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Review Article

The Role of Curcumin and Its Derivatives in Innate Immune Response of Macrophages

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Abstract: Curcumin, a diarylheptanoid, is the active compound isolated from the rhizomes of *Curcuma* species. Curcumin can modulate mechanisms in inflammatory-related immunomodulatory. Inflammation caused by microbial infection and tissue damage is an essential mechanism of the innate immune response. In contrast, chronic and uncontrolled inflammation often results in severe tissue damage resulting in the pathogenicity of an exaggerated immune response. Macrophages are crucial cellular components of innate immunity and the host's defense against foreign molecules. For this reason, this review aims to assess the role of curcumin and its derivatives in the innate immune response of macrophage cells. Curcumin modulates innate immune and inflammatory response by inhibiting NLRP3 inflammasomes, nuclear factor-kappa B, mitogen-activated protein kinase, and Janus kinase1/2-signal transducer and activator of transcription protein1 signaling pathway. Curcumin as an anti-inflammatory inhibits inflammation mediators release such as cytokines, nitric oxide, reactive oxygen species, and others. This review found that curcumin's thiol-reactive α,β-unsaturated carbonyl groups play a critical role in the anti-inflammatory effect. Therefore, curcumin derivatives mainly modify the structure by retaining the thiol-reactive α,β-unsaturated carbonyl groups. This review also discusses the effect of structure and formula modification of curcumin in the immune response of macrophages cells. Thus, the brief information provided in this review investigates the role of curcumin and its derivates in macrophage cells.

Keywords: curcumin; curcumin derivatives; innate immunity; macrophages; inflammation

1. INTRODUCTION

Curcumin is a natural phytochemical from *Curcuma* species, especially turmeric (*Curcuma longa* L.) [1]. Previous studies show that curcumin and its derivatives have anti-inflammatory, antioxidant, and immunomodulatory effects on macrophages polarization [2–4]. In addition, *in vivo* studies of curcumin have been evaluated in the treatment of conditions associated with an inflammatory or immune response such as inflammatory bowel disease, colitis, Crohn's disease, rheumatoid arthritis, psoriasis, and cancer [5].

Inflammation is one of the immune responses as a protective reaction after infection or injury [6]. However, an uncontrolled inflammatory response would cause disease risk, including asthma, pulmonary disease, and rheumatoid arthritis [7]. Macrophages are the innate immune cells and the first line of the host defense against many common microorganisms. These cells are one of the models to assess active compounds in inflammatory responses. In addition, several studies of curcumin used mouse bone marrow-derived macrophages (BMDMs), human THP-1, and murine RAW264.7 as macrophage models to identify its initial activity by *in vitro* study [8].

Curcumin has therapeutic effects on various diseases and is considered safe at high doses [9]. Unfortunately, it has low stability, solubility, and bioavailability. Therefore, curcumin's structure modification and formulation have been proposed to solve these problems. [10]. On the other hand, curcumin derivatives have anti-inflammatory activities as well as curcumin. For example, *ortho*-trifluoromethoxy-substituted 4-piperidine (N–H, N-methyl)-containing mono-carbonyl curcumin were potential anti-inflammatory agents [1]. Curcumin and its derivatives are promising active compounds to modulate inflammatory-related immunomodulatory. This review aims to accumulate all probable studies about the effect of curcumin and its derivatives in the innate immune response of macrophages.

2. MATERIALS AND METHODS

The literature search was performed in Scopus, PubMed, ScienceDirect, and Google Scholar to search for articles published in English. The following keywords were used "Curcumin" AND "Curcumin Derivatives" AND "Innate Immune" AND "Macrophages or Each Name of Macrophage Models". The inclusion criteria in this review were original articles from 2018 to 2021 and only *in vitro* studies. Articles were excluded from primary papers, which are conference articles and thesis. Only full-text relevant articles were included after the screening of titles and abstracts. From this process, 27 articles were included in this review.

3. RESULTS AND DISCUSSION

3.1. Curcumin, a dietary supplement, and structure-activity relationship

Curcumin or 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a diarylheptanoid. Curcumin is a natural yellow pigment and phenolic compound isolated from the rhizomes of *Curcuma* species, especially *Curcuma longa* L. In addition, curcumin has antioxidants, anti-inflammatory, anti-carcinogenic, anti-microbial, anti-radiation, osteoarthritis, anxiety, depression, metabolic syndrome, pathological pain, and cardiovascular protective effects [1,11,12]. The target mechanism of curcumin-associated inflammatory or immune response potential develops [5].

Chemically, curcumin has two phenolic functional groups connected to conjugated β-diketone (Figure 1) [13]. In addition, the ortho-substituents on the phenyl ring can improve the pharmacology effect. For example, recent studies show that *ortho*-trifluoromethoxy-substituted 4-piperidine (N–H, N-methyl)-containing mono-carbonyl curcumin derivatives were potential anti-inflammatory agents [1].

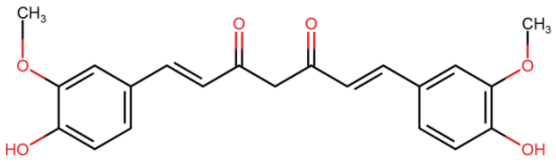


Figure 1. Chemical structure of curcumin

Curcumin has two methoxy groups (-OCH3) in its aromatic rings, which play an anti-inflammatory effect. In the previous study, curcumin-OH and curcumin-Br showed similar potency as curcumin to inhibit the NO and COX-2 production by reducing activation of NF-κB signaling in macrophage cells. However, another analog was less activity than curcumin, and the curcumin-NO_2 did not inhibit NO and COX-2 production. Substitution groups such as -OH, -Br, -H, -F, -CH_3, -Cl, and -NO_2 were evaluated to substitute the methoxy position. These substitution groups are electron-withdrawing (EWG) which act as the acceptor of the electron. Additionally, the -NO_2 group is the strongest EWG, while the -OH group is the weakest. The substitution groups on the methoxy position with the strength EWG could change the reactivity of the α, β-unsaturated carbonyl moiety. Indeed, the results showed that the EWG maybe have a reduced anti-inflammatory effect than curcumin [14].

3.2. Regulation of Innate Immune Responses in Macrophages

Macrophages play an essential role in innate immune responses, including infectious tissue damage and inflammatory disease. Macrophages are crucial to the host defense mechanism for recognizing and eliminating pathogens [15]. In addition, macrophages are well-known phagocytic cells for development, homeostasis, and wound healing [9,16,17]. Plasticity is a hallmark of macrophages, and these are the immune cells that exhibit diverse functions depending on their polarization state [18]. Macrophages are plastic cells that differentiate into other phenotypes depending on the signals they receive from their local microenvironment. Macrophages polarize into M1 (classically activated macrophages) and M2 (alternatively activated macrophages). M1 as pro-inflammatory to elicit disruptive tissue reactions. Besides, M2 is an anti-inflammatory to repair tissue remodeling and angiogenesis [19].

Several macrophage models include human monocyte-derived macrophages (hMDMs), mouse bone marrow-derived macrophages (BMDMs), human THP-1 and U937, the murine RAW264.7, and J774 cell lines. Macrophages from *Mus musculus* have a lesser range of variability than those from humans. THP-1 is a human monocytic leukemia cell line that differentiates into active macrophages after treating phorbol 12-myristate 13-acetate (PMA) [8]. On the other hand, RAW 264.7 macrophage cell lines are cells derived from BALB/c mice transforming the leukemia virus [20]. RAW 264.7 model as macrophage cell lines is commercial, accessible to culture, and available for large-scale screening. *In vitro* screens are initial studies to evaluate active sources in modulating inflammatory responses. [21]. Therefore, BMDMs, THP-1 cells, and RAW 264.7 cells are still used as a model of macrophages.

Many studies of curcumin's mechanism in the innate immune response of macrophages are reported. Curcumin as an anti-inflammatory agent inhibits the expression of mediator inflammatories such as IL-6, TNF-α, and COX-2 cytokines in LPS-induced RAW 264.7 macrophage cell line via suppressor of cytokine signaling (SOCS) and mitogen-activated protein kinase (MAPK)

signaling pathway. The suppressor of cytokine signaling (SOCS) proteins represent an endogenous negative regulatory mechanism of cytokine signaling and is essential to the normal immune. Still, they are also regulated in the development of immunological disorders. Besides, mitogen-activated protein kinase (MAPK) are well-known stress-activated kinases implicated in controlling the inflammatory and immune response [5]. In addition, the role of the NLRP3 inflammasomes is an essential innate immune sensor target of curcumin [22]. The application of curcumin as a treatment in several diseases such as atherosclerosis, gouty arthritis, anti-osteoclastogenesis, immune disorder, acute kidney injury, rheumatoid arthritis, antioxidant, adjuvant chemotherapy, trichomoniasis, pulmonary fibrosis, bone injury disease, and acute lung injury show its effect on macrophage (Table 1.). In this review, RAW 264.7 cells were dominantly to evaluate curcumin and its derivatives in the innate immune response.

Table 1. The curcumin effect in the innate immune response of macrophages

No.	Pharmacology activity	Induction/treatment	Results	Ref.
1.	Anti-inflammatory	LPS induced-(primed BMDMs) mouse bone marrow-derived macrophages and LPS induces-THP-1 cells	Inhibits NLRP3-dependent caspase-1 activation and IL-1β secretion	[22]
2.	Prevent osteolysis	Polyethylene induced-RAW 264.7	Inhibits RANK/c-Fos/NFATc1 signaling pathway	[23]
3.	Gouty arthritis	Monosodium urate 0.2 mg/mL induced-RAW 264.7	Prevent mitochondrial membrane potential reduction, decrease mitochondria ROS, and inhibit NLRP3 inflammasome	[24]
4.	Anti-osteoclastogenesis and immunomodulatory	RANKL 100 ng/mL induced-RAW 264.7	Reduce c-fos, NFATc1, Oscar, Sema-4A mRNA, TNF-α and IL-6 expression, Akt and NF-κB pathways; increase IL-4 and IL-10	[3]
5.	Renoprotective in acute kidney injury	LPS-induced-CRISPR/CAS9-mediated Mincle knock-out in RAW264.7 cell	Reduce TNF-α, IL-1β, IL-6, chemotactic factor (MCP-1) mRNA expression, Syk/NF-kB signaling	[25]
6.	Rheumatoid arthritis	LPS 10 μg/mL induced-RAW 264.7	Inhibition of the NF-κB signaling pathway, COX-2 expression, and the promotion of macrophage apoptosis	[11]
7.	Antioxidant	H_2O_2 500 μM induced-RAW 264.7	Increase cell viability, SOD, CAT, GSH-PX; decrease ROS production, cell apoptosis, MDA level, Nrf2, and Keap1 mRNA	[15]
8.	Periprosthetic osteolysis	RANKL 50 ng/mL induced-RAW 264.7	Enhance the cholesterol efflux in macrophages, maintain the	[26]

…continued Table 1

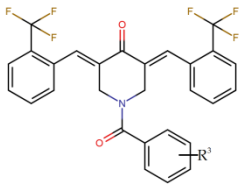
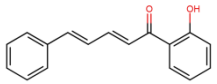
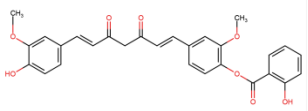
			M0-like phenotype; decrease IL-1β, TNF-α, and IL-6.	
9.	Adjuvant doxorubicin chemotherapy	LPS/IFN-γ (10 ng/mL/10 U/mL), doxorubicin 0.1 μM induced-RAW 264.7	Increase TLR4 mRNA levels; decrease NO production and IL-6 mRNA expression	[27]
10.	Trichomoniasis	*T. vaginalis* proteinases 50 μg/mL, LPS 100 ng/mL induced-RAW 264.7	Inhibit NO production, TNF-α, IL-1β, glucocorticoid receptor (mGR), and the chaperone heat shock protein 70 (Hsp70)	[28]
11.	Anti-inflammatory-mediated apoptosis of osteocytes	LPS 100 ng/mL and IFN-γ 2.5 ng/mL induced-RAW 264.7	Inhibits M1-type polarization via the Janus kinase1/2-signal transducer and activator of transcription protein1 (JAK1/2-STAT1) pathway	[4]
12.	Pulmonary fibrosis	N/A in RAW 264.7 cells	Increase hepatocyte growth factor (HGF), PPARγ, CD36, pCREB (ser133), cAMP response elemen, 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 expression	[29]
13.	Bone injury disease	LPS 20 ng/mL induced-RAW 264.7	Increase IL-4, IL-10; BMP-2 and TGF-β, and CD206, decrease IL-1β, TNF-α, CCR7, iNOS, Runx-2, OCN, OPN, and ALP activity.	[16]
14.	Acute lung injury	LPS (1 μg/mL) and ATP (5 mM) induced-RAW 264.7	Inhibits activation of NLRP3 inflammasome-induced pyroptosis and NF-κB; upregulates SIRT1 protein expression.	[30]

Lipopolysaccharide (LPS)

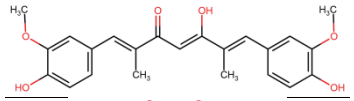
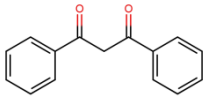
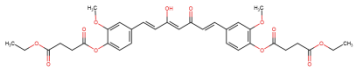
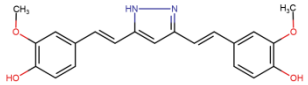
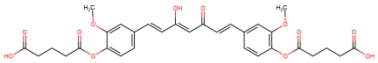
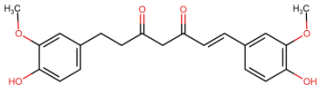
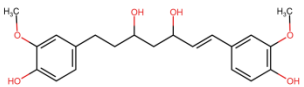
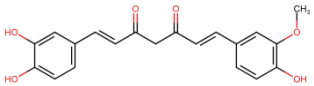
3.4. Derivatives, stability, bioavaibility, and safety of curcumin

Curcumin has poor bioavailability and instability, especially physiological conditions [1]. In addition, curcumin's poor water solubility, low absorption, rapid elimination, and rapid metabolism limited its clinical application [7,31]. Curcumin derivatives have been developed to solve this problem (Table 2.). Modification based on curcumin structure creates another potential active compound better than curcumin. Here, we hypothesized that curcumin's thiol-reactive α,β-unsaturated carbonyl groups play a critical role in the anti-inflammatory effect. Therefore, structural modification by retaining the thiol-reactive α,β-unsaturated carbonyl groups will fix the problem of curcumin while still providing activity in the inflammatory response.

Table 2. Modifications and derivatives of curcumin effect in RAW 264.7 cells

No.	Component	Structure	Pharmacology activity	Induction/treatment	Results	Ref.
1.	**C6** N-(3-methylbenzoyl)-3,5-bis-(2-(trifluoromethyl)benzylidene)piperidin-4-one) and **C10** (N-(2-chlorobenzoyl)-3,5-bis-(2-(trifluoromethyl)benzylidene)piperidin-4-one)	 **C6**: R^3= 3-CH_3 **C10**: R^3= 2-Cl	Anti-inflammatory	LPS 100 ng/mL induced-RAW 264.7	Supress TNF-α, IL-1β, IL-6, prostaglandin E2, and NO	[32]
2.	Diarylpentadienone derivatives		Anti-inflammatory	LPS 1 μg/mL induced-RAW 264.7	Decrease IL-6, TNF- α, p-p65, iNOS, and COX-2	[2]
3.	FM0807 (2-hydroxy-4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxo-1,6-heptadien-1-yl]-2-methoxyphenyl ester)		Sepsis	LPS 0.5 μg/mL induced-RAW 264.7	Inhibits TNF-α, IL-1β, IL-6, NOS, ROS, apoptosis, and ROS/JNK/p53 signaling pathway	[33]

…continued Table 2

4.	2,6-dimethyl-curcumin		Anti-inflammatory	LPS 100 ng/mL induced-RAW 264.7	Inhibit COX-2 and NF-κB activity	[34]
5.	Dibenzoylmethane		Anti-inflammation in diabetic nephropathy	LPS 100ng/mL induced-RAW 264.7	Inhibits macrophage activity	[35]
6.	Curcumin diethyl disuccinate		Anti-inflammatory	LPS 1 μg/mL induced-RAW 264.7	Decrease NO, TNF-α, and IL-6	[36]
7.	Hydrazinocurcumin		Tumor-associated macrophages	IL-4 20 ng/mL (M2-like polarization inducer) induced-RAW 264.7	Increase ROS, TNF-α, IL-6, IL-12, IFN-γ; decrease CD206 and arginase-1 (Re-polarization of M2-like cells towards M1-like phenotype)	[18]
8.	Curcumin diglutaric acid		Anti-inflammatory	LPS 1 μg/mL induced-RAW 264.7	Reduce NO, IL-6, TNF- α, COX-2, and MAPK activity	[37]
9.	Tetrahydrocurcuminand octahydrocurcuminin  Tetrahydrocurcumin  Octahydrocurcumin		Anti-inflammatory	LPS 100 ng/mL induced-RAW 264.7	Inhibits NO, MCP-1, NF-κB, and MAPKs pathways; increase Nrf2 activation	[7]
10.	Demethylcurcumin		Alzheimer's disease	LPS 500 ng/mL induced-RAW 264.7	Decrease NO production	[38]

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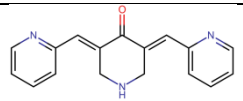
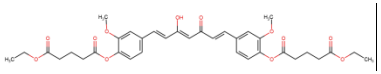
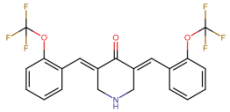
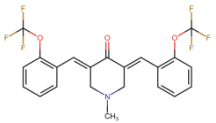
11.	AI-44		Gouty arthritis	100 ng/ml LPS and monosodium urate crystal-induced THP-1 cells; monosodium urate crystal-induced-BMDMs	Inhibits IL-1β secretion, the interaction between cathepsin B and NLRP3	[39]
12.	Curcumin diethyl diglutarate		Neuropathic pain	LPS 1 μg/mL induced-RAW 264.7	Reduce TNF-α, IL-6, COX-2, iNOS expression, p38, JNK, and ERK1/2 phosphorylation	[12]
13.	*ortho*-trifluoromethoxy-substituted 4-piperidione (*N*–H or *N*-methyl) -containing mono-carbonyl curcumin	 *ortho*-trifluoromethoxy-substituted 4-piperidione (*N*–H) -containing mono-carbonyl curcumin  *ortho*-trifluoromethoxy-substituted 4-piperidione (*N*-methyl) -containing mono-carbonyl curcumin	Inflammatory bowel disease (IBD)	*tert*-butyl hydroperoxide 2 mM, LPS 1 μg/mL induced-RAW 264.7	The cytoprotective effect inhibits NO, ROS, IL-1β, TNF-α, COX-2, NF-κB/MAPK signaling pathway, cell uptake ability, and metabolic stability	[1]

Lipopolysaccharide (LPS), mouse bone marrow-derived macrophages (BMDMs)

Curcumin has sensitive nature in an aqueous buffer at physiological pH. Degradation products of curcumin include alkaline hydrolysis and autoxidation products. Alkaline hydrolysis products include ferulic acid, vanillin, ferulaldehyde, and feruloyl methane. The hydroxyl ion (OH-) in the aqueous buffer attacks the carbonyl group of curcumin and produces decomposition products. Besides, autoxidation is a significant degradation product such as bicyclopentadione. Curcumin is converted to phenolic radicals, which then migrate to the conjugated heptadienedione chain to produce cyclic compounds. Recent studies show that degradation products have dramatically reduced anti-inflammatory activities in lipopolysaccharide-induced macrophage cells compared with curcumin. The degradation product had no effect of reducing LPS-induced inflammatory responses such as NO, iNOS, COX-2, and NF-kB signaling in RAW 264.7 cells [40]. Bicyclopentadione is an autoxidation stable product involving a reaction with oxygen. The methyl groups at the 2- and 6-position of the heptadione chain of curcumin maybe increase stability by preventing enzymatic reduction. The previous study showed that 2,6-dimethylcurcumin increases anti-angiogenic activity than curcumin [34]. Additionally, the thermal-induced degradation product of curcumin includes 4-vinyl guaiacol, ferulic acid, and vanillin. At 180°C 70 minutes, roasted curcumin decreased IL-6 gene expression in LPS-induced macrophage cells [41].

Many techniques to increase the curcumin bioavailability include liposome encapsulation, polymeric dendrimers [6], nanoparticles [42,43], polymeric prodrug [31,44], exosomes [13], and porous composite particles delivery system [45]. For example, modification of curcumin with polyethylene glycol (PEG) to increase solubility has been developed. PEGylated curcumin has decreased cytotoxicity compared to curcumin, inhibiting IL-6, TNF-α, COX-2, PG2, iNOS, NO, ROS, Nrf2 expression, c-Jun phosphorylation, and NF-κB pathway in LPS-induced RAW 264.7 cells [6]. Furthermore, acid-activatable curcumin polymer was used in osteoarthritis therapy by suppressing TNF-α and IL-1β expression of LPS-induced macrophage cell line [31].

Recently, nanoparticle delivery systems have been favored to improve curcumin's bioavailability without using a high dose. Methoxyl poly(ethylene glycol)-*block*-poly(phthalic anhydride-*alter*glycidyl propargyl ether) as a novel nanocarrier for curcumin were evaluated in lipopolysaccharide-stimulated macrophage cells. Curcumin-nanocarrier inhibits the level of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and increases the production of IL-10 cytokine [46]. On the other hand, carboxymethyl cellulose-conjugated chondroitin sulfate was potential in macrophage targeted drug delivery system [47]. The addition of polyvinylpyrrolidone (PVPK30) and sodium dodecyl sulfate (SDS) advantageously increased water solubility and bioavailability of curcumin. The nanotechnology approach is one of the formulas to improve the curative effect of sonodynamic therapy on atherosclerosis via apoptosis and polarization of RAW 264.7 cells [19]. Curcumin-loaded biodegradable microspheres inhibit TNF-α, IL-1β, NOS2, and COX-2 cytokines in LPS-induced macrophage cell lines [48]. Zein-polysulfobetaine encapsulated-curcumin decreases activation of macrophage [10]. Poly(oxalate-co-curcumin) increases the cell viability of H_2O_2-induced RAW 264.7 cells and decreases NO production of LPS+IFN-γ induced RAW 264.7 cells [44]. Acid-activatable curcumin polymer more effectively than curcumin. Acid-activatable curcumin polymer suppressed the ROS production and inhibited the cell death from H_2O_2-or LPS-induced RAW 264.7 cells. The level of TNF-α and IL-1β was decreased by treating acid-activatable curcumin polymer [31]. Nanocurcumin as immunomodulatory increase phagocytosis activity of LPS induced macrophage cells than curcumin. Moreover, the nano

curcumin showed more viable cells with the curcumin. In addition, the divalent cations, including Zn^{2+}, Mg^{2+}, Fe^{2+}, and Cu^{2+} that are a chelate complex with a keto-enol group of curcumin, enhanced the stability and absorption of the nano curcumin based formulation. [9].

These studies show that curcumin is safe to use in the development of therapies, especially anti-inflammatory agents. The toxicology studies of curcumin show that curcumin has no evidence of mutagenicity in the bacterial reverse mutation test and no effect of genotoxicity in mammalian tests. Curcumin does not show any mortality in clinical signs at no observed adverse effect level (NOAEL) until 1000 mg/kg BW from 90 days study for both male and female Wistar rats [49]. Additionally, the lethal dose 50 (LD_{50}) of solid dispersion of curcumin-loaded nanocomplexes in gums was 8.9 and 16.8 g/kg body weight in mice and hamsters, respectively [43]. Acid-activatable curcumin polymer at dose 20 mg/kg mice have no significant serum alanine aminotransferase (ALT) change and no change of the main organs. Therefore, acid-activatable curcumin polymer has a safety profile [31].

4. CONCLUSION

Curcumin is a phenolic compound from the *Curcuma* species. Curcumin can regulate innate immune responses such as macrophages. Therefore, it has various therapeutic activities toward immune system-related diseases such as gouty arthritis, anti-osteoclastogenesis, immune disorder, acute kidney injury, rheumatoid arthritis, antioxidant, adjuvant chemotherapy, trichomoniasis, pulmonary fibrosis, bone injury disease, and acute lung injury. On the other hand, curcumin has low solubility and bioavailability, so its clinical application is limited. Various ways to overcome these weaknesses are by changing the structure or formulation of curcumin. Derivatives of curcumin can reduce the problem and still provide its activity in the immune response of macrophage cells. In addition, curcumin is safe to use *in vivo* studies to develop potential curcumin into the product.

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