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THERAPEUTIC POTENTIAL OF CURCUMIN IN ARTHRITIS MANAGEMENT: MECHANISMS OF ACTION, SAFETY PROFILE, AND EXPERIMENTAL INSIGHTS

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Abstract

Chronic inflammatory diseases are now a major health concern as they cause a large number of death cases. It is therefore important to control inflammation using anti-inflammatory compounds that are safe and affordable. Many studies suggest that many compounds derived from plants have anti-inflammatory effects; one of which is Curcumin. Curcumin is a principal constituent of turmeric; which has high potential in improving chronic inflammatory disease with less side effects. A large number of studies have proven that curcumin has broad variety of biological functions; anti-inflammatory, anti-oxidant, wound-healing, anti-cancer and anti-arthritis, among which anti-inflammatory effect is a significant feature. This paper reviews the mechanism of action of curcumin on arthritis, safety and toxicity of curcumin, its bio-availability and experimental findings on curcumin's effect on arthritis; the latest research result on pharmacokinetics of curcumin. Curcumin has an anti-inflammatory effect by suppressing the action of pro-inflammatory cytokines such as interleukins, phospholipase A2, 5-lipoxygenase enzyme and cyclooxygenase-2. Curcumin has been proven to be safe and can be used as an agent to manage and treat arthritis.

Keywords: Curcumin, Anti-inflammatory, Arthritis, Phytochemical, Chronic inflammatory diseases, Bioavailability

Introduction

Since the dawn of mankind, natural products have been widely used as medicine for a wide range of disease that affects human health. Curcumin, a phytochemical, is a highly pleiotropic compound with anti-inflammatory, hypoglycemic, anti-oxidant, wound-healing and anti-microbial activity (Sharifi-Rad et al., 2021). It is the major active component of turmeric that gives it its yellow colour. It is a member of the curcuminoid family. Turmeric, a plant in the ginger family, is native to Southeast Asia, primarily in India. Its rhizome is ground into powder and used as culinary spice and as

traditional medicine. Historically, turmeric has been used as an alternative healer to treat pain and inflammation. In recent times, turmeric has been found to be a viable treatment for arthritis, with studies finding that the substance has anti-inflammatory and pain- relieving effect (Kunnumakkara et al., 2023).

History and Source of Curcumin

Curcumin (diferuloylmethane) is a bright yellow phytochemical which is derived from the rhizome of *Curcuma longa* of the ginger family (zingiberaceae), a spice often used in curry powder. *Curcuma longa* contains different curcuminoids, and curcumin was discovered to be the major component in 1815 (Vogel & Pelletier, 1815). Traditionally known for its anti-inflammatory effects, *C. longa* has a long history of curative use in the Ayurvedic and Chinese system of medicine. The discovery of curcumin dates to around two centuries ago when Vogel and Pelletier reported the isolation of the "yellow coloring-matter" in Turmeric and named it "Curcumin". The Curcumin structure was first proposed by Polish scientist in 1910. Around 500 BCE, turmeric emerged as an important part of ayurvedic medicine. Ayurveda is an ancient Indian system of natural healing. In ancient times, it was used as perfume and spice. The vibrant yellow natural pigment of turmeric has also been used to dye clothes and threads for centuries. Although the history of the golden spice turmeric goes back thousands of years, it is only in recent century that the chemistry of its active component, curcumin was studied.

Biochemistry of Curcumin

Curcumin (diferuloylmethane) is a symmetric molecule that is highly pleiotropic, having the ability to modulate the activity of numerous signaling biomolecules. This polyphenolic compound makes up to 2-6% of turmeric powder. Its IUPAC name is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It has the chemical formula $C_{21}H_{20}O_6$, molecular weight of 368.38 g/mole and melting temperature of 183^{o}C. The typical curcuminoids include Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (Santosh et al., 2007). Chemically, it exhibits keto-enol tautomerism, that is, it has a predominant keto-form in neutral and acidic solutions. However, the predominant form is the solid state and in an alkaline solution is its stable enol form (Sharifi-Rad et al., 2021). Curcumin is soluble in organic solvents such as ethanol, methanol and acetone but has poor solubility in water. Its chemical structure comprises of two aromatic-ring structure with methoxyphenol groups connected by a seven-carbon linker. Furthermore, Curcumin is sensitive to ultra-violet radiation and its degradation is accelerated by exposure to sunlight.

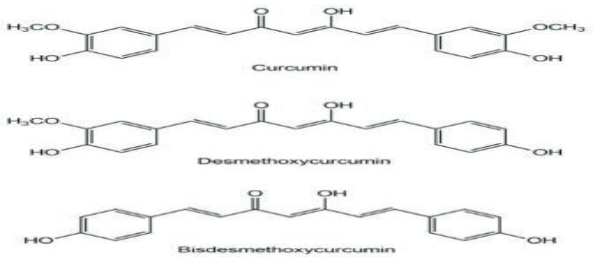

Figure 1. The three main curcuminoids found in *Curcuma longa* (Carvalho Henriques et al., 2020)

Biological Actions of Curcumin: Curcumin is a pleiotropic compound with its major bio-active effect being anti-cancer, anti-inflammatory and anti-oxidant (Sohn et al., 2021). Biological actions of curcumin include: Management and Prevention of Cancer: Cancer is a disease characterized by uncontrolled cell growth. The first report on the anticancer activity of curcumin was in 1987. Curcumin contributes to the death of cancer cells, reduces metastasis and reduces angiogenesis (formation of new of new blood vessels supplying tumors) (Giordano & Tommonaro, 2019). Treatment of Alzheimer's Disease: Alzheimer's disease is a disease that damages memory. Curcumin can cross the blood-brain barrier and lead to various improvements in the pathological process of Alzheimer's disease (Shabbir et al.,

2020). Boosts Brain-derived Neurotrophic Factor (BDNF)**:** Curcumin boosts level of this brain hormone. BDNF is a gene responsible for promoting the life of neurons. Curcumin also aids in improving memory, which is logical as it boosts BDNF level (Sarraf et al., 2019). Lowers Risk of Heart Disease**:** Curcumin can help reduce inflammation and oxidation, which can play a role in heart disease. Curcumin helps in improving the function of blood vessels endothelium (Cox et al., 2022).

Treatment and Prevention of Diabetes: Curcumin inhibits hyperglycemia, oxidative stress and inflammatory processes caused by Diabetes Mellitus (Marton et al., 2021). Improves Skin Health: The anti-inflammatory effect of curcumin helps in treatment of acne and eczema (Kasprzak-Drozd et al., 2024). Treatment of Arthritis: Arthritis is a disease characterized by inflammation of joints. Curcumin aids in the treatment of arthritis, as it has an anti-inflammatory effect. This paper focuses mainly on the effect of curcumin on arthritis.

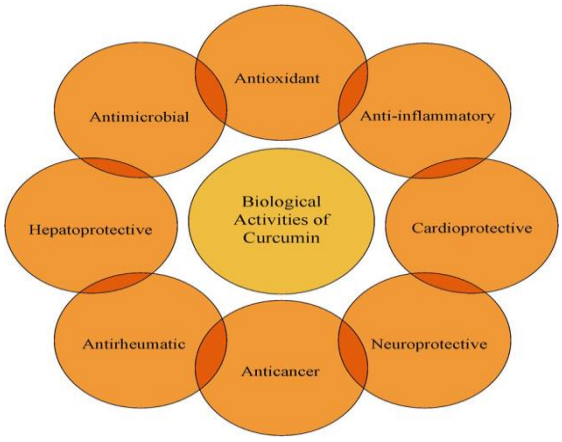

Figure 2. Schematic illustration of biological activities of curcumin (Sharifi-Rad et al., 2020).

Arthritis**:** Arthritis is a disease characterized by inflammation of the joint, usually joints in hand and feet. Inflammation is a mechanism of the healing process to defend the body against viruses and bacteria or it is a response to injuries like burns (Poudel et al., 2023).

Risk factors of Arthritis**:** Risk factors of arthritis includes the following: wear and tear of the joints due to overuse, age (arthritis is common among adults above the age of 50 years), injuries around the joint, obesity, autoimmune disorder, lack of exercise, smoking and family history.

Symptoms and Types of Arthritis**:** Symptoms of arthritis include: joint pain, swelling, muscle weakness around the joints, limited mobility, stiffness of joint and redness,

Types of arthritis include: osteoarthritis, rheumatoid arthritis, psoriatic arthritis and gouty arthritis. Individuals between the age of 50 - 60 have a higher risk of developing osteoarthritis.

Osteoarthritis: This is the most prevalent type of arthritis. It is more predominant among women than men. Wear and tear of joints due to overuse can cause osteoarthritis. An infection or injury to the joint can worsen this natural breakdown of cartilage. Cartilage is a solid but flexible connective tissue that protects the joints by absorbing pressure and shock. To compensate for the loss of cartilage tissue, the body starts to remodel the bone in an attempt to restore stability, forming unpleasant bony growths called osteophytes.

Rheumatoid Arthritis: This is an autoimmune type of arthritis which causes the body immune system to attack the synovium, a soft tissue in the joints that produces synovial fluids which lubricates the joints. This autoimmune disorder leads to destruction of bone and cartilage due to friction between joints. This causes inflammation of the joint. The exact cause of this autoimmune disorder is unknown.

Psoriatic Arthritis: Psoriatic arthritis, a type of inflammatory arthritis affects individuals with the skin disease, psoriasis. This disease is characterized by red patches on the skin. Psoriatic arthritis is caused by autoimmune disorder; when the body's immune system attacks healthy tissues. This leads to inflammation of the joints and overproduction of skin cells.

Gout**:** This is a type of metabolic arthritis caused by excess accumulation of uric acid in the body. Uric acid is gotten from the breakdown of purine in nucleotide metabolism. Excess uric acids accumulate and form needle-like crystals in the joint causing extreme joint pain.

Existing drugs for the treatment of arthritis are steroids, analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs) which reduce pain and inflammation. However, these drugs have a huge number of side effects. For example, NSAIDs causes severe gastrointestinal pain after drug treatment. Replacement therapy has gradually become an important part of the management and treatment of arthritis. Curcumin is a potential alternative for the treatment of arthritis with fewer side effects. Evidence from multiple clinical trials suggests that Curcumin can reduce pain and inflammation in arthritis.

Mechanism of Action of Curcumin on Arthritis: Curcumin has been used for centuries in traditional Chinese and Ayurvedic medicine due to its anti-inflammatory effect (Goel et al., 2008; Prasad & Aggarwal, 2011). Curcumin reduces joint inflammation and pain due to its anti-inflammatory and anti-oxidant and cartilaginous protective property. After the stimulation of osteoblast, chondrocyte, and synovial cells in joint injury or auto-immune disorder, inflammatory cytokines like IL-1b, IL-6, TNF-A and matrix degrading enzymes are produced leading to joint destruction and inflammation (Peng et al., 2021). The main cytokines involved in the inflammatory pathway of arthritis are Tumor Necrosis Factor-a (TNF-a), interleukins (IL-1 & IL-6). Curcumin affects the signaling of pro-inflammatory cytokines such as interleukins, phospholipase A2, 5-lipoxygenase enzyme and cyclooxygenase-2 by influencing NF Kappa Beta activity (Zhao et al., 2021). Nuclear factor-KB (NF-kB) exerts a critical role in the signal transduction pathway involved in inflammatory process. Curcumin has an anti-inflammatory effect by suppressing the action of NF-kB. Curcumin binds to toll-like receptors on cell membrane and regulates downstream nuclear factor-KB through acting on peroxisome proliferators-activated receptor gamma ($PPAR_Y$). Curcumin also inhibits matrix metalloproteinase MMP-1(interstitial collagenase) and MMP-3 enzyme (stromelysin) enzyme by inhibiting NF-kB signaling pathway activation (Hwang et al., 2013). These enzymes accelerate catabolic damage of articular cartilage and subsequently lead to development of arthritis. Gouty arthritis is caused by hyperuricemia and deposition of monosodium urate crystals in synovial membrane and joints. Curcumin prevents MSU-induced inflammatory response by inhibiting NF-kB signaling pathway.

Curcumin also reduces inflammation through its antioxidant activity (Menon & Sudheer, 2007). Oxidative stress enhances inflammation. Accumulation of reactive oxygen species causes inflammation by activating transcription factor. Curcumin reduces production of reactive oxygen species due to its effect on Nicotinamide Adenine Dinucleotide Phosphate (NADPH oxidase) and increasing the activity of anti-oxidant enzyme.

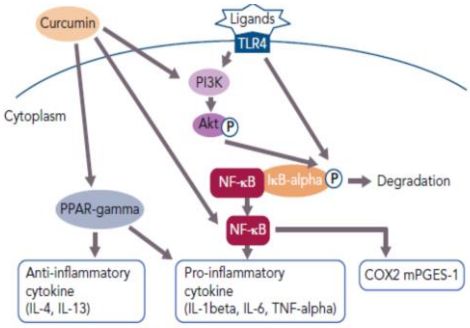

Figure 3. The Mechanism of Action or Curcumin on Arthritis (Kana et al., 2019).

Nutraceuticals like Curcumin are good participants in the management of osteoarthritis due to their safety and potential efficacy (Perkins et al., 2017). The term

"Nutraceuticals" is derived from two words; nutrition and pharmaceutical. It refers to food derived products that provide both health and medical benefits (DeFelice, 2002). The mechanism of action of Curcumin on osteoarthritis is shown below (figure 4).

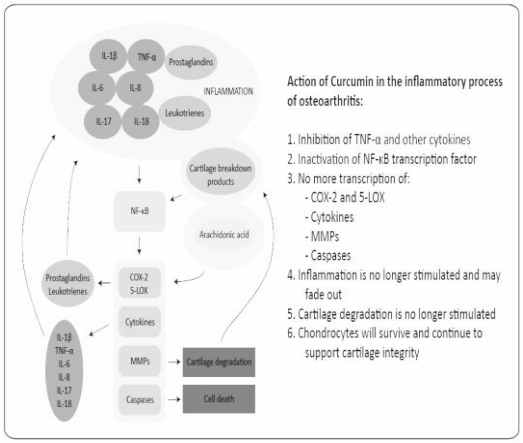

Figure 4. Action of Curcumin on osteoarthritis (Shukla et al., 2020).

Clinical Trials on the Effect of Curcumin on Arthritis

Curcumin is a phytochemical with anti-inflammatory and anti-oxidant property. Many evidences support the use of Curcumin in treatment of arthritis (Kunnumakkara et al., 2023). Therapeutically, Curcumin has exhibited promising potential in preclinical and clinical studies and it is currently used in human trials for the treatment of arthritis. In a randomized clinical trial, 45 patients diagnosed with rheumatoid arthritis were divided into three groups with patients receiving Curcumin (500 mg) alone daily and diclofenac sodium (50 mg) alone daily or the combination of Curcumin (500 mg) and diclofenac sodium (50 mg) daily (Chandran & Goel Chandran, 2012; Kou et al., 2023). After eight weeks, all the groups demonstrated improvement in disease activity scores (DAS). The greatest improvements in Disease Activity Score (DAS) was observed in "Curcumin only group" with fewer side effects compared to diclofenac sodium. The present clinical trial suggests that Curcumin could be used as a safe agent for the treatment of rheumatoid arthritis. Research on administration of curcumin for osteoarthritis is even more promising. Participants diagnosed with mild-to-moderate knee osteoarthritis who took curcumin supplement saw significant improvements in pain and inflammation after six weeks, compared to those who placebo was administered to.

Other studies have shown that curcumin is as effective as ibuprofen (a type of non-steroidal anti-inflammatory drug) for the management of osteoarthritis with fewer gastro-intestinal effects (Kuptniratsaikul et al., 2014). Clinical trials of Curcumin in treatment of arthritis have shown great results. A major setback in the use of Curcumin is its low oral bioavailability (Sohn et al., 2021).

Limitations of Curcumin in the Treatment of Arthritis and Solutions

Although, the anti-inflammatory effect of Curcumin is ideal, Curcumin has not been marketed as a therapeutic drug mainly due to the pharmacokinetic limitation of Curcumin (Peng et al., 2021). Most curcumin is quickly metabolized (via glucuronidation & sulfation) in the liver and intestine, leaving a very minute quantity detectable in tissues (Sharifi-Rad et al., 2020). Curcumin is hydrophobic, therefore, has poor bioavailability because of its fast metabolism in the liver and intestinal wall. After oral administration of curcumin, majority of it is excreted and only small amount enters the bloodstream for utilization. However, many researchers have developed various strategies to enhance Curcumin solubility and absorption (Zheng & McClements, 2020).

Piperine, extracted from black pepper, is one of the most popular natural bioavailability enhancer of Curcumin (Anshuly et al., 2020). Piperine increases the absorption of Curcumin by the stimulation of biliary excretion and by inhibiting the metabolism of curcumin. Curcumin is lipid soluble or lipophilic (Karlowicz-Bodalska et al., 2017). Hence, by increasing biliary excretion, it enhances lipid absorption, together with dissolved Curcumin. At a dose of 20 mg,

piperine enhances the absorption of Curcumin as much as 2000 times (Bertoncini-Silva et al., 2024).

There are several problems regarding bioavailability of oral curcumin, moreover, intravenous formulation has a greater absorption. Also, administering Curcumin with fat, phospholipids or in lipid processed nutraceutical forms can enhance its bioavailability. Other innovative forms include curcumin nanoemulsion, micellar curcumin, cyclodextrin curcumin, which also increases curcumin bioavailability in both nimal and human subjects (Rinkunaite et al., 2021). These new curcumin formulations not only enhance its bioavailability but also llows for longer circulation, better permeability and resistance to metabolic processes (Hegde et al., 2023).

Safety and Toxicity of Curcumin

Curcumin has been examined by many researchers for its safety through *in vitro* studies and clinical trials. The required daily dose of curcumin intake is 1000-2000 mg/day (Hewlings & Kalman, 2017). With a long-established safety record, curcumin has been found to be quite safe in humans up to 8 g/day. Interestingly, Doses higher than 8 g/day has been found to be intolerable in some patients. Despite its well-established safety, some reports have shown deleterious side effects of curcumin under certain conditions. Curcumin in the presence of copper and cytochrome p450 isoenzyme, leads to DNA fragmentation and base damage (Fuloria et al., 2022). About 150mg of curcumin per day did not show any side effects in humans (Sharifi-Rad et al., 2020). It has been reported that curcumin may alter fertility by inhibiting human sperm motility and also, it has a potential application as a novel intra-vaginal contraceptive (Sharifi-Rad et al., 2020). The same agent in turmeric that supports digestive health can lead to gastro-intestinal irritation when taken in large amounts (Prasad & Aggarwal, 2011). Curcumin stimulates the stomach to secrete more gastric acid, this can lead to peptic ulcer in some patients. Curcumin has anticoagulant and inhibitory effects on platelet aggregation (Hussain et al., 2022). Therefore, it is essential to consider this effect, as it can lead to serious consequences such as hemorrhages. However, curcumin has been proven to be extremely safe and well-tolerated, even at high doses (up to 8 g), without toxic effects. Moreover, the safety of curcumin is further explored, and long-term studies are needed for a better evaluation of possible adverse effects.

Conclusion

Curcumin, the vibrant compound found in turmeric, boasts remarkable anti-inflammatory and antioxidant properties that can be especially beneficial for those suffering from arthritis. It works by effectively lowering the levels of key inflammatory cytokines in the body, which are responsible for driving the inflammation associated with this condition. Furthermore, numerous clinical trials have demonstrated that curcumin is not only well-tolerated by participants but also exhibits minimal adverse effects. This safety profile makes it a compelling option for managing arthritis and enhancing overall joint health, allowing individuals to embrace relief without the worry of significant side effects.

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