CLINICAL REVIEW

Turmeric: Anti-inflammatory Effects and Evidence for Use in Osteoarthritis

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Abstract

Turmeric is a member of the ginger family Zingiberaceae that has been widely used as a medicinal plant for over 6,000 years. Curcumin is the active constituent of turmeric that has anti-inflammatory, antioxidant, antimicrobial, antirheumatic, and antidiabetic effects, as well as anti-proliferative and antineoplastic effects. Additionally, it exhibits hepatoprotective, nephroprotective, neuroprotective, and cardioprotective properties. The anti-inflammatory effects, particularly through the inhibition of, IL-1β and TNFα, underlie its use in treating osteoarthritis. Since the bioavailability of curcumin is low, other formulations, including a nanoparticle-dispersed product, have been engineered to increase bioavailability. Multiple randomized controlled trials have examined dietary curcumin use in the management of osteoarthritis, which is a degenerative disorder with inflammatory features. An increasing body of evidence demonstrates curcumin supplementation is an effective treatment for osteoarthritis with minimal adverse effects, and can be used as adjunct to standard therapies.

History of Turmeric/Curcumin

Turmeric is a rhizome that is a member of the ginger family Zingiberaceae native to Southeast Asia, and it has been used in India as a medicinal plant for over 6,000 years. Known as "the golden spice" and the "spice of life," the name derives from the Medieval Latin *terramerita* or "meritorious earth," a term used in early commerce to describe the powdered form. For centuries, turmeric has been utilized as a food preservative, coloring agent, and cosmetic, and in wound healing and religious rituals.[1] Ayurvedic medicine found applications for turmeric in respiratory, liver, and inflammatory illnesses, and in diabetic wound care. Ancient Hindu medicine applied it topically for sprains and swelling, and Traditional Chinese medicine administered turmeric for abdominal pain.[2] Europeans were first introduced to the benefits of turmeric in the 13th century by Marco Polo.[3]

Chemistry

Turmeric is comprised of three curcuminoids as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resin. The three curcuminoids are curcumin (Curcuma Longa), responsible for the vibrant yellow color and therapeutic effects of turmeric (77%), demethoxycurcumin (17%) and bidemethoxycurcumin (3%). Curcumin itself constitutes 2–5% of the ground turmeric powder[4] and was isolated in 1815 by Vogel and Pelletier.[5] A crystalline form was produced in 1870, and decades later, in 1935, the first study of the role of turmeric in human disease was published. In this experiment, subjects received an intravenous solution containing curcumin, which produced rapid gallbladder emptying, suggesting a potential benefit of curcumin in treating subacute, recurrent, or chronic cholecystitis.[2,6]

Curcumin is a polyphenol derivative that is lipophilic[4] and thus insoluble in water at acidic and neutral pH, and soluble in acetone, methanol, and ethanol.[5,7] Another unique property of curcumin is that it is rapidly decolorized by ultraviolet light exposure, and biological specimens require protection from light.[8]

Bioavailability

Curcumin's low aqueous solubility reduces its oral bioavailability. Interestingly, there is also low bioavailability with intravenous administration. Poor gut absorption, high rate of metabolism, and high systemic elimination all affect bioavailability. However, studies have shown that using higher oral doses of curcumin results in appropriate levels of curcumin necessary for clinical activity.[9,10] Coadministration with piperine, an extract of black pepper[11] or with lecithin can enhance solubility, and the former can increase plasma bioavailability by up to 2000%.[12,13]

Many other strategies have been innovated to increase oral availability, including use of nano/microparticles, solid dispersions, polymeric micelles, nanosuspensions, lipid-based nanocarriers, cyclodextrins, conjugates, and polymorphs. Mechanisms that can enhance bioavailability include increasing the intestinal stability of curcumin, changing the route of administration, and allowing for co-administration with other adjuvants.[10] Studies show that solid lipid particles, micellar systems, or hydrophilic nanoparticles can increase the concentration up to 15-20 fold.[12] A synthetic, nanoparticle complex, water-dispersible form of curcumin attained a higher bioavailability after one dose.[2,14]

Biological Effects

Curcumin has been described as a highly pleiotropic molecule with numerous biologic targets and mechanisms of actions. It is involved in modulation of enzymatic activity, growth factor

receptors, cofactors, and other molecules. Through these mechanisms, it exhibits antimicrobial, antioxidant, anti-inflammatory, antirheumatic, and antidiabetic effects, as well as anti-proliferative and antineoplastic effects. It has also demonstrated hepatoprotective, nephroprotective, neuroprotective, and cardioprotective properties. These characteristics provide the foundation for its therapeutic uses and the rationale for clinical trials.[2,4,6,7,15,16]

Anti-inflammatory Mechanisms

Animal studies demonstrate that increased cellular curcumin levels can modulate inflammatory mediators.[17] Use of cell lines and human studies have corroborated animal studies showing that curcumin modulates the immune response by: (1) down-regulating the activity of cyclooxygenase-2, lipoxygenase and inducible nitric oxide synthase enzymes; (2) down regulating mitogen-activated Janus kinases; and (3) inhibiting the production of tumor necrosis factor (TNF)-alpha, interleukins (ILs) 1, -2, -6.-8, and -12, monocyte chemoattractant protein and migration inhibitory protein.[5,6,8,9,16]

Safety

The United States Food and Drug Administration has labeled Curcumin as "Generally Recognized As Safe" (GRAS), a designation indicating that it is safe and effective for its intended use as a food additive, and that it does not require FDA review and approval for marketing. Curcumin use has now expanded globally and has been incorporated into medical supplements, drinks, soaps, and cosmetics.[6] Notably, in India, the average intake can reach 2000–2500 mg per day.[3]

Curcumin has shown a low risk safety profile. A 2011 safety analysis reviewed 40 clinical studies with over 800 participants and reported no significant toxicities.[7] Another study administered 8 g of curcumin daily for three months with minimal adverse effects.[18] Lao et al reported 12 g per day as well tolerated with minimal side effects in 30% of participants.[19] Side effects are gastrointestinal and include loose stools, reflux, bloating, and abdominal discomfort. Most adverse events occur with doses exceeding 4 g a day. Compliance is highest between doses of 2–4 g per day, and is limited by increasing capsule size.[2,7,18]

Impact of Curcumin Supplementation in Osteoarthritis

Because of its anti-inflammatory properties, curcumin has been studied in osteoarthritis, which has been reclassified as a chronic degenerative and inflammatory disease with elevated cytokine levels and possible association with systemic inflammation.[20,21] Inflammatory cytokines involved in osteoarthritis include IL-1β and TNFα, IL-6, IL-15, IL-17, and IL-18. The anti-inflammatory mechanisms of curcumin include inhibition of IL-1β and TNFα. Increasing numbers of randomized clinical trials demonstrate that curcumin has a beneficial role in the progression of disease in osteoarthritis.[22]

A 2019 review of sixteen randomized controlled trials examined curcumin efficacy in osteoarthritis. Yang et al concluded that curcumin supplementation appears to be an effective therapy for osteoarthritis with minimal-to-no adverse effects and can be used as an adjunct to standard of care therapies.[17] The clinical outcome measures used in these studies included the Western Ontario and McMaster Universities Arthritis Index (WOMAC), walking distance, visual analogue scale (VAS), Karnofsky performance scale, Lequesne's pain functional index (LPFI), Clinical Global Impression (CGI), and Knee injury and Osteoarthritis Outcome Score (KOOS). Of the 16 clinical trials, 14 randomized controlled trials reported significant improvements in multiple disease parameters. Trial length ranged from 6 to 40 weeks. Doses of curcumin administered were 100-2000 mg daily, and the mean curcumin dosage in studies demonstrating improvements in clinical or laboratory outcomes was 834 mg. In 13 of these studies, curcumin supplementation led to improvement in at least two clinical outcome measures, and 7 studies reported improvement of at least three clinical measures. Increased walking distance and decreased WOMAC scores were the most commonly reported positive clinical outcomes. Of five studies measuring inflammatory markers after curcumin supplementation in osteoarthritis patients, three studies showed a decrease in inflammatory markers and two reported no change in inflammatory markers. In four studies examining the efficacy of nonsteroidal anti-inflammatory drug (NSAID) use compared to curcumin supplementation in osteoarthritis patients, curcumin showed comparable efficacy and lower incidence of adverse effects, as reported by a decrease in use of NSAIDs and other analgesics and a decrease gastrointestinal complaints in the curcumin treatment group.[17] The most recent trials were published in 2014 by Kuptniratsaikul et al and Nakagawa et al.[23,24]

Kuptniratsaikul et al compared the effectiveness of curcumin with ibuprofen. The study randomized 367 patients with knee osteoarthritis to receive ibuprofen 1200 mg daily or curcumin 1500 mg daily for 4 weeks. Both groups demonstrated improved WOMAC pain and function scores with equal adverse events. However, in the ibuprofen group a significantly larger number of patients reported abdominal pain. The study concluded that curcumin supplementation for osteoarthritis is as effective as ibuprofen (NSAIDs) with less gastrointestinal side effects.[23] Nakagawa et al, also reported both reduction in use of NSAIDs and other analgesic medications in the curcumin treatment group as well decreased GI adverse effects. A 2009 study by Kuptniratsaikul et al had similar results, but cited no difference in GI complaints.[24]

In 2013 Kizhakkedath et al used a unique formulation of curcumin containing *Curcuma longa* and *Boswellia serrata* extracts and compared it to COX-2 inhibitor celecoxib.[25] The former group scored higher (positive outcome measures) in symptom evaluation and physical examination without difference between the groups in adverse effects.[2] Other systematic reviews by Daily et al[26] and Onakpoya et al[27] have shown benefits of

curcumin but were limited because of small sample[26] size and moderate risk of bias respectively.[27]

In a 2014 randomized, double blind, placebo-controlled prospective trial, the authors used a surface-controlled water-dispersible form of curcumin to increase bioavailability. In healthy volunteers, the area under the curve of the surface-controlled water-dispersible form of curcumin was 27 times higher than that of curcumin powder. The bioavailability is much greater than standard curcumin preparations. Fifty patients with osteoarthritis were randomized to either the water-dispersible form of curcumin versus placebo. Knee pain Visual Analog Scores (VAS) were significantly lower in the curcumin group, except in patients with the lowest initial VAS scores. Celecoxib dependence was also lower with curcumin administration, and no major side effects were observed.[24]

The number of studies evaluating the use of curcumin as a treatment for osteoarthritis continues to grow. A 2019 meta-analysis studied the efficacy and safety of curcumin use in osteoarthritis management and reached similar conclusions to previous work. The metanalysis included five studies and 599 patients. Curcumin was shown to significantly improve the WOMAC scores and VAS scores of osteoarthritis patients, without increasing the side effect rate which was 0.81 times the ibuprofen group.[28]

Conclusions

Curcumin is the active constituent of turmeric that exhibits anti-inflammatory effects. The anti-inflammatory properties, particularly through the inhibition of IL-1β and TNFα, underlie its use in treating osteoarthritis. Other formulations of curcumin, including the synthetic, nanoparticle-complex water-dispersed form of curcumin has been engineered to improve curcumin's intrinsically low bioavailability. Many randomized controlled trials have examined the use of dietary curcumin in managing osteoarthritis, which is a degenerative disease with inflammatory features. This review finds an increasing body of evidence demonstrating curcumin supplementation is an effective treatment for osteoarthritis. It has minimal adverse effects and can be used as an adjunct to standard therapies. Further studies with larger sample sizes and studies evaluating long term effects in osteoarthritis are future directions to consider.

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