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Review Article

Curcumin and Its Nanoformulations: A Comprehensive Review of Anti-inflammatory and Antioxidant Properties

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Abstract: Curcumin, the main bioactive compound derived from the rhizome of *Curcuma longa*, has gained significant scientific attention for its wide-ranging therapeutic properties, including anti-inflammatory, antioxidant, antimicrobial, and anticancer effects. However, its clinical utility has been limited due to poor water solubility, rapid metabolism, and low bioavailability. Recent advancements in nanotechnology have led to the development of curcumin-loaded nanoformulations, such as liposomes and nanoparticles, which enhance its solubility, stability, and targeted delivery. This review explores the chemical composition and molecular mechanisms of curcumin, focusing on its ability to modulate inflammatory cytokines (e.g., TNF-α, IL-6, IL-10) and oxidative stress markers (e.g., SOD, GSH, MDA). Curcumin suppresses key pro-inflammatory pathways, including NF-κB and COX-2, while enhancing the body's endogenous antioxidant defenses. Its nano-delivery systems show promising results in improving curcumin's pharmacokinetics and therapeutic efficacy in various disease models. Overall, curcumin represents a potent natural agent with multi-target effects, and its nanoformulations offer a promising platform for future therapeutic applications in managing chronic inflammatory and oxidative stress-related disorders. Continued research is needed to translate these findings into clinical practice and to establish standardized, bioavailable formulations suitable for human use.

Keywords: Curcumin, Nanoparticles, Anti-inflammatory, Antioxidants, Cytokines, IL-6, IL-10, TNF-alpha, SOD, GSH, MDA.

1. INTRODUCTION

Curcumin is a natural polyphenolic compound extracted from the rhizome of *Curcuma longa* (turmeric), commonly used as a spice and in traditional medicine for centuries. Its characteristic yellow color and distinctive aroma are due to the presence of curcuminoids, of which curcumin is the principal and most biologically active component. Recent pharmacological studies have highlighted curcumin's vast therapeutic potential, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective activities (Hewlings & Kalman, 2017; Gupta *et al.*, 2013). Despite its wide range of biological actions, the practical application of curcumin in clinical settings remains limited due to its poor water solubility, rapid metabolism, and low systemic bioavailability (Anand *et al.*, 2007).

To address these limitations, researchers have developed various nanoformulations of curcumin, such as liposomes, micelles, solid lipid nanoparticles, and polymeric nanoparticles, which significantly enhance its stability, absorption, and therapeutic efficacy (Yallapu *et al.*, 2012). These nano-delivery systems not only improve curcumin's bioavailability but also enable targeted delivery and controlled release at sites of inflammation or oxidative stress, making them promising tools in the treatment of chronic diseases.

From a mechanistic standpoint, curcumin exerts anti-inflammatory effects by modulating numerous signaling molecules, such as NF-κB, STAT3, COX-2, and pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 (Aggarwal&Harikumar, 2009). Moreover, its antioxidant action stems from its ability to scavenge free radicals, upregulate endogenous antioxidant enzymes such as SOD and GSH, and reduce lipid peroxidation markers like MDA (Menon&Sudheer, 2007).

Given the increasing interest in natural compounds with multi-target effects, curcumin, particularly in its nanoformulated forms, emerges as a promising therapeutic candidate in combating inflammatory and oxidative stress-related conditions. This review aims to provide a comprehensive overview of curcumin's chemical composition, its molecular actions on inflammatory cytokines and oxidative stress markers, and the advancements in its nano-delivery systems.

2. Curcumin

Curcumin is an active compound extracted from turmeric, a plant used in traditional cooking and considered to have potential health benefits. Curcumin has been used as an anti-inflammatory and antioxidant, and has potential benefits in treating chronic diseases (Moballegh Nasery *et al*., 2020). Curcumin nanoparticles represent an innovative and exciting area of medical research and development, offering a unique technology that enhances the effectiveness of curcumin, the active ingredient in turmeric. Nanoparticles are very small particles, typically between 1-100 nanometers in diameter, which means they are much smaller than human cells (Karthikeyan, Senthil, and Min 2020).

2.1 Chemical Composition of Curcumin

Turmeric has a complex chemical composition consisting of a variety of compounds. These compounds include about 60-70% carbohydrates, 6- 13% moisture, 6-8% protein, and 3-7% essential oils such as phellandrene, sabinene, cineole, and borneol, along with 5-10% fats, 3-7% minerals such as potassium, calcium, phosphorus, iron, and sodium, and 2-9% curcuminoids (Canistro *et al.* 2021).

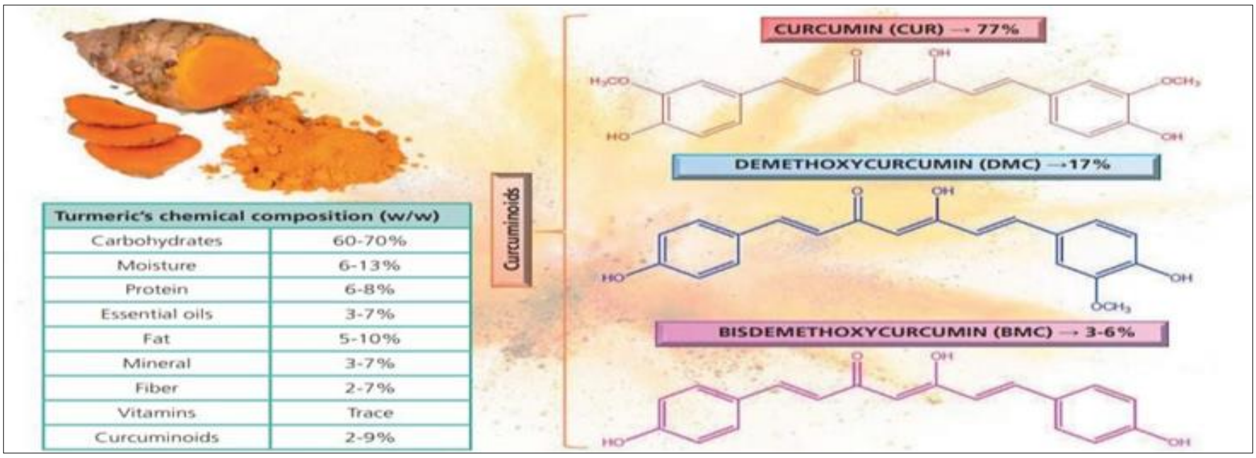

Figure 2.1: Representation of the major constituents of Curcuma longa L. Curcumin (CUR), demetoxycurcumin (DMC), and bisdemethoxycurcumin (BMC) are generally grouped together under the name curcuminoid, which represents 2-9% of turmeric by weight. Among the curcuminoids, CUR, DMC, and BMC account approximately for 77%, 17%, and 3-6%, respectively (Canistro *et al.* 2021)

2.2. Bioactivity

Curcumin exhibits a wide range of bioactivities, showing promise in combating various diseases like cancer, cardiovascular issues, neurological disorders, and autoimmune conditions. Its therapeutic potential lies in its ability to interact with numerous biological targets within the body. These targets include transcriptional factors, growth factors, inflammatory mediators, cytokines, cell cycle proteins, enzymes, protein kinases, and apoptotic proteins, among others. Through these interactions, curcumin can modulate cellular pathways involved in diverse physiological processes (Rauf *et al*., 2018). Nanoparticles allow better absorption of curcumin in the gastrointestinal tract and into the circulation. Its nano size helps to overcome obstacles that may face the absorption of traditional drugs. Curcumin nanoparticles can focus more precisely on target sites within the body. They can be directed precisely to affected tissues or cells, minimizing side effects on healthy tissues (Chopra *et al*., 2021). Nanoparticles may increase the effectiveness of curcumin in fighting inflammation and reducing the negative effects of environmental conditions in the body. Some researchers suggest that nanotechnology may enhance the body's benefits from curcumin's natural properties. There is increasing interest in the use of curcumin nanoparticles therapeutically, especially in areas such as treatments for arthritis and other inflammatory diseases (Hafez Ghoran *et al*., 2022).

2.3. Curcumin Anti-Inflammatory Effects

Curcumin exhibits potent anti-inflammatory effects by targeting pro- inflammatory cytokines such as Interleukin-4 (IL-4), IL-6, IL-8, and tumor necrosis factor alpha (TNF-alpha), which are commonly produced by tissues during inflammatory responses (Peng *et al*., 2021). It effectively suppresses the production and activity of these cytokines, thereby mitigating inflammation. Moreover, curcumin has been found to enhance the production of anti-inflammatory cytokines like IL-10 and soluble intercellular adhesion molecule (Makuch, Więcek, and Woźniak 2021). Preclinical studies have demonstrated curcumin's ability to alleviate skin inflammation in animal models and reduce inflammation in the respiratory tract caused by viral or bacterial infections (Dai *et al*., 2022). Clinical trials have shown promising results of curcumin therapy in reducing pain symptoms associated with osteoarthritis, mitigating tissue inflammation, and delaying the progression of articular cartilage loss, thereby improving patients' mobility and quality of life (Van Ameyde and Hodgden 2022).

2.4. Interleukin 6

Chronic inflammation is a hallmark of various diseases, and curcumin has shown therapeutic potential in several inflammation- related diseases (Derosa *et al*., 2016). It regulates different signaling molecules like transcription factors, chemokines, cytokines, and microRNAs. Interleukin-6 (IL-6) plays a crucial role in inflammation, including antibody production, T cell activation, B cell differentiation, acute-phase protein production, hematopoiesis, angiogenesis, and osteoclast differentiation (Ghandadi and Sahebkar 2017). IL-6 is also implicated in the pathogenesis of various inflammatory diseases. Numerous studies have demonstrated that downregulating IL-6 or inhibiting its signaling pathway contributes to the therapeutic effects of curcumin, suggesting that modulating IL-6 is a key mechanism underlying the anti-inflammatory effects of curcumin (Derosa *et al.,* 2016).

2.5. Interleukin 10

Interleukin-10 (IL-10) holds significance as a multifaceted and potent anti-inflammatory and immunosuppressive cytokine. It originates from various immune cells, including dendritic cells, macrophages, mast cells, natural killer cells, eosinophils, neutrophils, B cells, CD8+ T cells, TH1, TH2, TH17, and regulatory T cells. Notably, activation of the stress axis, either directly or indirectly, stimulates IL-10 secretion (Mollazadeh *et al*., 2019). The dysregulation of IL-10 is implicated in the development of numerous inflammatory diseases, such as osteoarthritis, rheumatoid arthritis and allergy (Wojdasiewicz, Poniatowski, and Szukiewicz 2014; Iyer and Cheng 2012). Curcumin, a natural anti-inflammatory compound, possesses the ability to induce the expression and production of IL-10, thereby enhancing its action in various tissues. In both in vitro and pre-clinical models, curcumin has demonstrated the potential to modulate the disease pathophysiology of pain, neurodegenerative diseases, bowel inflammation, allergy, infections, and cancer through its influence on IL- 10 secretion. In humans, there is evidence suggesting that at least some of the beneficial health effects of curcumin may be attributed to its capacity to potentiate IL-10-mediated effects (Mollazadeh *et al.,* 2019).

2.6. Tumor Necrosis Factor Alpha (TNF-Alpha)

Chronic inflammation is primarily driven by the molecular signaling of tumor necrosis factor (TNF)-α. These proinflammatory cytokines can also induce the expression of adhesion molecules, leading to vascular dysfunction. (Gorabi *et al.,* 2021). Curcumin is a bioactive polyphenolic compound extracted from the rhizomes of turmeric (Curcuma longa). It is renowned for its anti-inflammatory properties, making it a popular subject of research in the medical field. (Tung *et al.,* 2019). Curcumin may be helpful in treating a number of illnesses, including osteoarthritis, rheumatoid arthritis, metabolic syndrome, diabetes, obesity, anxiety, and depression, because of its broad pharmacological qualities, including its anti-inflammatory actions (Sharifi-Rad *et al.,* 2020). In addition to its anti-inflammatory properties, curcumin exhibits potent antioxidant effects. Its chemical composition grants curcumin a robust antioxidant potential, surpassing that of vitamin C by 2.75 times and vitamin E by 1.6 times (Ahmed *et al*., 2020). Curcumin acts as a natural scavenger of free radicals and stimulates the production of the endogenous antioxidant glutathione (GSH), which plays a crucial role in protecting cells and tissues from oxidative damage. Furthermore, curcumin enhances the activity of superoxide dismutase (SOD) and increases glutathione S-transferase (GST) levels in both cellular and serum compartments, as evidenced by in vitro and animal studies (Singh *et al.,* 2013). Ischemic-reperfused tissues, as observed in conditions like stroke, myocardial infarction, surgery, and organ transplantation, often experience oxidative stress due to the excessive generation of free radicals upon reperfusion. Curcumin administration has been shown to scavenge these free radicals, thereby reducing oxidative stress and mitigating tissue damage associated with ischemia-reperfusion injury. By attenuating oxidative stress and inflammation, curcumin offers protective effects against tissue damage and promotes overall tissue health (Yan *et al*., 2018).

2.7. Superoxide Dismutase (SOD)

The free radical theory of aging suggests that free radicals, a crucial determinant of lifespan, induce oxidative harm to critical biological molecules. A sustained or excessive surge in reactive oxygen species (ROS) can inflict indiscriminate damage on proteins, lipids, and nucleic acids. Superoxide dismutase (SOD) serves as a key parameter for evaluating antioxidant and oxidation levels associated with ROS. It is an indispensable enzyme in a network of endogenous biological antioxidants that neutralize superoxide radicals by converting them into hydrogen peroxide and oxygen (Shen *et al.,* 2013).

2.8. Glutathione (GSH)

Glutathione (GSH) is one of the most abundant thiol antioxidants in cells. Many chronic and age-related diseases are associated with a decline in cellular GSH levels or impairment in the catalytic activity of the GSH biosynthetic enzyme glutamate cysteine ligase (GCL).

Glutathione (GSH) is a prevalent antioxidant found in cells, particularly known for its thiol properties. Numerous chronic and age-related ailments correlate with decreasing cellular GSH levels or compromised catalytic activity of glutamate cysteine ligase (GCL), a crucial enzyme in GSH biosynthesis (Braidy *et al*., 2019). A study conducted previously suggested that the antioxidant and anti-inflammatory properties of curcumin might be mediated through intricate dose-dependent effects on the induction of enzymatic activities involved in the detoxification of the electrophilic products of lipid peroxidation, which is linked to glutathione (GSH) (Piper *et al*., 1998).

2.9. Malondialdehyde (MDA)

Malondialdehyde (MDA), a well-known byproduct of lipid peroxidation, increases in response to elevated free radical levels. Accordingly, the concentration of MDA serves as a marker for oxidative stress, with elevated levels of MDA contributing to the development of various metabolic conditions (Alizadeh and Kheirouri 2019).

Curcumin's potential as an adjunct therapy for individuals with oxidative stress was explored in a prior study, suggesting its possible benefits. The study proposed that administering piperine in combination with curcumin might enhance the efficacy of curcumin by strengthening the antioxidant defense system (Alizadeh and Kheirouri 2019).

3. CONCLUSION

Curcumin, particularly in its nanoparticle form, presents a potent and promising therapeutic agent for inflammatory and oxidative stress-related disorders. Its ability to modulate cytokines and enhance antioxidant defenses highlights its role in modern medical research. Further clinical trials are necessary to standardize dosing, improve formulations, and validate long-term safety.

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