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REVIEW ARTTICLE

Curcumin in Redox and Inflammatory Signaling: Mechanistic Insights into NF-κB and Nrf2 Pathway Regulation

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KEYWORDS

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ABSTRACT: Curcumin demonstrates its anti-inflammatory properties via a multitude of molecular pathways. It effectively prevents the activation of nuclear factor-kappa B (NF-κB), a vital transcription factor responsible for the production of modifiable pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. Additionally, curcumin downregulates the expression of cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), thereby reducing the production of pro-inflammatory eicosanoids. Furthermore, it suppresses the activity of inducible nitric oxide synthase (iNOS), resulting in reduced nitric oxide synthesis and disrupting the expression of chemokines and adhesion molecules. Moreover, curcumin modulates immune responses by influencing the functionality of various immune cell types ultimately leading to a reduction in inflammation. These diverse actions render curcumin a promising candidate for the therapeutic management of chronic inflammatory disorders. Beyond its anti-inflammatory effects, curcumin possesses significant antioxidant capabilities. It directly scavenges reactive oxygen species (ROS), counting the superoxide anion, hydroxyl radical, and nitrogen dioxide. Indirectly, curcumin augments endogenous antioxidant defenses. Additionally, curcumin inhibits lipid peroxidation, thereby preserving the integrity of cellular membranes and mitigating oxidative damage. To surmount these challenges, various methodologies have been devised, including the application of nanoparticles, liposomes, phospholipid complexes, and co-administration with bioavailability accompaniments. Due to its capacity to concurrently target inflammatory and oxidative stress pathways, curcumin exhibits significant potential as an adjunctive therapeutic agent in a range of diseases considered by these pathological mechanisms. Ongoing clinical trials are actively assessing its efficacy and safety within human populations.

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INTRODUCTION

Curcumin consequent from the rhizome of *Curcuma longa* (turmeric). It has garnered considerable interest within the realm of biomedical research owing to its powerful anti-inflammatory and antioxidant properties, thereby positioning it as an emerging option for the prophylaxis and management of various chronic illnesses [1-3] (Figure 1).

Inflammation activated by injurious factors and circumstances, forinstance infections and tissue impairment, to preserve homeostasis in the body. Acute inflammation is a temporary and typically beneficial process for the host. However, when inflammation persists, it transitions to a chronic state. It may result in various long-term health problems[4]. Investigating the inflammatory mechanisms associated with inflammatory bowel disease (IBD), arthritis, and atherosclerotic diseases has received considerable attention, with increased concentrations of inflammatory mediators identified at laceration sites. Inflammation can potentially worsen the disease, leading to further escalation of inflammation and establishing a harmful cycle that makes treatment more challenging [5].

Curcumin operates through several mechanisms, including the reduction of pro-inflammatory cytokines and transcription factors such as NF-κB, which play a decisive role in inflammation. Furthermore, curcumin's ability to act as an antioxidant reduces oxidative stress, thereby boosting its therapeutic potential [6]. Research conducted in both preclinical and clinical settings has shown that curcumin may effectively address inflammatory conditions, highlighting its anti-inflammatory and antioxidant properties despite concerns regarding its low bioavailability. In this review article, we aimed to assess the innovative methods by which curcumin exerts its anti-inflammatory and antioxidant effects in various diseases.

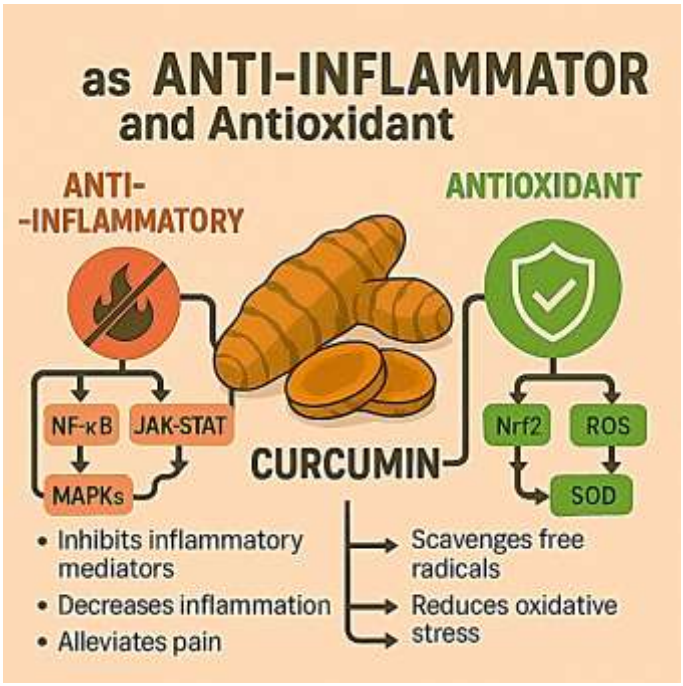

Figure 1. The anti-inflammatory and anti-oxidant pathways of Curcumin.

Curcumin

The rhizome of *Curcuma longa L.*, referred to as turmeric, has been recognized for its therapeutic benefits throughout history in various cultural settings, particularly within traditional medicinal systems such as those practiced in Iran, China, and Ayurveda. Its medicinal applications encompass various health concerns, including digestion, heart health, liver function, neurological conditions, and inflammatory ailments like arthritis. Central to the healing properties of turmeric is curcumin, a bioactive component celebrated for its anti-inflammatory, antioxidant, and anticancer

effects, as well as its dimensions to alleviate metabolic irregularities and enhance cognitive abilities[2].

Turmeric, a natural compound that garnered considerable scientific interest and study, is widely recognized worldwide for its health advantages and originates from Asia. It is classified as a polyphenol, known for its potent biological properties. Curcumin is a tasteless, orange-red powder sensitive to light, with a molecular weight of 368.39 g/mol . However, hydrophobic curcumin can dissolve in ethanol and acetone [7].

Due to its diverse biological properties, Curcumin is currently being explored across various fields, including medicine, cosmetics, and nutrition. It decreases inflammation by targeting multiple pathways and substances[8]. Specifically, it blocks the nuclear factor kappa B (NF–κB) signaling pathway and decreases the generation of inflammatory substances such as interleukins and tumor necrosis factor α (TNF–α), along with nitric oxide synthase (iNOS) and cyclooxygenase–2 (COX-2)[6,9].

Moreover, curcumin is an antioxidant that neutralizes free radicals that harm cells. It alleviates ache insight over its antinociceptive effects and encourages tissue regeneration, thereby facilitating wound remedial [9]. Curcumin exhibits antibacterial effects that notably influence the membranes of both Gram-positive and Gram-negative bacteria. Moreover, curcumin inhibits the aggregation of platelets induced by agents such as collagen, adrenaline, and arachidonic acid (ARA). Specifically, it regulates platelet aggregation by inhibiting cyclooxygenase, which decreases thromboxane (TX) production [10](Figure 2).

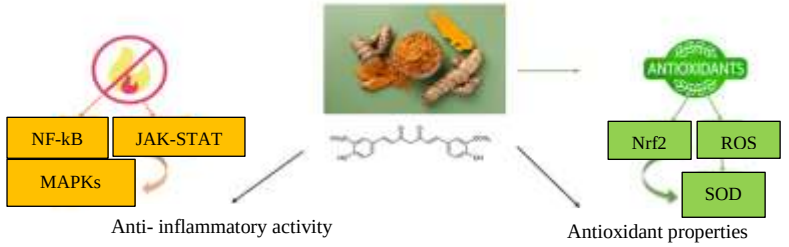

Figure 2. The schematic mechanism of Curcumin as a valuable antioxidant and anti-inflammatory agent.

Anti-Inflammatory belongings

Curcumin exerts its anti-inflammatory possessions over multiple mechanisms:

-Inhibition of Pro-inflammatory cytokines: Curcumin downregulates the manufacture of cytokines[11].

-Overthrow of NF-κB Pathway: Curcumin prevents the initiation of the nuclear factor-kappa B, a key transcription factor that regulates inflammatory gene expression[12].

-Inhibition of COX-2 and LOX enzymes: These enzymes synthesize pro-inflammatory prostaglandins and leukotrienes[13].

-Downregulation of iNOS: Curcumin suppresses nitric oxide synthase, reducing nitric oxide -mediated inflammation[14].

Curcumin has demonstrated impressive abilities in regulating inflammatory responses. The natural anti-inflammatory properties of curcumin are similar to those of steroidal and nonsteroidal drugs . Its effectiveness in decreasing inflammation appears to be associated with the inhibition of COX-2, LOX, the induction of iNOS, the release of cytokines and the activation of transcription factors [8,15].

Cyclooxygenase is crucial in converting arachidonic acid into prostaglandins (PGs). The researches propose

that curcumin reduces the expression of COX-2 [13]. Research has indicated that incorporating curcumin into the diet significantly reduces phospholipase A2 levels in the colonic mucosa and tumours, leading to the liberation of arachidonic acid from phospholipids, which modifies the functions of COX and lipoxygenase (LOX) and influences PGE2 concentrations. Unlike selective COX-2 inhibitors that directly impede COX enzymatic activity, curcumin diminishes COX-2 expression [16].

The NF-κB signaling pathway acts a vigorous role in regulatory pro-inflammatory genes and the cellular responses to inflammation-related triggers (including cytokines, UV, free radicals, and antigens). The activation of this possibly harmful pathway is closely linked to processes like angiogenesis, proliferation of cancer cells, tumour promotion, and the induction of metastasis[17,18]. Curcumin, specifically, has been shown to inhibit the activation of the NF-κB pathway by blocking the phosphorylation of the NF-κB inhibitor (IκB) through the action of the inhibitor kappa B kinase (IκK), as well as halting the degradation of IκBα. This action prevents NF-κB from translocating to the nucleus and starting the transcription process[15].

Furthermore, curcumin's inhibitory effects extend to other inflammatory pathways, such as the arachidonic acid (ARA) pathway including prostaglandins, leukotrienes, and thromboxanes. Curcumin can reduce ARA metabolism mainly by decreasing the activity of lipoxygenase (LOX) and COX-2, by directly blocking the enzyme's action, and by diminishing the transcription of oxidative stress factors [10,16,19].

iNOS promotes the oxidative deamination of l-arginine, leading to the formation of nitric oxide , a potent pro-inflammatory mediator. Augmented expression levels of iNOS and/or its enzymatic activity have been detected in various human tumor tissues and tumors persuaded by chemicals and inflammatory conditions [20,21]. It has been shown that iNOS regulates COX-2 and, consequently, the manufacture of pro-inflammatory prostaglandins[22].

Inflammation may simplify cancer metastasis by discharging detailed cytokines enhance the aggressiveness of cancer cells, thereby facilitating the metastasis process [23]. These cytokines can diminish the effectiveness of cytotoxic T cells and natural killer cells. Persistent inflammation can enhance the recruitment of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), which subsequently inhibit the immune response, enabling cancer cells to avoid detection and destruction by the immune system .Given the significant role of TNF in tumor progression, compounds that can block TNF activity may present therapeutic possibilities for conditions linked to TNF. Curcumin has been shown to have a notable ability to reduce TNF production [24].

Curcumin may help the body fight cancer if specific cells evade programmed cell death. Studies showed a rise in the quantity of CD4+ T-helper and B-type immune cells within the gut lining following the intake of curcumin. In addition to enhancing localized immune reactions, curcumin also improves overall immune function [25].

C-reactive protein (CRP) plays a vital role in the inflammatory response of the body. Its levels increase markedly during inflammatory processes, serving as an indicator for such occurrences. The liver generates CRP in response to signals emitted by adipocytes and certain pro-inflammatory cytokines. During inflammation, CRP mainly attaches to phosphocholine found on the surfaces of deceased or dying cells and some bacteria, initiating the complement system, a crucial part of the innate immune response [26].

Shakour N and her research team examined the binding affinities of four curcumin variants to CRP. The docking analysis indicated that curcumin creates a hydrogen bond with the Gln150 residue of CRP through its carbonyl group and another bond with Asp140 via its hydroxyl group, leading to a pKi value of 13.12. Demethoxycurcumin, which has a pKi of 9.40, formed a bond through an oxygen atom from its methoxy group to the Ser68 residue[27].

Research has shown that pretreating with this compound inhibits the translocation of NF-κB p65 and the phosphorylation of mitogen-activated protein kinases in dendritic cells (DCs) in response to lipopolysaccharides, resulting in decreased inflammation. A key role of curcumin in DCs is the inhibition of indoleamine 2,3-dioxygenase, exerting an anti-inflammatory effect comparable to corticosteroids[28]. Curcumin prevents the activation of the TH1 subset by reducing macrophage activation [29,30,31].

Antioxidant activity

Curcumin is a scavenger of reactive oxygen species and reactive nitrogen species (RNS), contributing to its antioxidant capabilities:

-Direct scavenging of free radicals: It neutralizes hydroxyl radicals, superoxide anions, and peroxynitrite[31,32].

-Upregulation of antioxidant enzymes: Curcumin boosts the function of natural antioxidants like superoxide dismutase, catalase, and glutathione peroxidase[33,34].

-Modulation of Nrf2 Pathway: Curcumin activates the Nrf2 signaling pathway, which regulates the expression of detoxifying and antioxidant response genes[35].

Curcumin is well-known for its protective properties against oxidative damage to biomembranes. The process of lipid peroxidation is recognized as a chain reaction driven by free radicals, leading to the impairment of cell membranes. Curcumin's ability to prevent peroxidation is primarily attributed to its effectiveness in neutralizing the reactive free radicals in this reaction[7].

Theoretical evaluations employing density functional theory (DFT) have shown that the enol structure of curcumin is meaningfully more steady than the diketo structure. It has also been observed that the antioxidant activity is influenced by the contributions of the phenolic and central methylenic groups, which vary based on the radical involved and the surrounding reaction conditions[36]. Litwinienko and Ingold recently assessed the degree coefficients for the reaction involving the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and curcumin in ionizing and nonionizing solvents, shedding light on the ongoing discussion about curcumin's antioxidant characteristics [37].

Curcumin possesses both antioxidant and pro-oxidant qualities due to its characteristics as a lipophilic, insoluble polyphenol in water. It is remarkably effective in protecting against reactive oxygen species, while also exhibiting pro-oxidant properties. When exposed to light, it can promote the generation of singlet oxygen, leading to the activation of endogenous copper ions that destroy cancer cells. This process produces anticancer, anti-tumor, anti-thrombotic, and apoptosis-inducing effects[38, 39].

Curcumin serves as a chain-breaking agent at the 3′ position when it interacts with oxidized linoleate as a fatty acid radical, employing an intramolecular Diels–Alder mechanism to neutralize lipid radicals, thus enhancing its role as a lipid peroxidation inhibitor. Also, it serves as a free-radical scavenger for multiple oxygen species produced by distinguished macrophages, such as superoxide anions, hydrogen peroxide, and nitrite radicals, while facilitating the downregulation of iNOS activity by preventing macrophages from generating nitric oxide, which can interact with superoxide radicals to create the harmful peroxynitrite, thereby reducing the production of ROS that contributes to oxidative stress[40].

Clinical implications

Since of its combined anti-inflammatory and antioxidant belongings, curcumin is being explored for application in managing:

-Chronic inflammatory diseases[41].

-Neurodegenerative diseases[42].

-Cardiovascular diseases.

-Cancer[43].

Dcodhar and his team allocated 18 patient role with rheumatoid arthritis to obtain curcumin (1200 mg/day) or phenylbutazone (300 mg/day) over 14 days. Those who took curcumin showed improvements in rheumatoid symptoms similar to those observed in patients administered phenylbutazone. No significant side effects were reported from the use of curcumin. Nevertheless, the long-term impact of curcumin on rheumatoid arthritis has yet to be described[44].

Tazeoglu et al. explored the anti-inflammatory effects of curcumin using a rat model of L-arginine-induced acute pancreatitis (AP). The team successfully created a model of acute pancreatitis by administering a dose of 5 g/kg of L-arginine, confirming the model's reliability through analysis of the rats in the AP group. Weight measurements among the different groups of rats showed no significant differences, as evidenced by a p-value of 0.76. This indicates that the treatment did not affect the subjects' overall weight. Laboratory tests and histopathological examinations showed that curcumin-treated rats had lower values than the AP group. This implies that curcumin positively impacted the

inflammation and tissue damage associated with acute pancreatitis. The decrease in laboratory values was significantly greater in the group receiving high-dose curcumin (200 mg/kg) than in the low-dose group (100 mg/kg), with a p-value of less than 0.001. The findings funding the latent use of curcumin as a beneficial mediator for managing inflammation related to acute pancreatitis[45].

Holt and colleagues outlined curcumin's role in treating inflammatory bowel disease. A group of fifteen patients with a diagnosis of ulcerative proctitis was given curcumin at a dosage of 550 mg twice daily for one month, which was then increased to 550 mg three times daily for additional month. All patients experienced some level of improvement. In a different cohort of five individuals with Crohn's disease, curcumin was ordered at a dose of 360 mg three times per day for one month, followed by an increment to 360 mg four times per day for an additional two months. Four out of the five patients with Crohn's disease showed signs of improvement, as evidenced by positive changes in surrogate markers [46].

In another investigation, eight individuals diagnosed with idiopathic inflammatory orbital pseudotumor, who had received corticosteroid therapy in the past, were given curcumin at a dose of 375 mg three times a day. One individual had a histological verification of their finding, while the others were diagnosed through clinical evaluations and imaging tests. Three of the individuals stopped the treatment after 2 to 8 weeks, among the five individuals who continued with the treatment for a period ranging from 6 to 22 months[47].

The impact of curcumin on traumatic brain injury (TBI) is elucidated through a review research conducted on animal models. Curcumin significantly reduced the concentrations of inflammatory cytokines, which are pivotal proteins involved in the inflammatory response. The findings revealed that curcumin augmented the activity of various oxidative stress markers, which are crucial for cellular defense mechanisms. Furthermore, curcumin reduced deleterious substances such as Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE). Curcumin exhibited a significant decrease in cerebral edema, characterized by fluid accumulation in the brain tissue. Curcumin enhanced the activity of Beclin-1 and Bcl-2, which are integral to autophagic processes and cellular survival, while concurrently diminishing the levels of caspase-3 and the apoptosis index. This implies that curcumin may play a role in qualifying cell death in the context of TBI. In conclusion, the evidence suggests that curcumin benefits TBI by attenuating oxidative stress and inflammatory responses, promoting neuroprotection, and facilitating recovery. However, the authors emphasize the necessity for further high-quality investigations and randomized controlled trials to substantiate these outcomes in human subjects[48].

Investigations indicated a reduction in the counts of white blood cells, neutrophils, and eosinophils, recognized as inflammation biomarkers. Moreover, administration of *C. longa* and CUR demonstrated defensive effects on serum concentrations of inflammatory mediators, including phospholipase A2 and total protein, across various inflammatory states [49]. It highlighted that *C. longa* and CUR have powerful antioxidant effects. They were shown to lower levels of malondialdehyde and nitric oxide, which are oxidative stress markers. Moreover, treatment with these compounds increased concentrations of beneficial antioxidants, including thiol, superoxide dismutase, and catalase, indicating a protective function against oxidative harm. *C. longa* and CUR enhanced immune responses by boosting immunoglobulin E (IgE) levels and pro-inflammatory cytokines . The research also observed an improvement in the equilibrium between type 1 and type 2 helper cells, vital for sustaining a healthy immune system. In summary, the results propose that *C. longa* and CUR hold considerable promise as therapeutic agents for addressing various issues related to inflammation, oxidative stress, and immune imbalance[49,50].

A systematic review was conducted on the clinical use of curcumin in treating rheumatoid arthritis (RA). The review included six clinical trials involving 259 patients with RA, with treatment durations ranging from 6 to 12 weeks. Curcumin treatment significantly reduced the Disease Activity Score in 28 joints (DAS-28) in four out of five studies included in the review. Pain levels, measured by the VAS, showed significant reductions in all three studies that assessed this parameter. In the three

studies that measured ACR-20 scores, curcumin significantly increased these scores, indicating improved patient outcomes. Out of six studies assessing ESR, four reported significant reductions in this marker following curcumin treatment. Similarly, five studies evaluated CRP levels, with four showing substantial decreases in response to curcumin supplementation. Significant reductions were observed in three studies that measured RF after curcumin consumption .Importantly, none of the studies reported serious adverse effects associated with curcumin consumption, suggesting that it is a safe option for RA treatment. In conclusion, the systematic review indicates that curcumin may be an effective and safe adjunct treatment for rheumatoid arthritis, warranting further validation through additional research[51].

It has been demonstrated to alleviate symptoms and prolong disease durations in those with rheumatoid arthritis by blocking the mitogen-activated protein kinase family, especially the extracellular signal-regulated protein kinase, as well as the activator protein-1 and nuclear factor κB signaling pathways [52]. Studies indicate that curcumin affects IL-10 secretion and immune regulation, assisting in the management of neurodegenerative diseases by enhancing anti-inflammatory and immunosuppressive roles. Curcumin boosts the anti-inflammatory role of the eicosanoid pathway in rheumatoid arthritis patients by normalizing serum lipid stages[53].

Reports indicate that plant enhances the effects of fibroblast-like synoviocytes in rheumatoid arthritis by modulating the inc00052/miR-126-5p/PIAS2 axis [54]. Curcumin is recognized for its ability to block the activation of the PI3K/AKT signaling pathway and the production of pro-inflammatory cytokines[55].

In Hamed, A. M et al., study, animals were administered either curcumin at 150 mg/kg, curcumin at 300 mg/kg, albendazole at 50 mg/kg, or a combination of curcumin at 150 mg/kg and albendazole at 50 mg/kg. These groups were compared to control groups of both infected and non-infected mice. Additionally, the local expression of cyclooxygenase-2 enzyme and CD34 in these samples was evaluated using immunohistochemistry. The findings indicated that curcumin was effective in reducing the parasitic load. It also decreased serum MDA levels and local COX-2 and CD34 expression. Therefore, curcumin can be a beneficial adjunct to traditional antiparasitic treatments and yield favourable outcomes when used alone at elevated doses[56].

In an experimental study, twenty-four Wistar albino rats with normal otomicroscopic examination results were chosen for the study. The study groups were formed after all the rats were inoculated with Streptococcus pneumoniae in the middle ear cavity. Findings indicated that malondialdehyde levels in the curcumin group were significantly reduced compared to the control group. At the same time, serum glutathione peroxidase activity was also lower than that of the control groups. No significant differences were detected among the groups regarding superoxide dismutase activity. Although histopathological findings did not show significant results, epithelial proliferation was concentrated in the antibiotic-treated groups compared to the control. Additionally, curcumin demonstrated a beneficial effect on inflammatory cell infiltration. No notable changes were found in vascular proliferation. In conclusion, with its broad and safe dosage range, curcumin provides hopeful prospects for anti-inflammatory treatment in cases of acute otitis media[57].

Curcumin exhibits significant therapeutic potential in inflammatory bowel diseases (IBD) by modulating various cellular targets and molecular mechanisms. It interacts with cytokines, oxidative stress-associated enzymes, and the intestinal microbiota, demonstrating anti-inflammatory effects. Curcumin inhibits key signaling pathways such as PI3/Akt and JAK/STAT, reduces proinflammatory enzyme expression, and curbs immune cell chemotaxis. Clinical trials indicate curcumin can induce remission in IBD without toxic belongings, making it a promising adjunctive therapy for managing these chronic inflammatory circumstances[58,59]. The randomized controlled trial conducted by Hanai et al.investigated the belongings of curcumin on clinical improvement in patients with quiescent UC. A significant bias in this research is that the authors assessed the properties of curcumin in subjects who did not have active disease[60].

The research conducted by Banerjee et al. inspected the properties of curcumin on enhancing clinical outcomes and achieving endoscopic diminution in individuals with active mild-to-moderate UC. The group receiving

curcumin was administered SMEDDS, a self-microemulsifying drug delivery system. The authors showed that merging bioenhanced curcumin with mesalamine effectively encourages remission while necessitating reduced doses of curcumin. Patient evaluations occurred after 6 weeks and at 3 months, demonstrating notable clinical enhancement in the curcumin group at both intervals[61].

Previous results highlight a reduction in total antioxidant capacity (TAC) in the kidneys of animals experiencing induced acute inflammation. Curcumin treatment resulted in notably lower average TAC values in the kidneys. TAC and GSH concentrations, along with the suppression of CAT, GPX enzyme activities, and SOD in human embryonic kidney cells[62].

In a model of acute kidney injury, administering Curcumin orally (200 mg kg-1 per day for a week) led to a notable increase in MDA levels, nitric oxide, and the presence of carbonylated proteins in the kidneys of rats subjected to bilateral renal ischemia followed by reperfusion. Conversely, Curcumin treatment enhanced renal function in mice models (assessed through blood urea nitrogen and albuminuria), correlated with reduced inflammatory markers and matrix proteins. Curcumin notably alleviated oxidative stress by lowering TAC and GSH levels, in addition to suppressing the activities of GPX enzymes, and SOD [63].

Individuals with COVID-19 exhibit elevated levels of inflammatory cytokines, colony-stimulating factors, and inflammatory chemokine's. Therefore, mitigating the heightened inflammatory response observed in COVID-19 may be beneficial in reducing the severity of the illness[64]. Improved clinical outcomes and recovery may result from nano-curcumin's ability to affect the rise in inflammatory cytokines, specifically IL-1β and IL-6 mRNA expression and cytokine release in patients. Curcumin reduced the frequency of Treg, Th17 cells, and the inflammatory markers linked to them in mild and severe patients compared to the placebo group [65]. Curcumin may have antiviral and anti-inflammatory benefits by preventing SARS-CoV-2 from entering cells and the virus from replicating. Given its wide range of pharmacological actions and excellent safety record, curcumin may be used as an adjuvant drug to treat COVID-19. An oral nano-formulation of curcumin at a dosage of 80 mg twice a day was demonstrated to significantly reduce the duration of hospitalization, improve oxygen levels, and shorten the resolution time of COVID-19 symptoms in a nonrandomized, open-label clinical study. Additionally, using piperine and curcumin orally as an accessary rehabilitation for COVID-19 treatment may significantly lessen morbidity and death while enhancing clinical symptoms[65].

Challenges and solutions

Despite its promising pharmacological effects, curcumin has poor bioavailability due to low solubility, rapid metabolism, and limited absorption. Strategies to overcome these challenges include:

-Use of adjuvants: e.g., piperine (from black pepper), enhances absorption.

-Nanoparticle formulations: liposomes, micelles, and polymeric nanoparticles to improve delivery.

-Conjugation with carrier molecules, such as cyclodextrins or phospholipids.

Future directions

The exploration of curcumin as a therapeutic agent presents numerous avenues for future research, particularly in enhancing its efficacy and bioavailability. Here are some potential directions:

Improving bioavailability

Research should focus on developing novel formulations that enhance the solubility and absorption of curcumin. Strategies such as using adjuvants like piperine, which has been shown to improve absorption, could be further investigated. Nanoparticle formulations, including liposomes and micelles, offer promising methods to enhance curcumin delivery and bioavailability, warranting more extensive studies.

Clinical trials

Larger clinical trials are required to determine ideal dosages and treatment protocols for curcumin in diverse conditions, such as rheumatoid arthritis, inflammatory bowel disease, and acute pancreatitis. These investigations should seek to validate its effectiveness and safety across various populations. Priority should be

given to long-term studies evaluating the effects of curcumin on chronic inflammatory conditions and its possible function in cancer prevention and therapy.

Exploring combinations with other therapies

Investigating the synergistic effects of curcumin when combined with other anti-inflammatory or antioxidant agents could enhance its therapeutic efficacy. This approach may lead to more effective treatment strategies for chronic diseases .

Targeting specific diseases

Future investigate should emphasis on the application of curcumin in specific chronic conditions, such as neurodegenerative diseases , cardiovascular diseases, and various cancers, to better understand its potential benefits and mechanisms in these contexts.

CONCLUSIONS

In conclusion, curcumin is a promising therapeutic agent with significant anti-inflammatory and antioxidant properties, creation it a valuable candidate for managing various chronic diseases. Clinical studies have demonstrated that curcumin can effectively reduce disease activity in rheumatoid arthritis and inflammatory bowel disease, resulting in improvements in clinical outcomes and inflammatory markers. Moreover, curcumin's capability to modulate inflammatory pathways, including the downregulation of pro-inflammatory cytokines and transcription factors like NF-κB, underscores its potential in treating chronic inflammatory conditions .The compound also protects against oxidative stress, further enhancing its therapeutic profile. Despite its benefits, the low bioavailability of curcumin remains a concern. However, combining curcumin with bioenhancers, such as piperine, may enhance its absorption and efficacy. Overall, the evidence supports curcumin's role as a beneficial adjunct in traditional treatments, with the potential for favorable outcomes in various inflammatory diseases. Continued research is crucial to understanding its mechanisms and optimizing its clinical applications.

CONFLICT OF INTERESTS

The authors confirmed that there is no conflict of interest.

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