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# Potential development of turmeric extract nanoparticles as a topical anti-inflammatory agent



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Nyoman Suryawati<sup>1\*</sup>, I Made Jawi<sup>2</sup>

## ABSTRACT

Turmeric is the most commonly studied herbal ingredient because it has antioxidant, anti-inflammatory, antimicrobial, and anticancer activity. Considering that most inflammatory skin diseases are localized, it is considered that the topical application of turmeric extract can be beneficial because it has a local effect on the skin. The topical application of turmeric extract has limitations because

the active ingredient content of curcumin (CUR) has poor solubility in water, low absorption, and rapid elimination of metabolites, which results in low bioavailability of the drug. Recent studies have focused more on nanoparticle formulations that can improve the stability and bioavailability of CUR.

**Keywords:** turmeric extract, nanoparticle, topical anti-inflammatory

**Cite this Article:** Suryawati, N., Jawi, I.M. 2020. Potential development of turmeric extract nanoparticles as a topical anti-inflammatory agent. *Bali Medical Journal* 9(3): 573-578. DOI: [10.15562/bmj.v9i3.2026](https://doi.org/10.15562/bmj.v9i3.2026)

<sup>1</sup>Dermatology and Venereology Department, Faculty of Medicine, Universitas Udayana-Sanglah Hospital, Denpasar, Bali-Indonesia

<sup>2</sup>Pharmacology Department, Faculty of Medicine, Universitas Udayana, Bali-Indonesia

## INTRODUCTION

Turmeric (*Curcuma longa*) is an herbal ingredient that is widely used in traditional medicine in society, such as in cases of wounds, joint pain, cardiovascular disease, and the nerve's inflammatory diseases. Recent research shows that the antioxidant content of turmeric is beneficial for the treatment of various inflammatory diseases. Since most inflammatory skin diseases are localized, it is considered that the topical application of turmeric extract can have a local effect on the skin. Topical application of turmeric extract has limitations due to its low absorption of active ingredients,<sup>1</sup> so it is necessary to review the potential use of topical turmeric extract in the form of nanoparticles for inflammatory skin diseases.

Turmeric is classified into kingdoms: Plantae; division: Magnoliophyta; class: Liliopsida; subclass: Zingiberidae; family: Zingiberaceae; genus: *Curcuma*; and species: *Curcuma longa*.<sup>2</sup> Turmeric powder is bright orange to yellow<sup>3,4</sup> because it contains curcuminoid, a nonenzymatic antioxidant polyphenol group.<sup>5,6</sup> Curcuminoid consists of diferuloylmethane (curcumin/CUR), demethoxycurcumin, bis-demethoxycurcumin, and cyclic curcumin.<sup>2</sup>

CUR is the most studied active ingredient because it has pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer.<sup>7</sup> The chemical structure of CUR

(C<sub>21</sub>H<sub>20</sub>O<sub>6</sub>) consists of three components: two aromatic ring systems are consisting of phenol o-methoxy groups, connected by seven carbon linkages consisting of α, unsaturated β-dicarbonyl groups.<sup>8</sup> The structure of the CUR is listed in Figure 1.

## Curcumin dermato pharmacokinetics

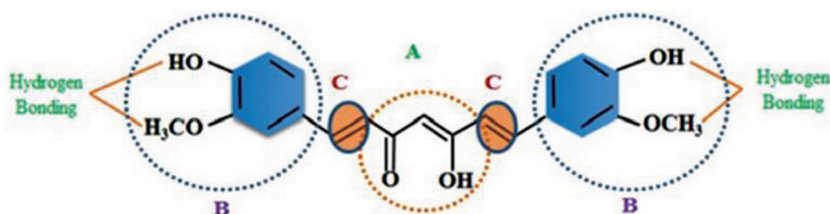
Based on the Biopharmaceutics Classification System (BCS), CUR is classified as a Class II drug, with poor water solubility and high permeability.<sup>9,10</sup> Topical application of turmeric extract has limitations because its active ingredient, CUR, has poor solubility in water, low absorption, and rapid elimination of metabolites, which results in low bioavailability of the drug.<sup>1</sup> Strategy for increasing absorption of topical drugs is choosing a vehicle system, adding substances that increase absorption (permeation enhancers), choosing a new drug delivery system, and transdermal patch form.<sup>11</sup>

Recent studies have focused more on the selection of nanoparticle drug dosage forms.<sup>1</sup> Nanoparticle is dispersing of particulates or solid particles with sizes in the range of 10 to 1000 nm. The primary purpose of nanoparticles as a drug delivery system is to control particle size, drug surface, the release of active pharmaceutical ingredients to reach the specific site of action of the drug and increase the drug's stability.<sup>12</sup> The properties of nanoparticles that can affect the penetration of nanoparticles through the stratum

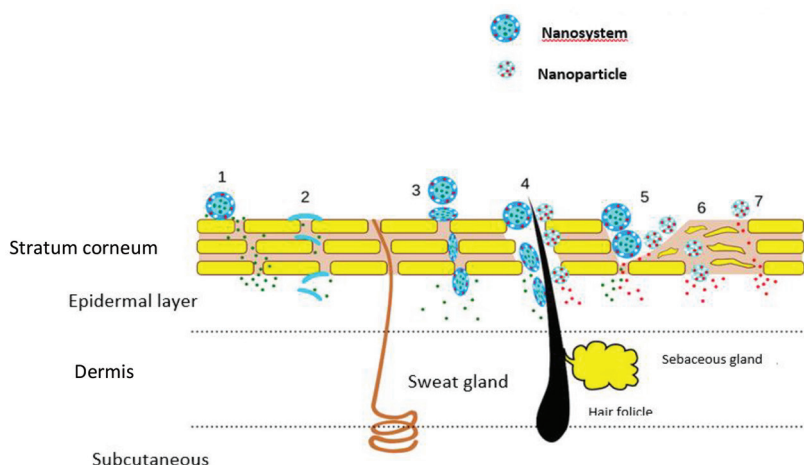
\*Corresponding to:  
Nyoman Suryawati;  
Dermatology and Venereology  
Department, Faculty of Medicine,  
Universitas Udayana-Sanglah  
Hospital, Denpasar, Bali-Indonesia;  
[suryawati@unud.ac.id](mailto:suryawati@unud.ac.id)

corneum, as well as the potential for deposition in the skin, appendage, and deeper layers of the skin, including size, shape, charge properties, surface properties such as coatings or functional groups, aggregation status on surface properties.<sup>13</sup> Vehicle components such as oil, surfactants, and alcohol interact with the stratum corneum, which affects the distribution and performance of drug nanoparticles in the skin.<sup>14</sup> Skin barrier disorders due to certain skin diseases can affect the degree and depth of nanoparticle penetration.<sup>13</sup> The main penetration path of nanoparticles is reported through the trans-appendicular pathway through the hair follicles and sweat glands.<sup>15</sup>

At present, nanosystems have been developed to help deliver drug molecules to specific drug targets and minimize side effects.<sup>16</sup> The forms of nanosystems include microemulsions (MEs), nanoemulsions (NEs), nanoparticles with various compositions including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and vesicles.<sup>13,17,18</sup> Nanosystems can provide significant advantages in the formulation of hydrophobic molecules, increasing their solubility and bioavailability.<sup>18</sup>



**Figure 1.** Structure of CUR (A) b-ketone or keto-enol; (B) phenolic; (C) carbon link.<sup>8</sup>



**Figure 2.** The nanosystem scheme determines the absorption of topical drugs and potential penetration routes. It is modified from reference.<sup>18</sup>

The microemulsion is a transparent, monophasic, isotropic, and thermodynamically stable colloidal dispersion, consisting of oil, water, surfactants, and cosurfactants with droplet sizes range of 10–100 nm.<sup>18</sup> The nanoemulsion is a transparent, monophasic, isotropic, and kinetic colloidal dispersion, consisting of oil, water, surfactants, and cosurfactants with droplet size less than 100 nm.<sup>18</sup> The solid lipid nanoparticle consists of dense lipids that are dense at room temperature with a surfactant surface to stabilize it as nanodispersion.<sup>18–20</sup> SLN increases drug penetration by prolonging contact with the skin surface, providing an occlusive barrier that hydrates the skin, and interacts with lipid bilayers in the stratum corneum.<sup>18</sup> The nanostructured lipid carrier is a colloidal system composed of a liquid lipid phase embedded in a solid lipid matrix or localized to the surface of solid platelets and surfactant layers.<sup>18,19</sup> Liposomes are round vesicles consisting of phospholipids and amphiphilic cholesterol, multilamellar, large unilamellar, and small unilamellar vesicles. Vesicles consist of materials that will join the bilayer structure but combine flexible components to allow vesicles to change shape, including ethosome (phospholipids with a high proportion of ethanol), niosome (non-ionic surfactant), invasome (phospholipid, ethanol, and terpene mixtures penetration enhancers), SECosome (surfactants, ethanol, and cholesterol), and PEV (penetration enhancers vesicles).<sup>18</sup> Among various carrier systems, NLC provides promising hope for increasing the solubility of less soluble materials such as herbal extracts.<sup>21</sup> The topical drug absorption nanosystem scheme is listed in **Figure 2**.

Various clinical studies have shown that the formulation of nanoparticles can improve the stability and bioavailability of CUR.<sup>7,8</sup> Various types of nano-carriers are used for formulations of CUR nanoparticles, such as polymeric nanoparticles, SLN, polymeric micelles, curcumin nanocrystal, NE, nano liposome-encapsulated curcumin, cyclodextrin, curcumin nanosuspension, and dendrimer.<sup>8</sup> Absorption of topical CUR can be increased if it is made in the form of formulations such as chitosan-alginate sponges, polymeric bandages, alginate foams, collagen films, nanoemulsion, hydrogels, and  $\beta$ -cyclodextrin-curcumin complex nanoparticle complex conditions.<sup>22</sup>

### The anti-inflammatory mechanism of turmeric extract

Inflammation is a complex process that occurs when tissue is infected or injured by dangerous stimuli such as pathogens, damage, or irritants. Immune cells, blood vessels, and molecular mediators are involved in this protective response.

The inflammatory process will activate mast cells, monocytes, macrophages, lymphocytes, and other inflammatory cells to the site of inflammation and form reactive oxygen species (ROS).<sup>23</sup> Reactive oxygen species production will modulate the expression of the nuclear factor- $\kappa$ B (NF $\kappa$ B) pathway and tumor necrosis factor (TNF)- $\alpha$ , which plays an essential role in the inflammatory response.<sup>24</sup> ROS will further suppress the antioxidant system and play a role in the pathogenesis of inflammatory and allergic diseases.<sup>25</sup>

The body has an antioxidant system to overcome ROS.<sup>26</sup> Nuclear factor-erythroid 2-related factor 2 (Nrf2) transcription factors are known to play a role in the regulation of oxidative stress and play a role in reducing acute and chronic inflammation.<sup>27,28</sup> The Keap1 [Kelch-like ECH-associated protein 1]/Nrf2 (nuclear factor (erythroid-derived 2)-like 2)/ARE (antioxidant response element) pathway regulates the expression of anti-inflammatory genes

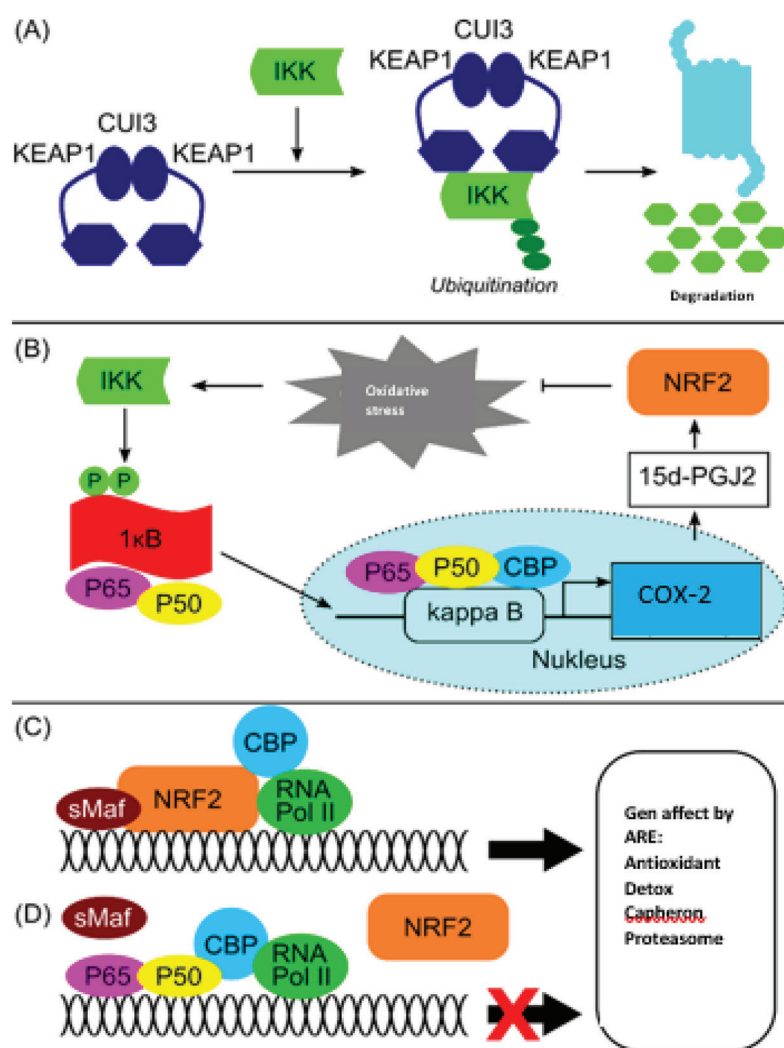
and inhibits the development of inflammation.<sup>23</sup> Nrf2 regulates antioxidant stress genes such as NAD(P)H quinone oxidoreductase (NQO1), heme oxygenase (HO-1), and phase II detoxification enzymes that play an essential role in the defense mechanism of cellular stress by binding to ARE.<sup>27</sup> When oxidative stress occurs, Nrf2 separates from Keap1, translocates to the nucleus, and activates cytoprotective genes to combat oxidative stress.<sup>29</sup> Nrf2 induction will increase antioxidant stress genes such as HO-1, which is anti-inflammatory by inducing anti-inflammatory cytokines IL-10.<sup>27</sup> CUR reduce oxidative stress, inflammation in chronic diseases through kinase stimulation, which activates the Keap1/Nrf2/ARE signal.<sup>27,28</sup>

Inflammatory cells, in addition to forming ROS, at the same time, also produce inflammatory mediators such as cytokines, chemokines, and prostaglandins. This mediator will then recruit macrophage cells to localize the location of inflammation and activate the signal transduction cascade and inflammatory-related transcription factors such as the NF $\kappa$ B signaling pathway, Janus kinase pathway/signal transducers and activators of transcription (JAK/STAT), and the mitogen-activated protein kinase pathway (MAPK). NF $\kappa$ B, JAK/STAT, and MAPK signaling pathways are involved in developing the classic inflammatory pathway.<sup>23,30</sup>

### NF $\kappa$ B signaling pathway

NF $\kappa$ B is a protein complex responsible for inflammatory reactions, apoptosis, immune responses, cell growth, and development.<sup>23,31</sup> NF $\kappa$ B includes five transcription factors namely, NF $\kappa$ B1 (p50), NF $\kappa$ B2 (p52), RelA (p65), RelB, and c-Rel.<sup>32,33</sup> In most cells, NF $\kappa$ B is present in the cytoplasm in an inactive form, bound to the I $\kappa$ B inhibitor.<sup>32,34</sup> NF $\kappa$ B can be provoked by several kinases such as protein kinase B (PKB), phosphoinositide-3 kinase (PI3K), and I $\kappa$ B kinase (IKK).<sup>35</sup> Under conditions of oxidative stress, IKK will be activated, which causes phosphorylation of I $\kappa$ B and NF $\kappa$ B release, and translocation occurs. NF $\kappa$ B causes transcription of proinflammatory mediators such as interleukin (IL)-1, IL-2, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF- $\alpha$ , inducible nitric oxide synthase (iNOS), and intracellular adhesion cyclooxygenase (COX)-2, lipooxygenase (LOX)-5.<sup>23,34</sup>

CUR is thought to suppress NF $\kappa$ B activation and proinflammatory gene expression through inhibition of IK inhibitory phosphorylation.<sup>30,31,36</sup> Researchers show the modulation of CUR in the serine/threonine-protein kinase Akt, which is a cell-signaling molecule that activates NF $\kappa$ B.<sup>37</sup> CUR



**Figure 3.** Crosstalk pathways Nrf2 and NF $\kappa$ B. It is modified from reference.<sup>25</sup>



works through the emphasis on the activation of Akt and Akt-IKK associations that affect NFkB.<sup>37,38</sup>

There is an interaction between the NFkB pathway and the Keap1/Nrf2/ARE pathway (Figure 3). NFkB can affect Keap1/Nrf2/ARE through mechanisms: (1) Keap1 degrades IKK $\beta$  through ubiquitination, which inhibits NF fosB phosphorylation; (2) oxidative stress activates IKK, which causes translocation into the nucleus and induces proinflammatory cytokines such as COX-2 which reacts with Keap1 and activates Nrf2 so that the process of gene transcription and inhibition of NFkB activity co-occur; (3) Nrf2 binds to CBP transcription cofactors (MAMP (Musculoaponeurotic fibrosarcoma) Maf (Musculoaponeurotic fibrosarcoma) and other transcription factors, to start the expression of ARE-driven genes; and (4) NFkB competitively binds to CBP, which will inhibit the activation of Nrf2.<sup>23</sup>

Studies show that CUR can induce endogenous antioxidant defense mechanisms by modulating the transcription factor Nrf2, activator protein-1 (AP-1), and NFkB.<sup>39</sup>

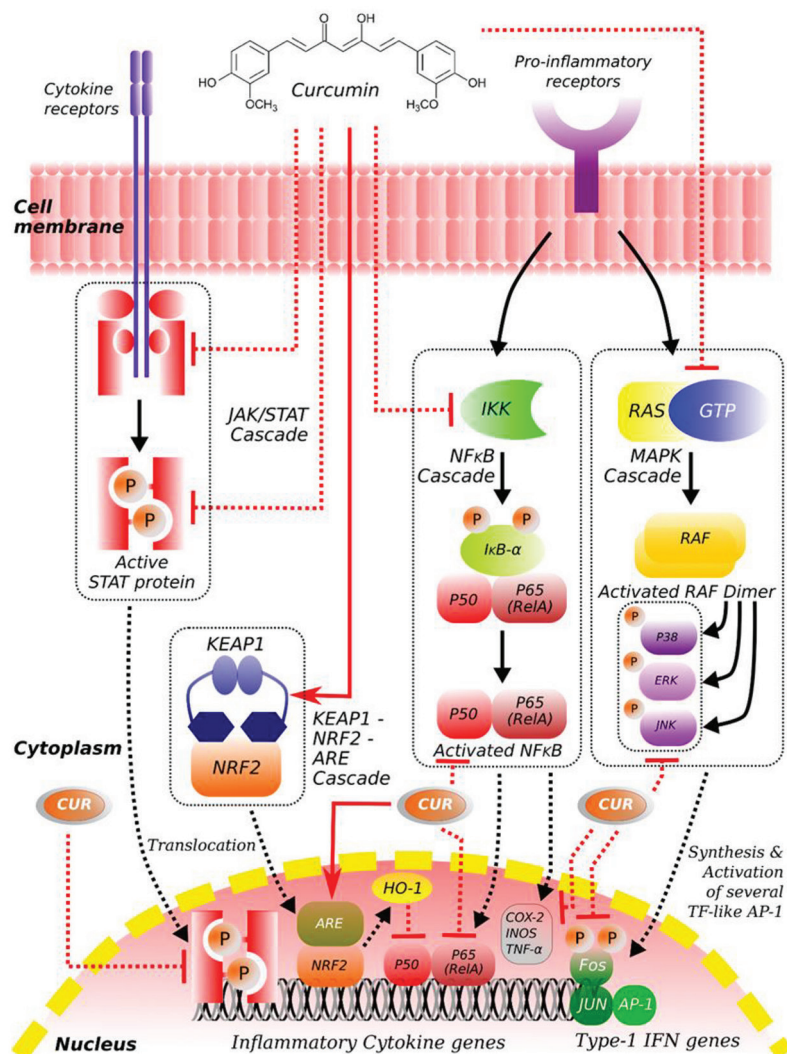
### JAK/STAT signaling pathway

STAT protein is important in growth, survival, and cell differentiation.<sup>40</sup> STAT is a cytoplasmic transcription factor only activated by Janus kinase activation at specific receptors.<sup>31</sup> The JAK/STAT signaling pathway allows for direct translation of extracellular signals into transcription responses. The STAT protein is translocated to the nucleus bound to the target gene promoter to regulate transcription of inflammatory genes.<sup>33</sup>

The anti-inflammatory effect of CUR is reported through suppression of the JAK/STAT signaling pathway.<sup>30</sup> CUR has been reported to inhibit STAT3 activation.<sup>37,41</sup> STAT3 is a cytoplasmic protein that acts as a transcription factor and induces various immune and inflammatory responses. Protein kinases such as JAK1, JAK2, and JAK3 are found to phosphorylate STAT3 and induce nuclear translocation.<sup>42</sup> CUR works by suppressing IL-6, a cytokine-dependent on NFkB, which induces STAT3 activation.<sup>42</sup> IL-6 binds to the JAK activation loop, thereby blocking further signals that require phosphorylation and STAT3 activation.<sup>41</sup>

### MAPK signaling pathway

MAPK is a serine/threonine-protein kinase group regulating cell proliferation, differentiation, survival, and apoptosis.<sup>33</sup> MAPK is the main inflammatory signaling pathway from the cell surface to the nucleus.<sup>43</sup> MAPK consists of the extracellular receptor-activated kinase (ERK1/2 kinase), p38 MAP Kinase, and c-Jun N-terminal kinases (JNK).<sup>33</sup> The MAPK signaling pathway consists of MAPK kinase (MAPKK), which activates MAPK kinase (MAPKKK), which in turn activates MAPK (ERK, JNK, p-38), which in turn activates NFkB, which leads to cell growth and survival.<sup>33,40,44</sup> MAPK activation, including ERK1/2, JNK, will cause phosphorylation and activation of the p38 transcription factor found in the cytoplasm or nucleus, which initiates the inflammatory response.<sup>33</sup> CUR has been reported to suppress inflammation through the MAPK signaling pathway through the interaction of JNK, p-38, and ERK.<sup>30</sup> CUR anti-inflammatory signaling pathways are listed in figure 4. Various studies show that CUR has strong and safe anti-inflammatory activity, so it is an ideal material that can be developed for the prevention and treatment of disease.<sup>45</sup>



**Figure 4.** Possible signaling mechanism for CUR anti-inflammatory action

## SUMMARY

CUR is a material that has potent anti-inflammatory activity. CUR antiinflammatory mechanism through three signaling pathways, namely the NF $\kappa$ B signaling pathway, JAK/STAT signaling pathway, and MAPK signaling pathway. Topical CUR applications have limitations due to poor solubility in water, low absorption, and rapid elimination of metabolites. The development of nanoparticle formulations, and the development of NLC formulations can increase CUR's stability and bioavailability as a topical anti-inflammatory.

## CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of this review.

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