suggests that the compound has potential as a modulator of 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 up to 8 g per day 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 a varied kind of targets including growth factors, enzymes and genes such as, *STAT3*, peroxisome proliferator-activated receptor-Υ (*PPAR-γ*) and nuclear factor kappa B (*NF-ĸB*)[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 (RXR) and bind to PPAR responsive element (PPRE) 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 have some roles in energy homeostasis. Whereas activation of PPAR-α/γ improves fatty acids hemostasis[19]. PPAR-γis involved in lipid anabolism, adipocyte differentiation inflammation, immune response[20]. PPAR-*α* is triggered by a wide diversity of fatty acids or their metabolite, 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-γis 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-γin systemic metabolic control is due its pivotal role in the homeostasis control of glucose and lipid homeostasis, lipid storage and adipogenesis[21]. Lately, PPAR-γ recognized to be the major player and has an key role in the immune response from its capability to prevent the production of inflammatory substance[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 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 revived the trans-activating activity in activated HSC, which is essential for the effects of the anti-inflammatory and antioxidant on reserve of HSC propagation and growth[38] (Figure 1).

In this review article, we presented the current literature to display the role of the 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-ĸB) and reduction in PPAR-γ expression modulates the expression of many genes, including *TGF-1β* and *MMP-2*[42-46].

Many *in vitro* studies have showed 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-ĸB, leptin, and insulin, mediated HSC activation by stimulating PPAR-γ activity[38,47-51] (Figure 2).

Shizhong *et al*[52] confirmed that inhibiting PPAR-γstimulation 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-γstimulation[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 rodent were not diminished by Cur. These findings demonstrated that HSCs could be possible target for Cur. Moreover, other studies have shown that Cur can inhibit VEGF expression in HSCs associated with interrupting mTOR pathway. PPAR-γ activation was reported to be essential for Cur to prevent the angiogenic in HSCs. The authors determined that Cur reduced sinusoidal angiogenesis in liver fibrosis probably by HSCs *via* a PPAR*-*γactivation-dependent pathway. Also, other studies showed that PPAR-γcould be a target molecule for decreasing pathological angiogenesis in liver fibrosis for rodent[37]. These studies offer new perspectives into the mechanisms underpin prevention of HSC activation by Cur and PPAR-γ ligands; inhibit HSCs 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]. Cur has some of its effects through the JAK/STAT pathway, which can decrease pro-inflammatory interleukins, and cytokines. Moreover, Cur suppress the inflammatory response by decrease the activity of cyclooxygenase-2 (COX-2), lipoxygenase, resulting in inhibition of STAT3 phosphorylation and consequent STAT3 nuclear translocation[55-58]. Cur suppression of COX-2 and iNOS may be via the inhibition of the NF-ĸB activation by this polyphenol group.

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

Cur has been reported to trigger PPAR-γ, but whether 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 stimulate PPAR-γ expression is still unknown. Given to important role of the Cur, two ways may be involved: Cur binds to its own receptor and the complex stimulates the up-regulation of PPAR-γ. Or, Cur is a ligand of PPAR-γleading 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 reached mostly through the down-regulation of NF-ĸB[4,16]. Most experiments have showed 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-ĸB and it’s products[65]. Nevertheless, it is reasonable that Cur prompted anti-inflammatory effect through the up-regulation of PPAR-γis closely related with the NF-ĸB pathway.

**CONCLUSION**

In this short review, we have highlighted the potential anti-oxidant and anti-inflammatory activity of Cur. We have discussed Cur’s significant impact on PPAR-γ receptor function. Cur prompts the expression of *PPAR-γ* gene causing its activation in cells activated HSCs and Hepatic fibrosis. This action of Cur and PPAR-γ together prevents cell growth from stimulation cell cycle and induction of apoptosis. It was also well-established that Cur has anti-inflammatory effects *in vivo* through regulation PPAR-γ receptor, which leads to the suppression of NF-ĸB, a pro-inflammatory mediator.

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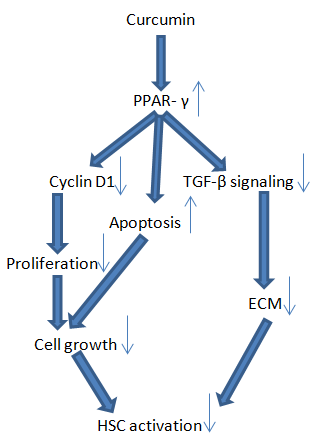
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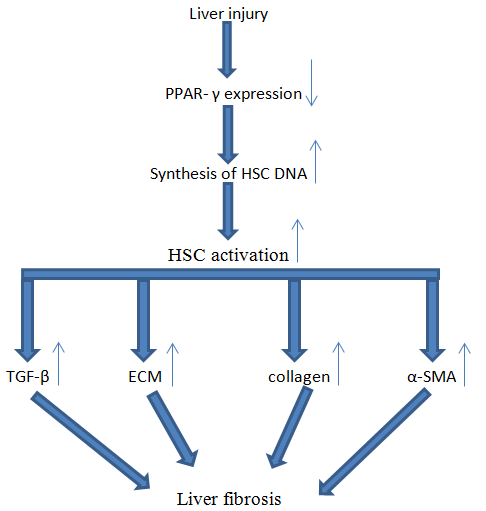
**Table 1 Molecular targets of curcumin and peroxisome proliferator-activated receptor-γ modulated by curcumin *in vivo* and *in vitro***

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

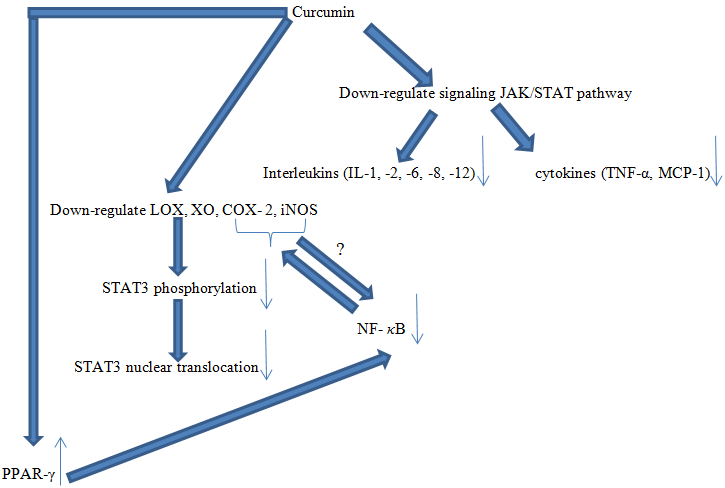
NF-ĸB: Nuclear factor kappa B; TGF: Transforming growth factor; LDL: Low-density lipoprotein; LOX: Lipoxygenase; COX: Cyclooxygenase.



**Figure 1 Possible mechanisms primary the inhibition of hepatic stellate cell activation by peroxisome proliferator-activated receptor-γ after modulate with curcumin.** PPAR-γ: Peroxisome proliferator-activated receptor-γ; HSC:Hepatic stellate cell; TGF: Transforming growth factor.



**Figure 2 Liver fibrosis creation followed down-regulating of peroxisome proliferator-activated receptor-γ after liver injury.** As shown in fig, decrease in PPAR-γ expression after liver injury cause increase in HSC DNA expression and HSC activation. Also this regulation resulting in increased expression of α-SMA, collagen, ECM and TGF-β and induce liver fibrosis. PPAR-γ: Peroxisome proliferator-activated receptor-γ; HSC:Hepatic stellate cell; TGF: Transforming growth factor.

 **Figure 3 Mechanisms anti-inflammatory of curcumin *in vivo*.** Curcumin with down-regulating some of factors involve in inflammation inhibit NF-ĸB activation and cause its anti-inflammatory effects. Also curcumin with increasing PPAR-γ expression, directly inhibit from NF-ĸB activation. NF-ĸB: Nuclear factor kappa B; TGF: Transforming growth factor; LOX: Lipoxygenase; COX: Cyclooxygenase; PPAR-γ: Peroxisome proliferator-activated receptor-γ.