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REVIEW

Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures

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Abstract: Curcumin is a natural compound with great potential for disease treatment. A large number of studies have proved that curcumin has a variety of biological activities, among which anti-inflammatory effect is a significant feature of it. Inflammation is a complex and pervasive physiological and pathological process. The physiological and pathological mechanisms of inflammatory bowel disease, psoriasis, atherosclerosis, COVID-19 and other research focus diseases are not clear yet, and they are considered to be related to inflammation. The anti-inflammatory effect of curcumin can effectively improve the symptoms of these diseases and is expected to be a candidate drug for the treatment of related diseases. This paper mainly reviews the anti-inflammatory effect of curcumin, the inflammatory pathological mechanism of related diseases, the regulatory effect of curcumin on these, and the latest research results on the improvement of curcumin pharmacokinetics. It is beneficial to the further study of curcumin and provides new ideas and insights for the development of curcumin anti-inflammatory preparations.

Keywords: anti-inflammatory, osteoarthritis, psoriasis, atherosclerotic, pharmacokinetics, prodrug

Introduction

Curcumin, chemically known as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, has anti-inflammatory, anti-oxidant, anti-tumor and other biological activities.[1] The anti-inflammatory properties of curcumin are considered to be the basis of its various biological activities and play an important role in the treatment of diseases. Curcumin is mainly derived from the root tuber of *Curcuma aromatica* Salisb and the rhizome of *C. longa* L. (Turmeric) of *Zingiberaceae*. They are traditional Chinese medicines that promote blood circulation and remove blood stasis, and have long been used in China to treat pain, inflammation and other diseases. Turmeric is a common spice in India and has been described in Ayurveda, as a treatment for inflammatory diseases.[2] In western herbalism, turmeric is primarily used as an anti-inflammatory agent.[3] Curcumin and curcuminoids, the active components of turmeric, are found as effective therapies over the years. Curcumin, demethoxycurcumin and bisdemethoxycurcumin, these three compounds are called curcuminoids (Figure 1). In addition, curcumin-containing dietary supplements are extremely popular, and there are many anti-oxidant and anti-inflammatory curcumin dietary supplements on the market.[4,5]

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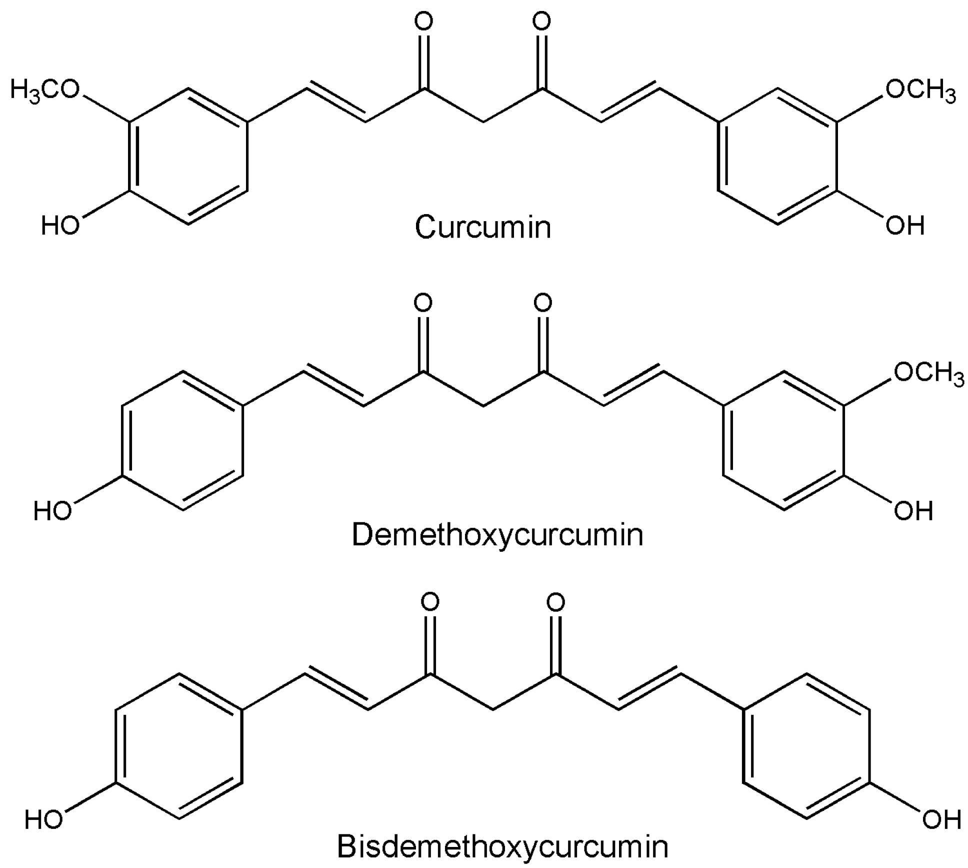

Figure 1 Chemical structure of curcuminoids (include curcumin, demethoxycurcumin, bisdemethoxycurcumin).

Inflammation is a complex physiological and pathological process. Inflammation is typically an adaptive response caused by harmful stimuli and conditions (such as infection and tissue damage) to keep the body homeostasis. Inflammation can be divided into acute inflammation and chronic inflammation. The acute inflammation lasts only a short time and is usually beneficial to the host. When inflammation persists for a long time, it becomes chronic and can contribute to a variety of chronic diseases, such as obesity, diabetes, arthritis, pancreatitis, cardiovascular, neurodegenerative, metabolic diseases, and some types of cancer.[6] Inflammatory mechanisms of inflammatory bowel disease(IBD), arthritis, psoriasis, depression, and atherosclerotic disease processes have attracted the attention of investigators, with elevated levels of inflammatory mediators detected at lesion sites. Inflammation worsens the disease, which in turn exacerbates the inflammation, creating a vicious cycle that poses challenges to treatment. Therefore, we need to make it clear that inflammation plays an important role in the occurrence and development of disease, and compounds with anti-inflammatory effects are the direction to look for therapeutic drugs.

The significant anti-inflammatory activity of curcumin has attracted a lot of researchers' interests and is considered to be one of the natural compounds with the greatest potential in the treatment of diseases. The anti-inflammatory mechanism and therapeutic effect of curcumin are the research hotspots. This paper will review the current studies on the anti-inflammatory mechanism of curcumin, curcumin in the treatment of inflammatory bowel disease, arthritis and other diseases, and analyze the relevant studies on improving pharmacokinetics, in order to provide suggestions for further research and application of curcumin in the anti-inflammatory effect.

Anti-Inflammatory Mechanism of Curcumin

The inflammatory pathway consists of four parts: inducers, sensors, mediators and effectors. The physiological and pathological mechanisms of inflammation caused by different Inflammatory triggers are different and have not yet been clarified.[7] In general, anti-inflammatory effects of drugs mainly include: acting on receptors and signaling pathways, regulating the response of target tissues to inflammatory mediators; reversing the effect of the medium on the target tissue; produce anti-inflammatory mediators and so on.[6] Curcumin exerts anti-inflammatory effects by regulating inflammatory signaling pathways and inhibiting the production of inflammatory mediators (Figure 2).

Curcumin binds to Toll-like receptors (TLRs) and regulates downstream nuclear factor kappa-B (NF-κB), Mitogen-activated protein kinases (MAPK), Activator Protein 1(AP-1) and other signaling pathways,[8–10] thereby regulating inflammatory mediators and treating inflammatory diseases. Curcumin can down-regulate NF-κB through acting on Peroxisome proliferator-activated receptor gamma (PPARγ).[11,12] Curcumin can also play anti-inflammatory effects by regulating The Janus kinase/Signal transducer and activator of transcription (JAK/STAT) inflammatory signaling pathway.[13,14] In addition, NOD-like receptor pyrin domain-containing 3(NLRP3) inflammasome is cytosolic multiprotein complexes that are involved in the development of a variety of inflammatory diseases. The NLRP3 complex consists of three components: a sensor protein, an apoptosis-associated speck-like protein containing a caspase recruitment domain and a protease caspase-1. Curcumin could directly restrain the assembly of NLRP3 inflammasome, or inhibits the activation of NLRP3 inflammasome by inhibition of NF-κB pathway, which may be one of the mechanisms of curcumin for the treatment of inflammatory diseases.[15,16]

In the studies of inflammatory cells and animals, curcumin decreased levels of pro-inflammatory mediators such as Interleukin-1 (IL-1), IL-1β, IL-6, IL-8, IL-17, IL-27, Tumor necrosis factor-α (TNF-α), Inducible nitric oxide synthase (iNOS), NO, Regulated upon activation normal T cell expressed and secreted factor(RANTES), Granulocyte colony-stimulating factor (G-CSF), and Monocyte chemotactic protein-1 (MCP-1).[17–22] Clinical trials have also shown that curcumin can reduce inflammatory mediators.[23] In a Randomized, Double-Blind, Placebo-Controlled Clinical Trial, daily 80 mg curcumin nano-micelle statistically significant improvement in plasma levels of C-reactive protein(CRP), and TNF.[24]

The regulatory effect of curcumin on immune cells is beneficial to its treatment of inflammatory diseases.[25,26] Curcumin mainly acts on dendritic cells, T helper 17 cell, T regulatory cell. Th17 is an important pro-inflammatory cell that produces IL-17, IL-22, and IL-23 and promote inflammation response. Treg cells inhibit the inflammatory response.[27] Changes in the number and function of Th17 and Treg can cause an abnormal immune response, leading to inflammation. Therefore, maintaining Th17/Treg balance is conducive to the maintenance of immune homeostasis and the treatment of inflammatory diseases.[28] Curcumin inhibits Th17 differentiation, and regulate

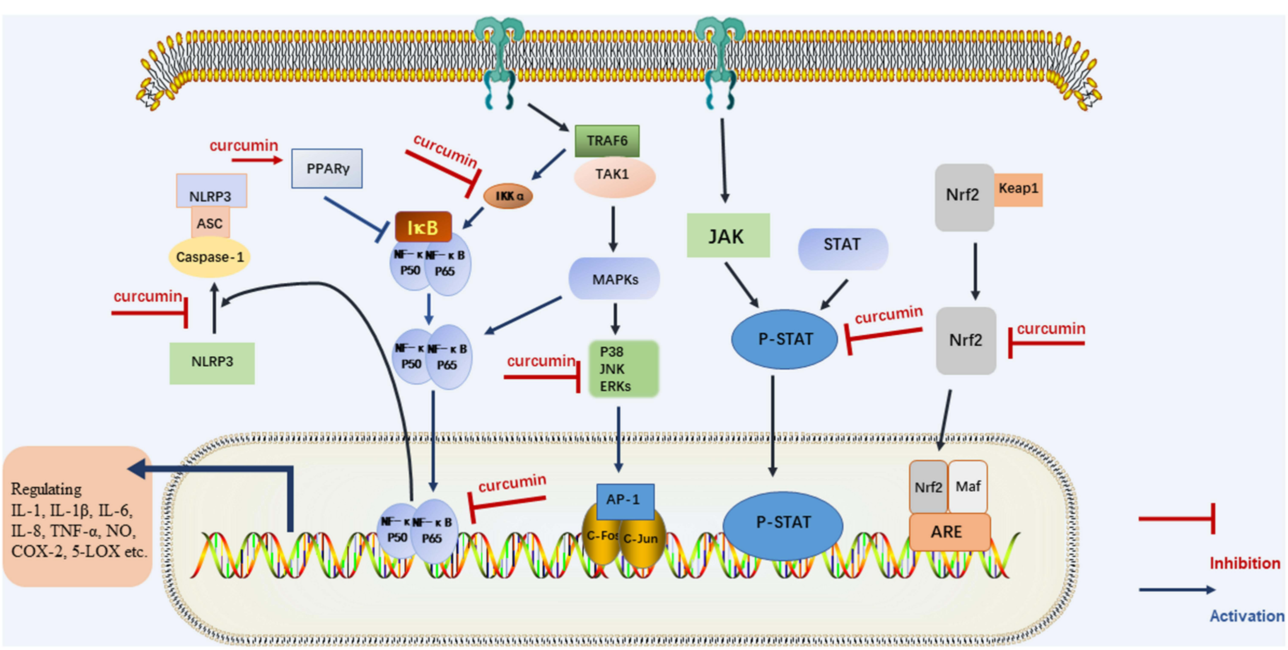

Figure 2 The regulatory effect of curcumin on inflammatory signaling pathway.

Treg/Th17 rebalance is by inhibit the IL-23/Th17 pathway.[29,30]

Oxidative stress is closely related to inflammatory processes. The accumulation of Reactive oxygen species (ROS) leads to oxidative stress, which enhances inflammation by activating transcription factors associated with inflammation. Curcumin reduces ROS production due to its effect on nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increasing the activity of antioxidant enzymes, and is related to Nrf2-Keap1 pathway.[31–33] Curcumin reduces inflammation through its antioxidant activity.

Anti-Inflammatory Effects of Curcumin in Several Inflammatory Diseases

Curcumin has significant anti-inflammatory effects, and a large number of preclinical or clinical researches have studied its effect on inflammatory diseases, among them, inflammatory bowel disease, arthritis, psoriasis, depression, atherosclerosis and COVID-19 are the focus of research hotspots. Current evidences suggest that curcumin is effective in reducing levels of inflammatory mediators, and that curcumin's anti-inflammatory properties may have a beneficial effect on these diseases (Figure 3). In this review, the inflammatory mechanism of above diseases, therapeutic effect and the current application of curcumin are described as follows. The related experimental/animal studies and clinical trials are summarized in Tables 1 and 2.

Effect of Curcumin on Inflammatory Bowel Disease

IBD is a chronic, recurrent inflammatory disease, mainly including ulcerative colitis (UC) and Crohn's disease (CD). The difference between the two is that CD can affect the gastrointestinal tract anywhere from the mouth to the anus and is typically characterized by transmural inflammation, while UC mainly affects the colonic epithelium. IBD has become a global disease. No matter in Western countries or in newly industrialized countries, the incidence of IBD is on the rise, causing a global economic burden.[34] Now, the etiology of IBD has not been fully elucidated, and may be related to genetic, environmental factors and immunity.

UC Patients have chronic and recurrent inflammation in the colon, leading to excessive production of pro-inflammatory factors, which in turn leads to destruction of the intestinal barrier. Gut mucosal barrier impairment in turn aggravates the inflammatory symptoms. In dextran sulfate sodium salt (DSS)-induced colitis mouse models, DSS triggers NLRP3 inflammasome activation through three main mechanisms, including the formation of ROS,

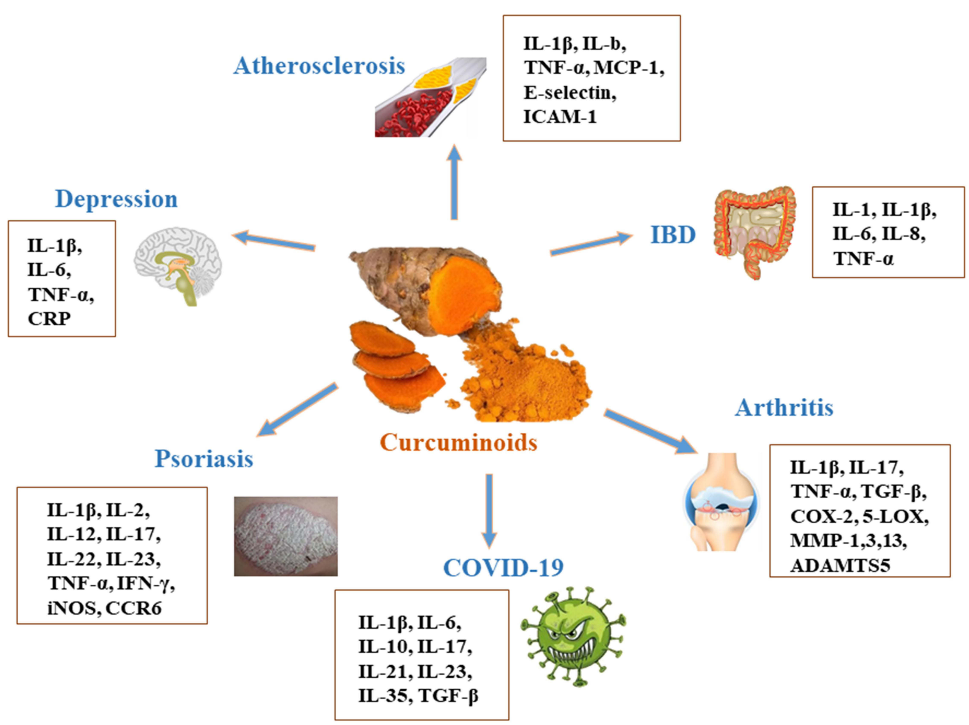

Figure 3 The effect of curcumin on IBD, arthritis, psoriasis, depression and atherosclerosis.

Table 1 Summary of Studies on Curcumin with Anti-Inflammatory Effect

Compounds	Experimental Models	Dosage and Administration	Effects	Ref
Curcumin	LPS-induced BV2 cells	1, 5, and 10μM	↓ NO, IL-1β, IL-6, iNOS ↑ IL-4, IL-10, Arg-1 promoted microglial polarization to the M2 phenotype	[8]
Curcumin	Subarachnoid hemorrhage mice models	100mg/kg, i.p.	↓ IL-1β, IL-6, iNOS, and TNF-α, CD86 protein, ↑ IL-10, TGF-β ↓ TLR4 signaling	[9]
Curcumin	Cigarette smoke extract-treated Beas-2B cells	2.5, 5 and 7.5μM	↑ PPAR-γ, ↓ NF-κB	[11]
Curcumin	Cigarette smoke-induced COPD rat models	100mg/kg, i.g.	↑ PPAR-γ, ↓ NF-κB, inflammation score ↓TNF-α, IL-6	[11]
Curcumin	Gp120-induced BV2 cells	10 μM	↓ MCP-1, IL-17	[17]
Curcumin	LPS-induced inflammation in vascular smooth muscle cells	5, 10, 30 μmol/L for 24 h	↓ MCP-1, TNF-α, iNOS, NO ↓ ROS	[19]
Curcumin	Palmitate-induced inflammation in skeletal muscle C2C12 cells	40 μM	↓ TNF-α, IL-6 ↓ ROS	[20]
Curcumin	TNBS-Induced Colitis Rats	100mg/kg, i.g.	↓ TLR4, NF-κB, IL-27	[21]
Curcumin	dextran sulfate sodium-induced colitis mice	100 mg/kg, i.g.	↓ IL-6, IL-17, IL-23 ↑ IL-10 regulating the Re-equilibration of Treg/Th17	[30]
Curcumin	DSS-induced colitis mouse model	100 mg/kg, intraperitoneally injected	↓ IL-1β, IL-6, MCP-1	[35]
Curcumin	DSS-induced ulcerative colitis mice model	50 mg/kg, standard diet supplemented	↓ TNF-α, IL-6	[44]
Curcumin	DSS-induced acute colitis in mice	15, 30, 60 mg/kg, intraperitoneally injected	↓ TNF-α, IL-6, IL-17 ↑ IL-10	[45]
Curcumin Curcumin nanoparticles	Post-traumatic osteoarthritis mouse model	50 mg/kg, i.g. 0.07 mg of 10 μg curcumin/1 mg nanoparticles, topical application	↓ MMP-1, MMP-3, MMP-13, ADAMTS5, IL-1β, TNF-α	[57]
Acid-activatable curcumin polymer	Monoiodoacetic acid-induced osteoarthritis mouse model	2.5, 5 mg/kg, intramuscular injection	↓ IL-1β, TNF-α	[58]
Curcumin	Collagen-induced rat arthritis model	100, 200 mg/kg, oral	↓ TNF-α, IL-17, IL-1β and TGF-β	[59]
Curcumin	Anterior cruciate ligament transection rat model	50μL, Intra-articular administration	↓ IL-1β, TNF-α	[61]
Curcumin loaded hyalurosomes	Fibroblast-like synovial cells		↑ IL-10 ↓ IL-6, IL-15, TNF-α	[68]
Curcumin	Primary rat abdominal macrophages MSU-induced gouty arthritis rat model	1 μM 100, 150, 200 mg/kg, intraperitoneal administration	↓ IL-1β, TNF-α, NLRP3, caspase-1	[70]

(*Continued*)

Table 1 (Continued).

Compounds	Experimental Models	Dosage and Administration	Effects	Ref
Curcumin	Imiquimod-induced differentiated HaCaT cells	25, 50 μM	↓ IL-17, TNF-α, IL-6, IFN-γ	[80]
Curcumin	Transgenic mouse model of psoriasis	40 mg/kg	↓ IFN-γ, TNF-α, IL-2, IL-12, IL-22, IL-23	[82]
Curcumin	TPA-induced K14-VEGF transgenic psoriasis	Topical 50mg/cm^2 curcumin gel, twice daily	↓ IFN-γ	[83]
Curcumin nanohydrogel	imiquimod-induced psoriasis model		↓ TNF-α, iNOS	[84]
Curcumin	Chronic unpredictable mild stress-induced rats model	100 mg/kg, daily	↓ IL-1β, IL-6, TNF-α ↓ NF-κB activation ↓stressed-induced P2X7R/NLRP3 inflammasome axis activation	[102]
Curcumin	Chronic unpredictable mild stress-induced rats model	20mg/kg, oral	↓ IL-6, TNF-α	[103]
Curcumin	CUMS depression model	40 mg/kg, i.p.	↓ IL-1β	[104]
Curcumin	ApoE-/- mice	0.1% w/w, diet addition	↓ TLR4, IL-1β, TNF-α, VCAM-1, ICAM-1, NF-κB,	[122]
Mannich Curcuminoids	TNBS-induced colitis rats model	40 mg/kg, orally	↓ NF-κB, IL-6, IL-4, TNF-α	[149]
TRB-N0224	A rabbit anterior cruciate ligament transection injury-induced model of OA.	25, 50 mg/kg/day	↓IL-1β, IL-6, TNF-α, MMP-9, MMP-13	[150]
Curcumin analogue AI-44	MSU-induced THP-1 cell	3 μM	↓TNF-α, IL-1β	[157]
Curcumin diglutaric acid	LPS-stimulated RAW 264.7 macrophage cells	1, 5, 10, 20, and 50 μM	↓ NO, IL-6, TNF-α, iNOS, COX-2	[160]
Curcumin-galactomannoside (CGM)	Acetic acid-induced colitis	250 mg/kg bwt	↓ COX-2, PGE2, iNOS, TLR4, IL-6, TNF-α	[171]
Next Generation Ultrasol Curcumin (NGUC)	MIA-induced OA	1100, 2200 mg/kg(20, 40 mg/kg of curcuminoids)	↓ TNF-α, IL-1β, IL-6, COMP, CRP, MMP-3, 5-LOX, COX-2, NF-κB	[174]

the release of cathepsin B, and the excretion of K+. Stimulated NLRP3 promotes the maturation and secretion of a pro-inflammatory cytokine, IL-1β, which is involved in the development of many inflammatory diseases, including IBD. Curcumin significantly protects against severe DSS-induced colitis by inhibiting activation of NLRP3 inflammasomes and production of IL-1β, resulting in improved weight loss, reduced disease activity index and increased colon length.[35] Curcumin can inhibit the production of pro-inflammatory factors such as IL-1, IL-6, IL-8, and TNF-α by regulating the TLR4/NF-κB/AP-1 signaling pathway, which is beneficial to improve intestinal inflammation in patients with IBD.[36,37] Curcumin can effectively induce and maintain symptom relief in patients with UC, reduce inflammatory markers and improve the quality of life of patients.[38,39] Theracurmin has demonstrated significant clinical and endoscopic efficacy and good safety in patients with active mild to moderate Crohn's disease.[40]

Table 2 Clinical Trials Regarding Anti-Inflammatory Effects of Curcumin in Treatment of Diseases

Curcumin	Disease	Dose(s)	Duration	Outcome(s)	Ref
Curcumin	Metabolic syndrome	1 g daily	8 weeks	↓ TNF-α, IL-6, TGF-β and MCP-1	[23]
Curcumin nanomicelle	Male factor infertility	80 mg daily	10 weeks	↓ CRP, TNF-α	[24]
Sinacurcumin®	Osteoarthritis	80 mg daily	3 mouths	↓ Visual Analog Score (VAS), CRP, CD4+ and CD8+ T cells, Th17 cells and B cells frequency	[25]
Theracurmin®	Crohn's disease	360 mg daily	12 weeks	Significant clinical and endoscopic efficacy together with a favorable safety profile.	[40]
IQP-CL-101(Each IQP-CL-101 softgel contains 330 mg proprietary mixture of curcuminoids and essential oils.)	Irritable Bowel Syndrome	Two softgels daily	8 weeks	Beneficial in the improvement of IBS symptom severity, improve quality of life in patients suffering from abdominal pain and discomfort.	[52]
Curcuma longa extract	Knee osteoarthritis	CL extract 500 mg along with Diclofenac twice a day	4 months	Suppresses inflammation and brings clinical improvement in patients of KOA, which may be observed by decreased level of IL-1β and VAS/WOMAC scores, respectively.	[71]
Curcuma longa extract	Knee osteoarthritis and knee effusion-synovitis	2 capsules of CL, daily	12 weeks	CL was more effective than placebo for knee pain but did not affect knee effusion–synovitis or cartilage composition.	[72]
Herbal formulation "turmeric extract, black pepper, and ginger"	Knee osteoarthritis	Curcumin (300 mg), twice a day	4 weeks	↓ PGE2	[73]
Curcumin	Rheumatoid arthritis	500mg, twice daily oral	8 weeks	Improvement in overall DAS and ACR scores.	[74]
Curcuminoid C3 Complex	Psoriasis	4.5g,	12 weeks	The response rate was low and possibly due to a placebo effect or the natural history of psoriasis.	[89]
Curcumin	Major Depression	500–1500 mg/day	12 weeks	Significant antidepressant effects.	[113]
SinaCurcumin	COVID-19	40 mg, twice daily	2 weeks	Significantly improve recovery time.	[139]
Curcumin with Piperine	COVID-19	Curcumin (525 mg) with piperine (2.5mg) in tablet form twice a day.	14 days	Substantially reduce morbidity and mortality, and ease the logistical and supply-related burdens on the healthcare system.	[140]
Theracurmin®	Knee osteoarthritis	6 capsules of Theracurmin per day	6 months	shows great potential for the treatment of human knee osteoarthritis.	[169]
Curcumagalactomannoside complex (CurQfen)	Knee osteoarthritis	400 mg, daily	6 weeks	exerted beneficial effects in alleviating the pain and symptoms.	[170]

(*Continued*)

Table 2 (Continued).

Curcumin	Disease	Dose(s)	Duration	Outcome(s)	Ref
CuraMed® Curamin®	Osteoarthritis	500-mg capsules (333 mg curcuminoids) 500-mg capsules (350 mg curcuminoids and 150 mg boswellic acid) taken orally three times a day	12 weeks	Reduces pain-related symptoms in patients with OA.	[183]
LI73014F2	Knee osteoarthritis	200, 400 mg/day	90 days	Significant pain relief, improved physical function, and quality of life in OA patients.	[184]

Autophagy is an important intracellular catabolic process, which plays a mitigating role in the occurrence and development of UC. Current studies suggest that the interaction between autophagy, inflammation and gut microbiota affects the disease course of IBD together.[41–43] Curcumin is derived from natural products, with high safety, has the capacity for anti-inflammatory, antioxidant, and regulating autophagy and gut microbiota.[44,45] The regulatory relationship among gut microbiota, inflammation and autophagy, as well as their roles in the occurrence and development of IBD, is a new direction to reveal the pathological mechanism of IBD and to search for therapeutic drug targets.

Curcumin is a safe and effective adjuvant agent in the treatment of IBD.[36,38,46] In patients with IBD, curcumin has a beneficial effect on clinical symptoms, endoscopic relief, reduction of oxidative stress or inflammatory markers. However, due to the lack of unified standards for curcumin administration form, administration method, dosage and model selection indexes, as well as the limited bioavailability of curcumin, there is still no sufficient clinical evidence to prove that curcumin is a therapeutic agent for IBD. Some studies suggested that oral curcumin was no better than placebo in alleviating clinical symptoms of UC.[47] Now, researchers generally agree that curcumin is used as adjuvant therapy, and when mesalazine is used in the treatment of UC, adding appropriate amount of curcumin can improve the therapeutic effect.[48–50]

Alternatively, curcumin can also play a beneficial role in a more common intestinal disease.[51] Irritable bowel syndrome(IBS) is a functional bowel disorder that classically presents with symptoms of abdominal pain, bloating, and altered bowel habits of diarrhea or constipation. The Irritable Bowel Syndrome- symptom severity score (IBS-SSS) was used to evaluate the effect of curcumin on patients with IBS. Curcumin can effectively improve IBS-SSS, abdominal pain and other symptoms, and improve the quality of life of patients.[52] Research suggest that the beneficial effects of curcumin on IBS may be due to its anti-inflammatory effect.[53]

Effect of Curcumin on Arthritis

The main types of arthritis are osteoarthritis (OA), rheumatoid arthritis (RA), gouty arthritis. Osteoarthritis, the most common joint disease, is a degenerative joint disease associated with inflammation. Osteoarthritis is more common in people over the age of 50 and in female.[54] Cartilage, subchondral bone, and synovial inflammation may all play a key role in the pathogenesis of osteoarthritis. After the stimulation of osteoblasts, chondrocytes and synovial cells, inflammatory cytokines such as IL-1β, IL-6, TNF-α and matrix degrading enzymes are produced, leading to joint destruction and clinical symptoms such as joint swelling and pain.[54,55] Matrix metalloproteinase (MMP)1, 3.13 and a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS)-5 are the major matrix degrading enzymes in osteoarthritis.[56]

Curcumin can reduce joint inflammation and alleviate pain symptoms, mainly due to its anti-inflammatory and cartilaginous protective effects. In primary cultured chondrocytes, curcumin inhibited the mRNA expression of pro-inflammatory mediators IL-1β and TNF-α, MMPs 1.3 and 13, and ADAMTS5, and upregulated the chondroprotective transcriptional regulator Cbp/p300 interacting transactivator with ED-rich tail 2(CITED2).[57] Curcumin reduces the synthesis of inflammatory mediators, such as TNF-α, IL-17, IL-1β, transforming growth factor-β (TGF-β), and cyclooxygenase-2 (COX-2), and reduces the cartilage and synovial inflammation of rat models of arthritis induced by lipopolysaccharide(LPS), Collagen II and Monoiodoacetic acid.[58–61] Curcumin exerts an anti-inflammatory effect by inhibiting TLR4 pathway and its downstream NF-κB signaling pathway.[61,62] Activation of NF-κB pathway not only down-regulates pro-inflammatory factors, but also inhibits the expression of matrix degrading enzymes. Curcumin inhibited IL-1β-induced MMP-1 and MMP-3 production by inhibiting AP-1 and NF-κB signaling Pathway activation. Moreover, as one of the metabolites of curcumin, tetrahydrocurcumin and curcumin had a similar efficacy for preventing the exacerbation of OA by decreasing the expression of cytokines and MMP3, MMP13 in the articular cartilage.[63]

RA is an inflammatory autoimmune disease characterized by chronic inflammation of the synovial joint that can lead to severe joint injury. IL-10 plays an important role in the development of rheumatoid arthritis.[64] Curcumin has anti-inflammatory effect and can regulate TLR-4 receptor and its downstream pathway.[65] Curcumin can down-regulate the levels of TNF-α, IL-1β, IL-6, IL-12, IL-15, and IL-8 in macrophages, and up-regulate the level of IL-10.[66–68] Curcumin salicylate monoester (FM0807), a curcumin derivative, that incorporates a salicylate into curcumin and retains the β-dike tone structure. FM0807 might exert its anti-arthritic agent through inhibition of expression of inflammatory factors.[66]

Gouty arthritis, or gout, is a metabolic disorder characterized by recurrent inflammatory arthritis that is caused by hyperuricemia and the deposition of inflammatory monosodium urate (MSU) crystals in the synovium and joints. It often occurs in adults over the age of 40 years. Curcumin effectively alleviates MSU-induced inflammatory response by inhibiting TLR4/NF-κB signaling pathway and NLRP3 inflammasome activity.[69,70]

Curcumin is a natural anti-inflammatory drug. Numerous preclinical studies have demonstrated its beneficial effect on arthritis. Clinical trials focused on the treatment of knee osteoarthritis. In a clinical trial of turmeric extract in the treatment of knee osteoarthritis, turmeric extract inhibited inflammation and improved clinical symptoms, as well as reduced IL-1β and oxidative stress [60].[71] Turmeric extract was more effective than placebo for knee pain, but did not affect knee effusion - synovitis or cartilage composition.[72] Motahar Heidari-Beni et al produced an herbal formulation consisting of turmeric extract, black pepper and ginger. In patients with knee osteoarthritis, this compound raises prostaglandin E2 (PGE2) levels similar to naproxen.[73] In a randomized, pilot study, 45 patients diagnosed with RA were randomized into three groups with patients receiving curcumin (500 mg) and diclofenac sodium (50 mg) alone or their combination. Results show that curcumin administration showed the significantly improvement in overall Disease Activity Score and American College of Rheumatology compare with diclofenac sodium.[74] Clinical trials of curcumin in the treatment of arthritis have produced promising results. However, curcumin is not yet available as a treatment for arthritis due to limited data. Currently curcumin-containing dietary supplements are widely used for joint health. Larger, in-depth studies of arthritis patients are needed in the future.

Effect of Curcumin on Psoriasis

Psoriasis is a chronic inflammatory skin disease that affects at least one million people worldwide. The etiology of psoriasis is related to genetic, autoimmune and environmental factors. Psoriasis is often accompanied by comorbidities such as psoriatic arthritis, cardiovascular disease, obesity, metabolic syndrome, liver disease, kidney disease, and depression. Their pathogenesis is thought to be related to inflammation.[75] Dendritic cells are known to play an important role in the initial stage of psoriasis.[76] The secretion of IL-23 and IL-12 by myeloid dendritic cells activates IL-17-producing T cells, Th22 and Th1 cells, leading to the production of inflammatory cytokines such as IL-17, IFN-γ, Interferon-gamma (TNF) and IL-22, which in turn activates the psoriasis-associated inflammatory cascade.[77] This leads to the development of psoriasis, characterized by keratinocyte proliferation, erythema resulting from thickening of the skin, and local tissue infiltration. Curcumin has anti-inflammatory, anti-oxidative and immunomodulatory effects, and can inhibit T cell activation, proliferation and production of pro-inflammatory factors by acting on MAPKs, AP-1, NF-κB pathways.

Curcumin can maintain DC in an immature state which, in turn, impacts on antigen presentation, cytokine production and activation of adaptive T cell responses. Curcumin reduces IL-17 production by CD4(+) T cells.[78] In peripheral blood mononuclear cells of psoriasis stimulated in vitro, curcumin can effectively inhibit T cell proliferation, proinflammatory cytokines and multifunction, and inhibit T cell production of IFN-γ, IL-17, Granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-22.[79] Curcumin down-regulation pro-inflammatory cytokines, IL-17, TNF-α, IFN-γ, and IL-6 then inhibits the proliferation of imiquimod-induced differentiated HaCaT cells.[80]

Vascular endothelial growth factor (VEGF) transgenic mice can be used as a model to study psoriasis.[81] Because in the transgenic rat model of keratin (K) 14-VEGF, the inflammatory skin condition has psoriasis-like cellular and molecular characteristics, including characteristic vascular changes and epidermal changes. Cytokine levels of TNF-α, IFN-γ, IL-2, IL-12, IL-22 and IL-23 were reduced to normal level after curcumin treatment. This may be due to the curcumin inhibits currents of Kv1.3 channel and thus inhibits proliferation of T cells, or curcumin influence MAPKs, AP-1 and NF-κB signaling pathways in the psoriasis mice.[82] Furthermore, research shows that curcumin is capable of relieving TPA-induced inflammation by directly down-regulating IFN-γ production.[83] In an imiquimod-induced psoriasis model, curcumin nanohydrogel restored the normal distribution of TJs proteins ZO1 and occludin and reduced the expression of TNF-α and iNOS.[84] After topical administration to mice, the curcumin could alleviate inflammation symptoms; lower TNF-α, IL-17A, IL-17F, IL-22, and IL-1β mRNA levels; and lower CC Chemokine receptor 6(CCR6) protein expression.[85]

There have been some clinical trials of curcumin for psoriasis, but the level of evidence is low and the sample size is small.[86–88] A Phase II, open-label, Simon's two-stage trial of 4.5g/d of oral Curcuminoid C3 Complex in plaque psoriasis patients. Oral curcumin was well tolerated, but it was not proven whether the responses were due to a placebo effect or a natural disease remission.[89] Curcumin has a variety of mechanisms for psoriasis, curcumin can keep dendritic cells in immaturity, to accelerate the anti-inflammatory macrophage phenotype polarization,[90] inhibiting proinflammatory factor and T cell, restrain the vascular endothelial growth factor, effect on psoriasis susceptibility genes,[91,92] and so on, has great potential. Curcumin is derived from natural plant ingredients, which has good safety and can be used for a long time without causing serious toxic and side effects. Nanogels prepared with appropriate substrates can enhance transdermal absorption, and topical curcumin has a good development prospect in the treatment of psoriasis.[84]

Effect of Curcumin on Depression

Depression is a serious psychological disorder with a global incidence of about 4%. The pathophysiological mechanism of depression is not yet clear, but it is generally believed to be closely related to inflammation, monoaminergic neurotransmitters, neurotrophic factors and the hypothalamic-pituitary-adrenal axis. It is well known that psychological and social stress is an important inducement of depression. Studies have suggested that stress can activate inflammatory response through NF-κB and other pathways, and the cytokines produced can affect neurotransmitter metabolism and synaptic plasticity and other processes, thus leading to depression.[93] Current research evidence shows that inflammation is closely related to depression.[94–96] In animal models of depression, proinflammatory cytokines TNF-α and IL-1 were administered to induce depression-like behavior.[95,97] Therefore, anti-inflammatory and anti-cytokine drug therapy may be an effective way to improve and treat depression.[98–100]

Curcumin is found in the traditional Chinese medicine Jieyu-wan and Xiaoyao-san, which are prescribed to manage stress and mood disorders.[101] Curcumin has anti-inflammatory, antioxidant and neurotrophic properties, suggesting it has strong potential for relieving depression. Chronic unpredictable mild stress induced rats showed depressive-like behaviors, and increased cytokines level associated with depression, which is the classic model for studying depression. According to the relevant test results, such as the Social Interaction Test, Sucrose Preference Test, Forced Swimming Test, Open Field Test, and the High Level Maze Test, curcumin treatment successfully corrected the depression-like behavior of stressed rats.[102–105] Administration of curcumin also decrease mRNA expression of proinflammatory cytokines IL-1β, IL-6, and TNF-α, through down-regulation IL-1β/NF-κB signaling,[105] inhibit the NLRP3 inflammasome activation.[102] Curcumin improves IL-1β-induced neuronal apoptosis by inhibiting the P38 pathway in chronic unpredictable mild stress induced rats.[104] Curcumin's anti-inflammatory effect is one reason for its improvement in depression, but it is not conclusive. In addition to its anti-inflammatory properties, curcumin also inhibits the release of monoamine oxidase, serotonin and dopamine, and regulates the hypothalamus pituitary adrenal axis, neurotrophic factors, and hippocampal neurogenesis and neuroplasticity.[106–108] Curcumin can improve the depressive behavior of ovariectomised rats, as well as fluoxetine and estradiol, which has similar efficacy with fluoxetine and estradiol oestradiol.[109]

Curcumin has shown favorable antidepressant effects in animal models of depression, but clinical trials have not yielded consistent, positive results.[101,110–114] In a meta-analysis of nine clinical trials, curcumin may improve symptoms of depression and anxiety in patients with depression.[101] In randomized controlled trials and other clinical trial designs, there was no convincing evidence that patients with major depression were better off with different curcumin extracts (doses of 500–1000 mg/d) than with placebo (or without treatment) after 5–8 weeks of monotherapy or antidepressant enhancement therapy.[114] But in another double-blind, placebo-controlled trial, adjuvant curcumin (doses increased from 500 mg/day to 1500 mg/day) showed a significant difference between curcumin and placebo at weeks 12 and 16.[113] Due to the low bioavailability of curcumin, the clinical efficacy of curcumin for depression needs to be verified by larger sample trials, and the dosage and usage of curcumin as well as the assessment tools for the severity of depression should be regulated.

Effect of Curcumin on Atherosclerosis

With the development and progress of society, the incidence of cardiovascular diseases is increasing, which has seriously affected human health. Atherosclerosis is a common cardiovascular disease with complex pathogenesis and close relationship with hypertension, hyperlipidemia, coronary heart disease and other cardiovascular diseases. Atherosclerosis is a disease characterized by mild chronic inflammation of the arterial wall, which is the potential cause of many cardiovascular and cerebrovascular diseases.

Inflammation plays an important role in both atherosclerotic plaque formation and rupture. The modified lipoprotein activates endothelial cells and chemokines mediate the recruitment of adherent monocytes and lymphocytes to the forming lesion site; cytokines and growth factors produced by the inflammatory intima induce the differentiation of monocytes into macrophages accompanied by the upregulation of the scavenger receptors and TLRs; When activated, macrophages form foam-like cells or activate an inflammatory cascade that leads to atherosclerotic plaque formation. TLR4 is a pattern recognition receptor of innate immunity that is involved in the pathogenesis of atherosclerosis. TLR4 is expressed in a number of different cell types present in the atherosclerotic plaque, such as monocytes, neutrophils, mast cells, T lymphocytes, macrophages and so on. TLR4 binds to the ligand and activates the NF-κB pathway and subsequent pro-inflammatory gene transcription, leading to NLRP3 inflammasome activation, further promoting the inflammatory response and causing instability of atherosclerotic plaques.[115] Studies have shown that the expression of NLRP3 inflammasome-related genes is significantly increased in human atherosclerotic lesions, which may be activated by the accumulation of lipoproteins in macrophages and dendritic cells, and inflammasome-related activation leads to increased IL-1β.[116] Macrophages play a central role in atherosclerosis. Macrophages have two types of proinflammatory (M1) and anti-inflammatory (M2) phenotypes, and both types of macrophages maintain homeostasis in normal tissues. In atherosclerotic plaques, M1 macrophages were dominant, and the related inflammatory cytokines IL-6, iNOS, and IL-1β were increased, which worsened the atherosclerotic lesions. Atherosclerotic plaques are mainly composed of macrophages, T cells and monocytes.[117] Activation of plaque inflammation leads to protease secretion, tissue destruction, and plaque rupture. In turn, thrombosis produces ischemia and infarction, thus can lead to a series of serious and even life-threatening cardiovascular diseases.[118,119]

Currently, two knockout mouse strains with hypercholesterolemia and atherosclerosis have been used to study the rat model of atherosclerosis: apolipoprotein E homozygous knockout (−/−) (apoE$^{-/-}$) mouse; LDL receptor (−/−)(Ldlr$^{-/-}$) mouse.[118] Animal studies have shown that curcumin has an anti-atherosclerosis effect, possibly through its anti-inflammatory properties. Curcumin reduces the activation of M1 macrophages.[120] Curcumin regulates the polarization and plasticity of macrophages by affecting TLR4/MAPK/NF-κB pathway, which is beneficial to reduce atherosclerosis.[121,122] In ApoE$^{-/-}$ mice fed a high-fat diet supplemented with 0.1% curcumin significantly decreased TLR4 expression in atherosclerotic plaques and reduced the development of atherosclerosis. In addition, curcumin supplementation can inhibit the activation of NF-κB in aorta and the levels of IL-1β and TNF-α in aorta and serum.[122] Activation of the NF-κB pathway leads to activation of NLRP3 inflammasome. Inhibition of NLRP3 inflammasome improves atherosclerotic lesions in ApoE$^{-/-}$ rats,[123] and anti-inflammatory therapy targeting IL-1β reduces the recurrence rate of cardiovascular events.[124] Curcumin can inhibit NF-κB-mediated NLRP3 expression, thereby inhibiting vascular smooth muscle cell migration, and alleviating hypertension, vascular inflammation and vascular remodeling in spontaneously hypertensive rats, which is beneficial to cardiovascular diseases including atherosclerosis.[125] In ApoE$^{-/-}$ mice, atorvastatin calcium and curcumin synergistically inhibited adhesion molecules and plasma lipid levels, reducing foam cell formation and inflammatory cytokines secretion by blocking monocyte migration to the intima.[126]

Curcumin has significant efficacy in the treatment of atherosclerosis in animal models, but the relevant clinical evidence is insufficient. Clinical evidence in non-atherosclerotic populations suggests that curcumin can reduce lipid levels and inflammatory responses, as it did in a mouse model.[127] A meta-analysis of 20 randomized controlled trials with 1427 participants suggested a significant decrease in plasma concentrations of triglycerides and an elevation in plasma high-density lipoprotein cholesterol (HDL-C) levels.[128] However, in another meta-analysis of clinical trials related to the effect of curcumin on lipid levels, curcumin supplementation did not show a significant effect on serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride, and HDL-C levels.[129] To date, there is a clinical trial that investigates the anti-inflammatory effect of curcumin on atherosclerosis with Curcumin Supplementation, but the status and results of the tests are unknown (NCT02998918). Due to the lack of relevant clinical trials and inconsistent results, more comprehensive clinical trials are needed in the future to better demonstrate the beneficial effects of curcumin on patients with atherosclerosis. The anti-inflammatory properties of curcumin may be the focus of research and observation.

Effect of Curcumin on COVID-19

Coronavirus disease 19 (COVID-19/2019-nCoV) is an infectious disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 12th August 2021, the cumulative cases of COVID-19 are 205,549,209, cumulative death cases are 4,337,638.[130] The clinical manifestations of COVID-19 including acute respiratory distress syndrome (ARDS), typical pneumonia, and multi-organ failure.[131] ARDS is the leading cause of COVID-19 mortality, mostly due to cytokine storm syndrome. Patients with COVID-19 showed high levels of inflammatory cytokines (TNF, IL-1β, IL-6, IL-8), colony-stimulating factors (G-CSF and GM-CSF) and inflammatory chemokines (MCP1, IP10, and MIP1α).[132–134] Thus, suppressing the elevated inflammatory response that occurs during COVID-19 may be useful in preventing the severity of the disease. Curcumin, a natural compound with anti-inflammatory effect, could as an adjuvant drug in COVID-19 treatment.[135]

As described in the previous section, it is clear that curcumin may play an anti-inflammatory role by regulating inflammatory mediators and immune cells. Nano-curcumin can regulate the rate of increase of inflammatory cytokines, especially IL-1β and IL-6 mRNA expression and cytokine secretion in COVID-19 patients, which may lead to improved clinical manifestations and overall recovery.[136] Compared to the placebo group, curcumin could reduce the frequency of Th17 cells, Treg and their related inflammatory factors in both mild and severe COVID-19 patients.[137,138] In addition to anti-inflammatory effect, curcumin can also play an antiviral role by inhibiting SARS-CoV-2 entry into cells and inhibiting viral proliferation. Curcumin has a variety of pharmacological effects and high safety, which makes it an adjunctive drug for the treatment of COVID-19.

In an open label nonrandomized clinical trial, oral nano-formulation of curcumin with dose of 80 mg twice daily could significantly fasten the resolution time of COVID-19-induced symptoms, improve oxygenation, and reduce hospital stay time in comparison with control group.[139] In addition, orally administered curcumin with piperine as adjuvant therapy in COVID-19 treatment could substantially reduce morbidity and mortality, improve the clinical symptoms.[140]

Limitations and Countermeasures of Curcumin in the Treatment of Diseases

Limitations

The above descriptions fully illustrate that curcumin has significant anti-inflammatory effects, and has great potential in the treatment of IBD, arthritis, psoriasis and other diseases mentioned above, with broad application prospects. However, in clinical application, the anti-inflammatory effect of curcumin is not ideal, and curcumin has not been marketed as a therapeutic drug, mainly due to the pharmacokinetic limitations of curcumin. After oral administration of curcumin, most of it is excreted with metabolites and only a small amount enters the bloodstream for utilization, which is significantly lower than the concentration required to inhibit most of the anti-inflammatory targets of curcumin.[141]

The process of drugs in vivo determines the fate of drugs. Appropriate rates of absorption, distribution, metabolism and excretion make drugs act on the human body and play a therapeutic role. Low water solubility, poor absorption, elimination and rapid metabolism limit the utilization of curcumin. The water solubility of curcumin is poor and its physical and chemical properties are unstable Only a small amount of curcumin is dissolved in the gastrointestinal tract and the effective components are limited. Curcumin is a strong hydrophobic compound with solubility of about 11ng/ mL (https://pubchem.ncbi.nlm.nih.gov/compound/curcumin). Curcumin is extremely unstable in alkaline environment, resulting in degradation and autooxidation products such as ferulic acid, feruloylmethane, vanillin and bicyclopentadione.[142,143] Absorption is the process by which a drug enters the bloodstream from the administration site, and curcumin is poorly absorbed from the gastrointestinal tract. Oral curcumin of 12g/ day is considered to be the maximum safe dose of curcumin, but the final serum curcumin level at this time is only about 50ng/ mL.[144] This may be due to P-glycoprotein action and liver first pass effect. Curcumin is a substrate for P-glycoprotein, a transmembrane ATP-dependent drug effluence pump that expel curcumin from the intestinal membrane, thereby limiting its permeability.[145] In addition, the hepatic first-pass effect causes some curcumin to be metabolized in the intestinal mucosa and liver, leading to reduced drug absorption.[146] The rapid metabolism of curcumin is one of the main causes of poor bioavailability. After entering the blood, curcumin is rapidly metabolized as an inactive substance. Curcumin is reduced to di-, tetra-, hexa- and octahydrocurcumin after I metabolism, then, the above forms, as well as curcumin, demethylcurcumin and bimethylcurcumin, are metabolized in the II phase to conjugate glucuronide and sulfate to form non-bioactive glucuronide and sulfate conjugates.[145,147] The related degradations and metabolites of curcumin are shown in Figure 4.

Countermeasures

Improve the bioavailability and stability of the curcumin is curcumin research hot spot and the basis for the development of curcumin related preparation. The current research mainly concentrated in curcumin derivatives and prodrug, pharmaceutical strategies, and combination drug therapy, in order to make curcumin in the target position and to play a better therapeutic effect.

Derivatives and Prodrugs of Curcumin

Structural modification and analogues synthesis of natural products are important strategies for drug discovery. In order to improve the properties of curcumin, the main direction for the development of curcumin preparation is to use curcumin as the parent nucleus to modify the structure and synthesize analogues. A large number of curcumin analogues, derivatives and prodrugs have been prepared, some of which have improved their physicochemical properties and have significant anti-inflammatory effects.[148]

The β-diketone portion of curcumin is thought to be responsible for its instability, rapid degradation and low bioavailability. At present, the structural modification and modification strategies of curcumin mainly include: modification of active methylene; introducing groups in the benzene ring; preparation of single carbonyl derivatives.

The introduction of several functional groups into the active methylene part of curcumin attracted the attention of researchers. For example, Mannich curcuminoids are attached with aryl groups to curcumin active methylene to enhance the stability of β-dione and thus enhance the biological activity. Among them, C142 or C150 showed strong anti-inflammatory activity in TNBS induced colitis model.[149] TRB-N0224 introduces N-phenylformamide onto the active dimethyl and has a 1, 3-diketone component similar to tetracycline and the inherent anti-inflammatory properties of curcumin itself, regulating the levels of matrix metalloproteinases and cytokines.[150] The stability of the compound can also be enhanced by the substitution of the active methylene with nitrogen to form a pyridine ring.[151] The two benzene rings of curcumin are the basis of the antioxidant activity of curcumin. Therefore, attaching Br, F, NO2, OH, CH3 and other groups to the benzene ring is a method to improve the biological activity of curcumin, which is of great significance.[152] The structure-activity relationship of various groups on the benzene ring affects the physicochemical properties and activity of the compounds. The pharmacokinetic properties of curcumin are improved by adding electron-withdrawing groups, which increase the acidity of the enol system. CURC-MPEG454 was modified with polyethylene glycol to increase its solubility and improve the physicochemical properties of curcumin.[153]

Now, mono-carbonyl derivatives are a major direction in the structural modification of curcumin. In the structural design of mono-carbonyl curcumin derivatives, ketenone[154] is commonly used to replace β-dione, and can also be combined with cyclopentanone, cyclohexanone,[155,156] 4-piperidone[157] or N-substituted −4-piperidone.[158,159] At the same time, the "ortho effect" of the ortho substituents on the benzene ring is emphasized and utilized. It is beneficial to improve the biological activity by attaching F, Br, NO2, CF3 groups on the ortho of the benzene ring. C66, a mono-carbonyl derivative of curcumin, is ortho-bonded to the benzene ring with CF3, which plays an anti-inflammatory role by inhibiting

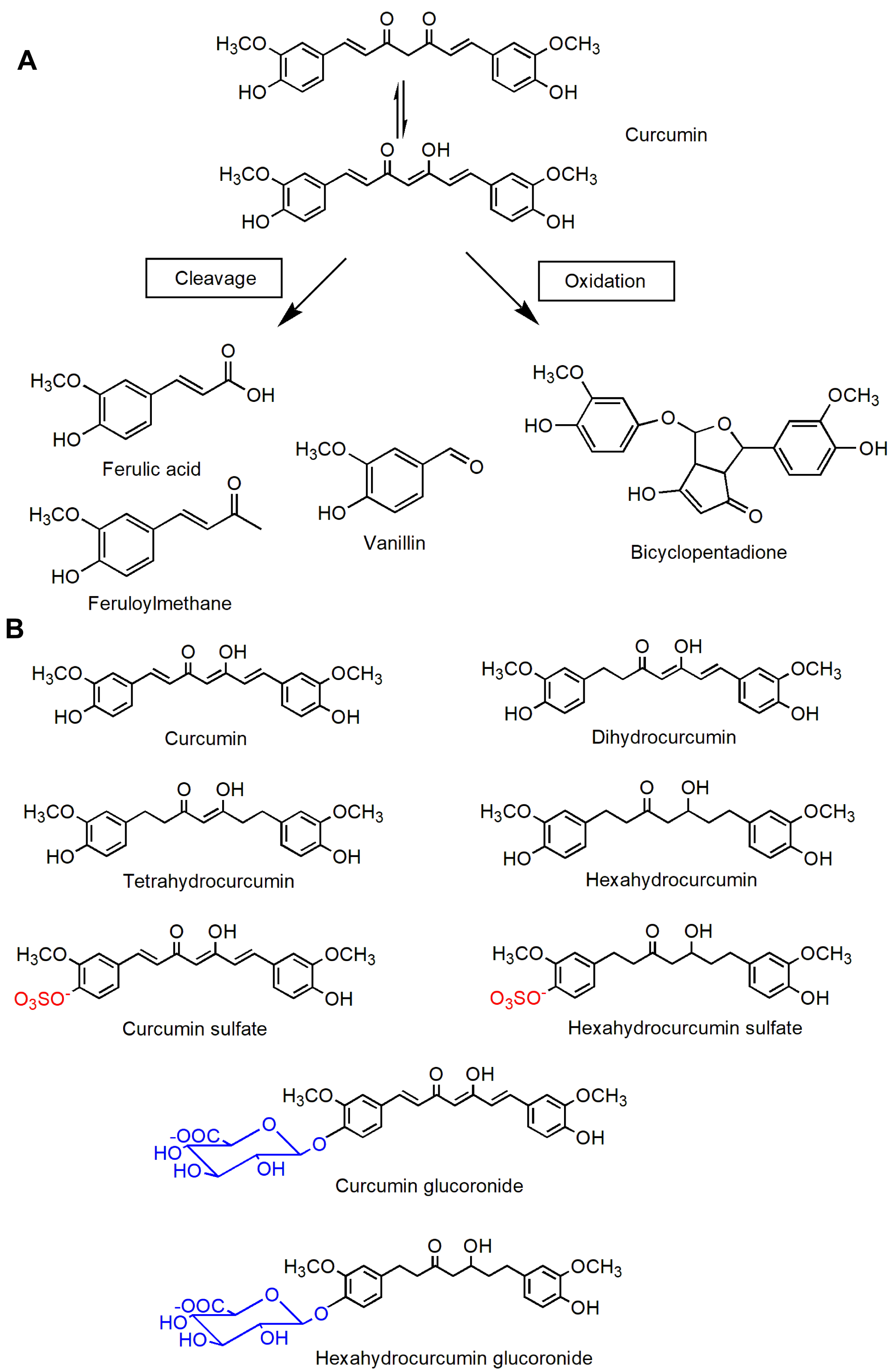

Figure 4 Chemical structure of curcumin-related products. (**A**) Curcumin degradation products; (**B**) curcumin metabolites.

the JNK pathway.[155] Some of the mono-carbonyl derivatives showed excellent anti-inflammatory properties. Two ortho-trifluoromethoxy-substituted 4-piperidone-containing mono-carbonyl curcumin derivatives exhibited excellent anti-inflammatory effects in DSS-induced mouse colitis models. They effectively inhibit ROS, COX-2, IL-

1β and TNF-α levels, phosphorylation of MAPKs, and nuclear translocation of p65.[158]

The prodrug refers to the chemical compound which has no activity in vitro or little activity after the chemical structure modification of the drug and plays a role by releasing the active drug through enzymatic or non-enzymatic transformation in vivo. The anti-inflammatory prodrugs of curcumin mainly include curcumin diglutaric acid (CurDG),[160,161] curcumin diethyl disuccinate (CurDD),[162,163] and curcumin diethyl diglutarate (CurDDG).[164] Compared with curcumin, it has higher bioavailability and pharmacological activity, and has the potential to be further developed as therapeutic drugs. Curcumin diglutamic acid (CURDG) was synthesized by ether bond between curcumin and glutaric acid, which significantly improved water solubility.[161] Compared with curcumin, CURDG exhibited better anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophage cells and carrageenan-induced mouse paw edema model.[160] In LPS-induced RAW 267.4 macrophages, the anti-inflammatory activity of CURDDG was stronger than that of curcumin. CurDDG significantly decreased the expression of TNF-α and IL-6, decreased the levels of COX-2 and iNOS, and decreased the phosphorylation of p38, JNK and ERK1/2.[164] Although CURDDG bypasses the Phase II metabolism of curcumin through gluconaldification and sulfation, its water solubility is lower than that of curcumin, limiting its clinical application. Therefore, coating CurDDG with polymer to prepare nanoparticles may be an effective measure to improve the water solubility of CurDDG.[165]

Pharmaceutical Strategies

Improving the absorption, distribution, metabolism and excretion of drugs by pharmaceutical strategies is an important approach to drug development. At present, the measures to improve the bioavailability of curcumin mainly include the addition of lipids, the adsorption and dispersion of substrates, the reduction of particle size, and the preparation of nano preparations.[147] Using these techniques, a large number of curcumin preparations have been marketed as dietary supplements, which are popular with the general public for the improvement and maintenance of joint and cardiovascular health. Now, the common curcumin preparations on the market include BCM-95®, C3Complex®, Meriva®, Theracurmin®, CurQfen ®, Theracurmin®, Longvida®, etc.

Theracurmin is a colloidal dispersion of nanoparticles, which contains 10 w/w % curcumin, 2% of other curcuminoids, 46% of glycerin, 4% of chama, and 38% of water. The mean particle size of Theracurmin (D50% diameter) was 0.19μm. The mean particle size of curcumin powder was 22.75μm. Theracurmin can be dissolved in water, greatly improving the bioavailability of Theracurmin.[166] Compared with curcumin, Theracurmin can significantly inhibit NF-κB transcriptional activity, and then regulate the expression of pro-inflammatory factors to play an anti-inflammatory role.[167] Currently, Theracurmin is used as a dietary supplement to inhibit alcoholism and protect the liver, which is manifested by a reduction in acetaldehyde concentration in the blood[166] and is often used as a hangover agent. Theracurmin is believed to be beneficial to the improvement of cognitive impairment,[168] clinical symptoms of CD patients,[40] and joint health[169] in drug research.

Curcumagalactomannoside complex (CurQfen) has been used for short-term relief of pain and symptoms in patients with arthritis.[170] In the acetic acid induced ulcerative colitis model, curcumagalactomannoside significantly enhanced antioxidant activity, decreased the level of inflammatory mediators, and inhibited the expression of inflammatory markers.[171] The amphiphilicity of phospholipids can improve the gastrointestinal absorption of curcumin. Studies have showed that the biological activity of the phospholipid complex is 5 times higher than that of ordinary curcumin, and the absorption rate is higher. A lecithin delivery system(Meriva®) effectively relieves and treats OA.[172,173] A novel curcumin formulation consisting of 95% curcumin extract, phospholipids, monoglycerides, and acidifiers shows better bioavailability and treatment for MIA-induced OA.[174]

Curcumin nanocarriers are the focus of research at present. Due to the high surface area to volume ratio provided by nanocarriers, the solubility and dissolution rate of drugs can be improved. In addition, small particle sizes can prolong the maintenance time of drugs in the systemic circulation, alter drug distribution, and allow drug targeting and trans-barrier transport.[144] Curcumin is a highly hydrophobic compound, and a large number of studies have been conducted on its nano preparations, in order to improve the water solubility of curcumin, enhance transdermal absorption, and target positioning. Common curcumin nanocrystals include liposomes, polymer particles/micelles, nanoemulsions, nanogels, nanocrystals, solid liposome nanoparticles, etc.[144,145,175] At present, there are many kinds of carriers and preparation methods of curcumin nanometer preparations, and they are often modified to obtain the desired properties.[176,177] For example, using hyaluronic acid to modify the surface of curcumin nanoparticles can maintain a high level of curcumin in the colon tissue, reduce the proinflammatory factors and reduce the inflammatory response in the colon, which is conducive to the treatment of ulcerative colitis.[178,179] In some inflammatory diseases with superficial disease sites, such as psoriasis and arthritis, nano-emulsion and nanogel can enhance the penetration and accumulation of curcumin in the skin through local administration, which can be used as a direction of preparation research.[57,180] There are many related preparations with varying quality, which will not be described in detail in this paper.

Combination Drug Therapy

Combination drug therapy refers to the simultaneous or successive application of two or more drugs for the purpose of treatment. In the application of curcumin, combination therapy is an effective method to improve pharmacokinetics and anti-inflammatory effect of curcumin. Curcumin is used in combination with natural ingredients such as emu oil, tetramethylpyrazine, resveratrol, and Vitamin D to enhance its anti-inflammatory effects.[181] Piperine is an effective inhibitor of gluconaldification and p-glycoprotein. Combined with piperine, curcumin can synergistically improve anti-inflammatory and antioxidant activity.[145] Combinations of curcumin with piperine and quercetin have been successfully used for the bio-enhancement of curcumin. Frankincense exerts anti-inflammatory effects by inhibiting leukotriene synthesis, cyclocythase 1/2 and c(5-LOX).[182] The combination of curcumin complex and frankincense is effective in alleviating pain related symptoms in patients with osteoarthritis, possibly due to the synergistic effect of curcumin and boswellic acid.[183] Li73014F2 is a novel compound prepared from the extracts of Terminalia chebula fruit, Curcuma longa rhizome and Boswellia serrata gum resin, which has synergistic inhibitory effect on 5-LOX. In clinical trials, LI73014F2 significantly reduced pain and improved physical function and quality of life in patients with osteoarthritis.[184] Currently, the use of curcumin alone in the treatment of diseases is limited, and it has achieved good results as an adjuvant therapy, possibly because of the synergistic effect of curcumin when used in combination with other drugs. For example, the Mesalazine adjuvant curcumin has been shown to be effective and safe in inducing clinical remission, endoscopic remission, and endoscopic improvement in ulcerative colitis.[48]

Conclusion

In conclusion, curcumin has good anti-inflammatory properties, and curcumin regulates NF-κB, MAPK, AP-1, JAK/STAT and other signaling pathways, and inhibiting the production of inflammatory mediators. Curcumin in the treatment of IBD, arthritis, psoriasis, depression and atherosclerosis and other diseases, can reduce inflammatory response, effectively improve symptoms, play a role in the treatment of diseases. Now, the pharmacokinetics and anti-inflammatory effects of curcumin have been improved to some extent by the structural modification and modification of curcumin, preparation research and drug combination therapy. Among them, curcumin dietary supplement or adjuvant drug has significant therapeutic effect, which is the most feasible way for curcumin application at present.

Abbreviations

IBD, inflammatory bowel disease; TLR, Toll-like receptors; NF-κB, Nuclear factor kappa-B; MAPKs, Mitogen-activated protein kinases; AP-1, Activator Protein 1; PPARγ, Peroxisome proliferator-activated receptor gamma; JAK/STAT, The Janus kinase/Signal transducer and activator of transcription; NLRP3, NOD-like receptor pyrin domain-containing 3; IL-1, Interleukin-1; TNF-α, Tumor necrosis factor-α; iNOS, Inducible nitric oxide synthase; RANTES, Regulated upon activation normal T cell expressed and secreted factor; G-CSF, Granulocyte colony-stimulating factor; MCP-1, Monocyte chemotactic protein-1; CRP, C-reactive protein; ROS, Reactive oxygen species; NADPH, Nicotinamide adenine dinucleotide phosphate; UC, Ulcerative colitis; CD, Crohn's disease; DSS, dextran sulfate sodium salt; IBS, Irritable bowel syndrome; IBS-SSS, Irritable Bowel Syndrome- symptom severity score; OA, osteoarthritis; RA, rheumatoid arthritis; MMP, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin-like motifs; CITED2, Cbp/p300 interacting transactivator with ED-rich tail 2; TGF-β, transforming growth factor-β; COX-2, cyclooxygenase-2; LPS, lipopolysaccharide; MSU, monosodium urate; PGE2, prostaglandin E2; IFN-γ, Interferon-gamma; GM-CSF, Granulocyte-macrophage colony stimulating factor; VEGF, Vascular endothelial growth factor; CCR6, CC Chemokine receptor 6; apoE-/-, apolipoprotein E homozygous knockout (−/−); Ldlr−/−, LDL receptor (−/−); HDL-C, high-density lipoprotein cholesterol; LDL-

C, low-density lipoprotein cholesterol; 5-LOX, 5-lipoxygenase; COVID-19, Coronavirus disease 19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome.

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