Curcumin – The golden herb: From kitchen to the clinics – A review

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Background

Turmeric is traditionally used as an herbal remedy for a variety of diseases in India and China and as an over-the counter supplement worldwide.[1] Turmeric is a rhizomatous herbaceous perennial plant (Curcuma longa) of the ginger family (Fig. 1). The chemically active component of turmeric, curcuminoids, also called diferuloylmethane (Fig. 2), is the natural hydrophobic polyphenol.[2] The primary active constituent of turmeric, which is responsible for its vibrant yellow color, is curcumin, which was first identified in 1910 by Lampe and Milobedzka. The molecule is lipophilic and consists of two aromatic rings connected by two unsaturated carbonyl groups; therefore, it has poor solubility in water.[3]

For the treatment of topical inflammatory diseases, dried rhizomes of the plant Curcuma Longa is used for centuries.[4] Turmeric products have been characterized as "Generally recognized as Safe" (GRAS) by the Food and Drug Administration (FDA) in the USA, the Natural Health Products Directorate of Canada, and the Joint Expert Committee of the Food and Agriculture Organization/World Health Organization (FAO/WHO).[5] To the date, no significant toxicity has been found related to the use of curcumin, in various preclinical or human studies.[6,7]
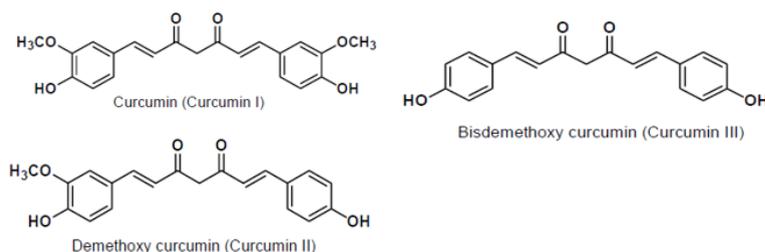

Fig. 1: Photograph of Curcuma Longa

Fig. 2: Chemical structure of Curcumin[5]

Pharmacology

Pharmacokinetics: In various preclinical studies carried out on the rodents for pharmacokinetic data related to Curcumin, it was established that curcumin undergoes a rapid and efficient metabolism. It was found that around 75% of the administered dose was excreted in feces. Thus, It was hypothesized that curcumin undergoes biotransformation during absorption in the intestinal tract and enterohepatic recirculation.[8]

From the data of pilot and phase I clinical study, it could derive that curcumin has low systemic bioavailability after the oral administration. After the oral administration, curcumin goes through efficient first-pass and some degree of intestinal metabolism, particularly glucuronidation and sulfation, which might be the possible reason for its poor systemic availability. A daily dose of 3.6 gm of curcumin could achieve detectable levels in the local colorectal tissue with little distribution in the other tissue beyond GIT. This further supports the local distribution of the traditional curcumin.[8]

Role of curcumin in Clinical Practice

Different mode of actions like anti-inflammatory, anti-oxidant, anti-carcinogenic, immunomodulatory, anti-infective and free radical scavenging in various literatures.

Curcumin has been shown to impart the positive effects in diseases of different systems in various clinical trials. (Fig. 3)
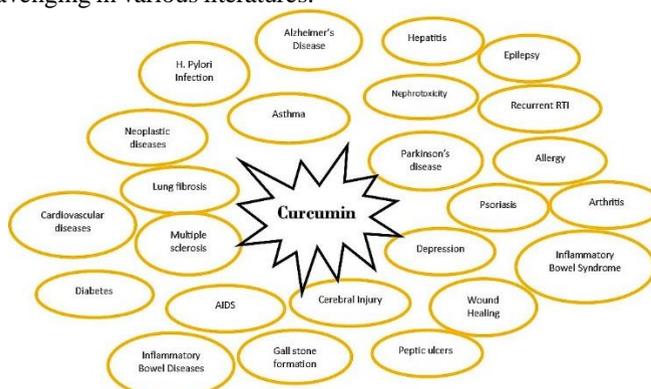

Fig. 3: effects of curcumin in various diseases

Inflammatory Bowel Diseases (IBD)

The most worked about condition for the use of curcumin is inflammatory bowel diseases. There have been many successful clinical trials also proving the role of curcumin in IBD. Ability of curcumin to interact with various molecular targets like receptor, growth and transcription factors, cytokines, enzymes and genes are responsible of favorable effects of curcumin in IBD.[9] The basic mechanism of inflammation involves the role of nuclear factor K beta (NFκβ) activation in the inflamed tissue. The NFκβ remains in the inactivated form in the normal tissue, which is maintained by a molecule called inflammatory kinase beta (IKβ). Any kind of insult to the cell leads to phosphorylation of IKβ, which resultantly leads to activation of NFκβ. Activated

NFκβ enters the nucleus of the cells leading to release of various pro-inflammatory cytokines like TNFα, IL-1, IL-6, IL-12 & IL-23. These cytokines are directly involved in the mucosal tissue damage typically occurring in IBD.[10] TNF-α is also able to up-regulate the production of NFκβ, resulting in a cyclical feedback loop of inflammation.[11]

Curcumin blocks NFκβ and prevents its activation. Blocking of NFκβ would down regulate the release of proinflammatory cytokines. Curcumin has been shown to attenuate colonic inflammation through direct inhibition of neutrophil chemotaxis and chemokinesis, and partly through inhibition of the chemokine expression.[11] (Fig. 4)
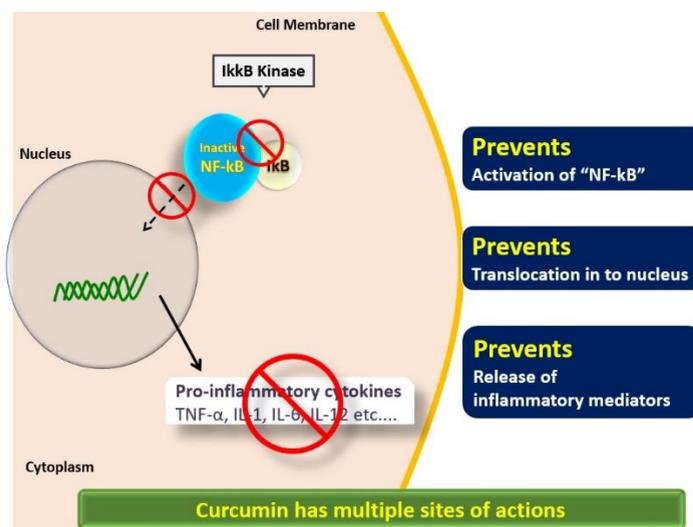

Fig. 4: Mechanism of action of curcumin in inflammation

Arthritis

Inflammatory process is the basic pathogenic factor associated with the symptoms of osteoarthritis and rheumatoid arthritis. In **osteoarthritis**, loss of articular

cartilage leads to various cellular and biochemical changes resulting in to secondary changes like bone remodeling, formation of osteophytes, change in the synovium, joint capsule, ligaments and meniscal tears. All

collectively leading to inflammation of the involved joint.[12] **Rheumatoid arthritis** is an auto immune disorder leading to chronic inflammation involving the synovial membrane of joint, which leads to various symptoms.[13]

Inhibition of NFκβ and various key regulators of inflammation like, cyclooxygenase-II, Lipo-oxygenase, activator protein-1, JNK, MAPK and PI3K/Akt contributes to protective effect of curcumin in arthritis. (Fig. 5) Inhibition of NFκβ by curcuminoids blocks the catabolic actions of down-stream products, most

importantly matrix metalloproteinase (MMP) enzymes. By inhibiting MMPs, curcuminoids promote extracellular matrix accumulation and prevent cartilage degradation. Curcumin also increases chondrocyte survival by down regulating the inflammation induced apoptosis. Free radicals produced by abnormal chrondrocytes, playing a pivotal role in osteoarthritis disease process, are scavenged by curcumin.[14]
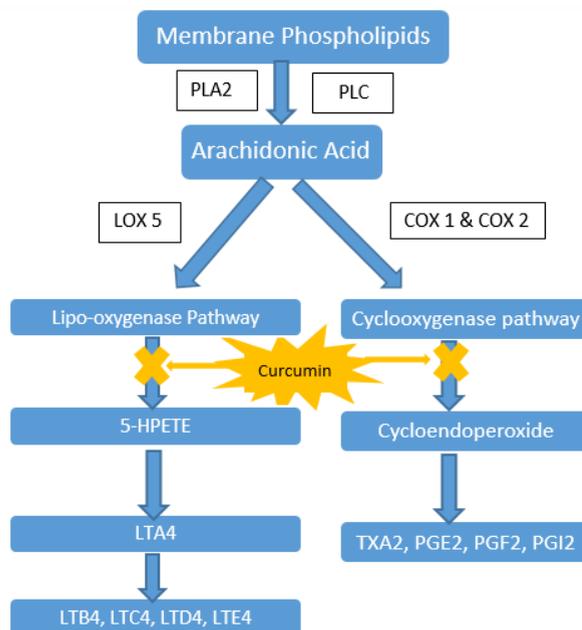
PL = Phospolipase; LOX = Lipooxygenase; COX Cyclocoxygenase; HPETE = Hydroperoxyeicosatetraenoate; LT = Leukotrienes; PG = Prostaglandin; TX = Thromboxane.

Fig. 5: Effects of Curcumin on lipoxygenase and cyclooxygenase pathway

Oncology

Curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis. It has also been found to possess proliferation inhibitory effects in many cancers. Curcumin has been shown to inhibit NFκβ, c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-α, interleukins and MMP-9.[15] Curcumin has got its effect on a variety of growth factor receptors and CAMs (cell adhesion molecules) which are involved in tumor growth, angiogenesis and metastasis.[15]

Curcumin in was found to present a safe and less toxic mode of treatment as an adjuvant therapy in head and neck **squamous cell carcinoma**.[15] In **breast cancer,** curcumin impedes tumor growth, malignant progression and spread.[16] It was also found that curcumin significantly inhibited the growth of human breast cancer cell MCF-7 by inducing apoptosis in a dose and time dependent manner, accompanied by a decrease in MCF-7 cell viability.[17] For the treatment of **Chronic Myeloid Leukemia**, Curcumin was found to be beneficial when

used in combination with Imatinib as compared to placebo.[18] Curcumin was also found to have a lot of potential to act as an adjuvant remedy in **liver cancer**. Curcumin as an adjunct would have a synergistic anti-cancer action and would also protect against the side effects of the current chemotherapeutic agents.[19] Many trials in **colorectal cancer** cases found that curcumin decreases glutathione – S – transferase activity, PGE2 production, M1G levels and serum TNFα. Curcumin was also found to be reducing the number and size of polyps. Curcumin reduced the lipid peroxidation and increased GSH content in patients with **pancreatic cancer**. In patients of **prostate cancer**, curcumin reduced the serum PSA content when used in combination with isoflavones.[20] In vitro trial of curcumin used against the hepatic cancer cells, it was derived that curcumin alone or in combination with cisplatin or doxorubicin exerted cell growth inhibitory and apoptotic effects. The effect may also be the result of changed levels of NFκβ.[21] In several studies carried out in mice, curcumin was shown to exhibit anticancer activities and a potential as a therapeutic in liver cancer.[22]

Diabetes

Curcumin was also found to decrease hepatic glucose metabolism, suppression of inflammatory response stemming from hyperglycemia, increase in GLUT2, GLUT3 and GLUT4 gene expression, and increase the glucose intake of cells. These actions contribute to the decrease in **insulin resistance** and blood sugar. Curcumin is also found to be decreasing blood sugar level via activation of peroxisome proliferator activated receptor ɣ in animals.[23]

For the patients of diabetes, use of curcumin, was found to be associated with reduction in fasting blood sugar from 140 to 70 mg/dl. Curcumin also improved endothelial function and reduced levels of oxidative stress and inflammatory markers. In the patients of diabetic nephropathy, curcumin attenuated proteinuria, TGFβ and IL 8.[20]

Hepatology

In various experimental trials, curcumin exhibited strong ***hepatoprotective effects*** against different hepatotoxic agents, like cholestasis, alcohol, xenobiotics and fatty infiltration. In animal experiments, curcumin was found to decrease lipid peroxidation, NFκβ binding, TNF-α, IL-12, monocyte chemotactic protein-1, macrophage inflammatory protein-2, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and nitrotyrosine formation in the alcoholic fatty liver. Curcumin also blocked endotoxin-mediated activation of NFκβ and suppressed the expression of cytokines, chemokines, COX-2, and iNOS in Kupffer cells.[24] Transforming growth factor- β (TGF-β) plays a pivotal role in the development of fibrosis in ***hepatic cirrhosis***. TGF-β plays a central role in initiation and promotion of activation of hepatic stellate cells to myofibroblasts during hepatic fibrogenesis. The TGF-β levels are also found to be elevated in human liver diseases ranging from hepatitis and cholestasis to cirrhosis. Curcumin blocks the profibrotic actions of TGF-β and there by prevents the fibrosis of liver significantly.[25] Curcumin was also found to increase the bile production by approximately 62%. It was observed that curcumin increases the excretion of bile salts, cholesterol and conjugate bilirubin and thereby decreasing the formation of ***gall stones***.[3] Curcumin was found to strongly inhibit the proliferation of ***Hepatitis B*** virus via down-regulation of PGC-1α, a starvation-induced protein that initiates the gluconeogenesis cascade and that has been shown to robustly co-activate the HBV transcription.[26]

Cardiovascular diseases

It has been established that the basic mechanism responsible for occurrence of Cardiovascular diseases are inflammation and oxidant stress, activation of pro-inflammatory cytokines, chronic transmural inflammation and C-reactive protein. Curcumin is said to protect against inflammation, cardiac hypertrophy and fibrosis by inhibition of p300-HAT activity and downregulation of NFκβ, GATA4 and other signal pathways. Lipopolysaccharides induced overexpression of inflammatory mediators in vascular smooth muscle cells of rat have been seen to be suppressed by curcumin. This is brought about via inhibition of TLR4-MAPK/ NFκβ pathways, and partly due to blockade of NADPH mediated intracellular reactive oxygen species production.[27] Curcumin is found to decrease ischemia via activation of JAK2/STAT3 signal pathway in animals.[23]

Obesity

Decrease in production of new adipocytes is brought about by curcumin via suppression of mitogen activated protein kinases. Curcumin also decreases the macrophage infiltration, leptin and leptin receptor levels in the adipose tissue. Production of adiponectin is increased due to effects of curcumin which is associated with positive effects against ***obesity***.[28,29] Curcumin also stops the differentiation of adipocytes and promotes antioxidant Properties. This diverse mechanism of action of curcumin brings about reduction in obesity and prevents adverse health effects caused by obesity.[30]

Neurological disorders

The oxygen derived free radical scavenging activity of curcumin is stated to be neuroprotective.[31] Antioxidant and anti-inflammatory properties of curcumin is said to be imparting various therapeutic benefits via reducing b-amyloid plaques, microglia formation and delayed deterioration of neurons in patients of **Alzheimer disease**.[32] The antioxidant properties of curcumin has been found to be associated with maintaining the levels of dopamine in substantia nigra and thereby decreasing symptoms of **Parkinson's disease**. Multiple sclerosis is a chronic inflammatory disease characterized by degradation of myelin sheath in CNS. Curcumin is shown to be regulating inflammatory cytokines and associated JAK-STAT, AP-1, and NFκβ signaling pathways. Th17 cells – an important factor associated with the pathophysiology of **multiple sclerosis** – are suppressed by curcumin via down-regulation of IL-6, TGF-b, IL-1b, IL-23, and STAT3-phosphorylation.[23]

Dermatological disorders

Free radical scavenging and NFκβ and cytokine suppressing properties of curcumin has been stated to be beneficial in various skin diseases like **dermatitis, psoriasis and scleroderma**.[23] Various skin disorders have been found to be benefitted by the protective properties of curcumin. Curcumin imparts its effects by on skin by reducing inflammation and scavenging free radicals via modulation of TGF β, NFκβ and mitogen activated protein kinase pathway. Phase II detoxification enzymes are also regulated by curcumin which are crucial for the detoxification reaction and oxidative stress. Curcumin is also said to affect the disease process of **psoriasis** by inhibiting keratinocyte prolilferation.[27]

Respiratory system

Various allergic reaction related to respiratory tract is seen to be decreased by curcumin. It is also found to be having positive effect against **asthma** via relaxation of the constricted air passages and increasing the antioxidant capacity.[23] Some in vivo and in vitro experiments suggest that it can help clear constricted airways and bring about rise in the antioxidant levels. Curcumin has beneficial effects in **allergies, bronchitis and asthma** by inhibition of NFκβ, TNF α and other proinflammatory cytokines along with vitamin IgE.[27]

Others

In a trial, 80% patients of **chronic anterior uveitis** were relieved of eye discomfort after a few weeks of therapy. When the curcumin was compared with phenylbutazone for the anti-inflammatory properties in post-operative inflammation, curcumin was found to be superior.[20]

Clinical Data

Role of curcumin for the treatment of various chronic inflammatory conditions like inflammatory bowel diseases, osteoarthritis and rheumatoid arthritis have been established in various clinical studies.

Table 1: Clinical Studies on curcumin in IBD

Author/Year	Type of study	No. of patients	Disease	Dose of curcumin	Duration	Markers studies	Findings
Holt et al (2005)	Pilot	10	UC CD	550 mg BID followed by 550mg TID for UC 360 mg TID followed by 360mg QID for CD	2 months for UC 3 months for CD	Global scale (UC) CDAI ESR (CD)	Improved global scale (p<0.02, UC) 55-point decrease in CDAI & 10 mm/h drop in ESR (CD)
Hanai et al (2006)	Double blind, placebo controlled	89	UC	1gm BID	6 months	CAI and EI	Improved CAI (p<0.038) and EI (p<0.0001)
Singla et al (2014)	Randomized, double blind, pilot study	45	UC	140mg/20ml curcumin enema	8 weeks	UCDAI, Endoscopic activity	In PPA, clinical response – 92.9%, clinical remission – 71.4%, Endoscopic improvement – 85.7%
Lang A et al (2015)	Randomized, placebo controlled, multi-centric, double blind	50	UC	3 gm/day oral	1 month	SCCAI, Clinical and endoscopic response	53.8% patients achieved remission Clinical response – in 65.3% Endoscopic response – in 38%
Banerjee et al (2017)	Randomized, placebo-controlled study	47	UC	50 mg BID (Valdone)	3 months	Clinical response, Endoscopic remission	Clinical response 63.1% Endoscopic remission – 26.3%
Masoodi et al (2018)	Randomized double-blinded controlled trial	56	UC	80 mg TDS	4 weeks	SCCAI, Clinical Response	Significant reduction in symptoms in study group, Mean SCCAI score Vs Placebo - (1.71 ± 1.84 vs 2.68 ± 2.09, p = 0.050).

BID = Two times a day; TID=three times a day; QID=four times a day; CDAI=Crohn's Disease Activity Index; ESR = Erythrocyte Sedimentation Rate; CAI = Clinical Activity Index; EI = Endoscopic Index; SCCAI = Simple Clinical Colitis Activity Index; UCDAI = Ulcerative Colitis Diseases Activity Index; PPA = Per protocol analysis

Clinical studies on IBD (Table 1)

Various human trials have been carried out till now in order to evaluate the effects of curcumin in IBD. All of the studies have shown positive results and further large scale studies in order to strengthen the data have been strongly advocated by the authors.

Holt et al,[33] carried out a small, open labeled pilot study on 5 patients of ulcerative colitis and crohn's disease each in 2005, in order to evaluate the role of curcumin in reduction of inflammation along with reduction of other concurrently given medication.

1. All the ulcerative colitis patients were given 550 mg curcumin twice daily for one month and then after thrice daily for next month. All the patients improved by the end of the study as judged by a global score (P < 0.02). The major change was found in the number and quality of stool. Two subjects eliminated their pre-study 5-Aminosalicylic acid (ASA) medications, two subjects reduced their medications (including termination of the prednisone therapy in one subject), and one continued taking 5ASA suppositories.

2. The patients with crohn's disease, were given 360 mg thrice a day for 1 month and for four times a day for next two months. The Crohn's Disease Activity Index (CDAI) scores for all completed subjects fell, with a mean reduction of 55 points; sedimentation rate fell as well, with a mean reduction of 10 mm/hr. During follow up visits, four patients showed improvement in the clinical symptoms in terms of more formed stools, less frequent bowel movements, less abdominal cramps and pain.

In another study, Hanai et al,[34] assessed the role of curcumin as a maintenance therapy in a randomized, multicenter, double-blind, placebo-controlled trial. Out of total 89 patients recruited for trial, 45 patients in the curcumin group received 1 gm curcumin twice a day whereas 44 patients in the control group received placebo along with sulphasalazine (SZ)/mesalamine for 6 months. The patients received only SZ or mesalamine during the six-month follow-up and were followed throughout the study period. 4.65% (2 out of 43) patients in the curcumin group relapsed as compared to 20.51% (8 out of 39) in the control group (P=0.040). In intension to treat analysis, recurrence rates showed significantly difference between curcumin and placebo group (P = 0.049). Curcumin was also found to improve both Clinical Activity Index (p = 0.038) and Endoscopy Index (P = 0.0001).

The role of curcumin in combination with mesalamine for induction of remission in patients with mild to moderate ulcerative colitis was established by Lang et al[35] in a multicenter randomized, placebo-controlled, double-blind study. Out of 50 mesalamine-treated patients with active mild-to-moderate Ulcerative Colitis, 26 were given curcumin (3 gms/day) and 24 were given identical placebo for 1 month. In the intention-to-treat analysis, 53.8% patients (14 out of 26) receiving curcumin achieved clinical remission at week 4, compared with none of the patients receiving placebo (P=0.01). Clinical response (reduction of ≥3 points in Simple Clinical Colitis Activity Index) was achieved by 65.3% patients (17 out of 26) in the curcumin group as compared to 12.5% patients (3 out of 24) in the placebo group (P < .001). Endoscopic remission (partial Mayo score ≤1) was observed in 8 out of 22 patients evaluated in the curcumin group (38%), compared with 0 out of 16 patients evaluated in the placebo group (P=0.043). Adverse events were rare and comparable between the two groups.

Singla V et al[36] carried out the a randomized, placebo-controlled, pilot study to evaluate the role of curcumin for induction of remission in mild to moderate left sided ulcerative colitis. 45 patients were randomized to receive either curcumin enema plus oral 5-ASA or placebo enema plus oral 5-ASA. The duration of study was 8 weeks. 56.5% of the patients in the curcumin group responded to the treatment as compared to 36.4% patients in the placebo group (P=0.175). At the end of the study duration, clinical remission was observed in 43.4% of the patients in curcumin group as compared to 22.7% patients in placebo group (P = 0.014). While assessing the improvement on endoscopy, 52.2% of the patients in curcumin group showed positive response as compared to 36.4% patients in control group (P = 0.29). Per protocol analysis revealed significantly better outcomes in curcumin group in terms of clinical response (92.9% vs. 50%, p = 0.01), clinical remission (71.4% vs. 31.3%, p = 0.03), and improvement on endoscopy (85.7% vs. 50%, p = 0.04).

In another randomized, placebo controlled trial, conducted at Asian Institute of Gastroenterology, India, the novel bio-enhanced curcumin (Valdone) given along with mesalamine appeared to be safe & effective for induction of remission in active mild to moderate Ulcerative Colitis. It was also observed that Valdone was required to be given in smaller doses than previously studied conventional curcumin. A total of 47 patients with mild to moderate ulcerative colitis patients were randomly assigned to receive either 50mg bio enhanced curcumin (Valdone) BID (n=22) or an identical placebo (n=25) for 6 weeks of duration. The standard of care with oral & rectal mesalamine was continued in both groups. Clinical response at the end of the study duration was achieved by 42.1% (8 out of 22) patients in curcumin (Valdone) group as compared to 13.04% (3 out of 25) patients in control group (p=0.0414). After 6 months, 63.1% (12 out of 19) in study group and 21.73% (5 out of 23) patients in control group showed clinical response (p=0.0087). After 6 weeks, endoscopic remission was observed in 10.5% (2 out of 19) patients in study group compared with none out of 23 patients in the control group (p = 0.228). At the end of 3 month, 26.3% (5 out of 19) patients in study group showed endoscopic remission compared to none of 23 patients in control group (p = 0.057).[37]

Masoodi et al[38] conducted a randomized double-blinded controlled trial to evaluate the effectiveness of a nanoformulation of curcuminoids in the treatment of ulcerative colitis. 56 patients, confirmed with diagnosis of mild to moderate UC were randomized to receive either 80 mg of curcuminoids nanomicelles three times a day plus mesalamine (3 g/24 hours, orally) or placebo plus mesalamine (3 g/24 hours, orally) for a period of four weeks. The severity of disease was assessed at baseline and at the end of the second and fourth weeks of the treatment according to the Simple Clinical Colitis Activity Index (SCCAI). At the end of four weeks, the score for urgency of defecation was found to be reduced significantly more in the study group. The patients in the study group experienced better general condition than the control group at the end of the study. The mean SCCAI score was significantly lower in the patients received curcuminoids nanoparticles in comparison to the control group (1.71 ± 1.84 vs 2.68 ± 2.09, $p = 0.050$). It was concluded in the study that curcuminoid nanomicelles as an add-on therapy to conventional mesalamine treatment in patients of UC significantly improves the symptoms including reduction in frequency of urgent defecation and clinical activity.

Table 2: Clinical studies on Curcumin in arthritis

Author/Year	Type of study	No. of patients	Disease	Dose of curcumin	Duration	Markers studies	Findings
Panahi Y et al	Randomized, double blind, placebo controlled, pilot	40	OA	1500mg/day	6 weeks	WOMAC VAS LPFI	Significantly greater reduction in all the indices in the curcumin group. Significant reduction in the usage of concurrent Naproxen in curcumin group.
Kuptniratsaikul V et al	Randomized, multicentric	367	OA	1500mg/day	4 weeks	WOMAC	Significantly greater reduction in WOMAC scores in the curcumin group. Curcumin – non inferior to Ibuprofen and lesser side effects
Kuptniratsaikul V et al	Randomized	107	OA	2 gm/day	6 weeks	Pain on level walking Pain on stairs Knee functions	Significant improvement in the scores for curcumin group.
Belcaro G et al	Observational	124	OA	500mg/day	4 months	KI WOMAC Treadmill test	Significant improvement in all the scores in curcumin group Walking distance increased in the treadmill test Reduction in the need of concomitant drugs
Madhu K et al	Randomized, placebo controlled	120	OA	500 mg BD	42 days	WOMAC CGIC VAS	All the scores were significantly reduced in curcumin group Tolerability, acceptability better
Chandran B et al	Randomized pilot	45	RA	500 mg BD	8 weeks	DAS ACR	Highest percentage of improvement was found in curcumin group. Better than diclofenac

OA = Osteoarthritis; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = Visual Analogue Scale; LPFI= Lequesne's pain functional index; KI = Karnofsky Index; BD = two times a day; CGIC = Clinician Global Impression Change Scale; RA = Rheumatoid Arthritis; DAS = Disease Activity Scores; ACR = American College of Rheumatology criteria.

Clinical Studies on Osteoarthritis (Table 2)

Panahi Y et al,[14] studied the effects of curcumin in osteoarthritis in a randomized, double blind, placebo controlled, pilot study carried out on 40 mild to moderate osteoarthritis patients. 19 patients were assigned to curcumin group who received 1500 mg curcumin per day and 21 patients were assigned to receive the identical placebo for the duration of 6 weeks. The efficacy measures used to assess the response were changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analogue scale (VAS) and Lequesne's pain functional index (LPFI) scores. A significantly greater reduction in WOMAC (p = 0.001), VAS (P<0.001) and LPFI (p=0.013) scores was observed in the treatment group when compared with placebo. With respect to WOMAC subscales, significant improvements in the pain and physical function scores (P<0.001) were found with curcumin group. With respect to LPFI and VAS scores, curcuminoid group showed significant reductions by the end of trial (p<0.001) whilst no significant change occurred in the control group (p>0.05). During the trial, patients were allowed to use Naproxen as and when required. The proportion of patients in whom the use of naproxen was reduced by the end of trial was significantly greater in the study group (84%) as compared to placebo group (19%) (p<0.001). No considerable side effects were observed in either of the groups.

In a multicentric study carried out by Kuptniratsaikul V et al[39] 367 patients of primary osteoarthritis with pain score of 5 or higher were randomized to a group receiving either ibuprofen 1200 mg/day (n=182) or 1500 mg/day curcumin (n=185) for 4 weeks. The main outcomes were WOMAC total, WOMAC pain, WOMAC stiffness and WOMAC function scores. At weeks 0, 2 and 4, the mean of all WOMAC scores showed significant improvement when compared with base line in both groups. The curcumin group was found to be non-inferior to ibuprofen group, when tested for the mean difference of WOMAC total, WOMAC pain and WOMAC function scores at week 4 adjusted by values at week 0 (P=0.010, P=0.018, and P=0.010, respectively) except for the WOMAC stiffness subscale, which showed a trend towards significance (P=0.060). The number of patients who developed adverse effects was comparable between two groups. Number of events of abdominal pain/discomfort were significantly higher in ibuprofen group (p = 0.046). Two third of the subjects rated themselves as improved in global assessment. 96-97% of the patients were satisfied with the treatment.

Kuptniratsaikul V et al[40] studied the efficacy and safety of curcumin in 107 patients of osteoarthritis with pain scores of ≥ 5. 52 patients were randomized to receive 2 gm/day curcumin and 55 patients were subjected to receive 800 mg/day ibuprofen for the duration of 6 weeks. Improvement in pain on level walking, pain on stairs and knee functions were considered as the main outcomes, which were assessed by time spent during 100mt walk and going up and down a flight of stairs. At 0, 2, 4 and 6 weeks, the mean scores of the aforementioned outcomes were significantly improved in the curcumin group when compared to the control group. No difference was found in those parameters between both the groups except pain on stairs (p = 0.016). No significant difference between the groups was found with respect to the occurrence of adverse events.

The role of curcumin in osteoarthritis was compared with chondroitin used along with glucosamine by Belcaro G et al[41] in total of 124, grade 1-2 knee osteoarthritis patients in a 4 month duration observational study. 63 patients received lecithin delivery form of curcumin along with glucosamine whereas 61 patients received chondroitin sulphate + glucosamine. Taking the Karnofsky Index and WOMAC scores in account, the patients of the curcumin group showed significantly higher rates of improvement in comparison to the comparator group. After the end of 1 month, the waking distance at treadmill test was also significantly higher in the curcumin group. Same result was sustained until the end of 4 months. At the end of the study, both group showed reduction in the need of concomitant drugs and medical attention, this reduction was more evident in the curcumin group patients. It was concluded in the study that 4 month administration of curcumin along with glucosamine results in a faster onset of action and improved outcomes than the administration of chondroitin sulphate along with glucosamine.

A randomized, placebo-controlled trial was carried out on the patients with painful knee osteoarthritis by Madhu K et al,[42] in order to evaluate the safety and efficacy of curcumin for the treatment. A total of 120 patients were randomized to four various group (n = 30), one receiving placebo (400 mg BD), second received curcumin (500 mg BD), third received glucosamine sulphate (750 mg BD) and the last group received combination of curcumin and glucosamine sulphate for 42 days. The efficacy of the treatment was assessed during 21st and 42nd day. The patients receiving curcumin showed significant decrease (p < 0.05) in the post treatment scores measured using VAS, WOMAC and CGIC (Clinician Global Impression Change scale). The use of the rescue medicine was significantly (p<0.01) reduced in the curcumin group along with clinical and subjective improvement in the curcumin group as compared to placebo. During the trial period, the tolerability and acceptability of the curcumin was found to be better.

Chandran B et al[43] studied the efficacy and safety of curcumin in a randomized pilot study, for the treatment of active rheumatoid arthritis. A total of 45 patients with active RA were randomized to three groups with patients receiving either curcumin (500mg), Diclofenac sodium (50mg) or the combination of both twice daily for 8 week. Patients in the all three groups showed statistically

significant changes in Disease Activity Scores (DAS). With respect to overall DAS and ACR (American College of Rheumatology criteria) scores, the curcumin group showed the highest percentages of improvement. These scores were significantly better than the patients in the diclofenac sodium group. The mean Visual Analogue Scores for pain in all the groups were comparable at the baseline with highest reduction in the scores from baseline be found in curcumin group (59.9%). It was concluded in the study that efficacy of the curcumin in active RA was better than that provided by diclofenac sodium. It was established in the study that curcumin when given along with diclofenac sodium, it lacks synergetic or additive efficacy. The curcumin treatment was found to be safe and not related to any adverse events.

Limitations

Despite the encouraging biological effects of traditional curcumin, the usage of the curcumin for the treatment of human ailments has been handicapped by its poor bioavailability. Being a hydrophobic molecule, low water solubility and extensive presystemic metabolism, the pharmacokinetics of the traditional curcumin is unfavourable.[44] The positive results of the various clinical studies may be because of the higher doses used for the treatment in order to overcome the poor bioavailability issue. The higher doses used may be one of the causes for the GI intolerance observed with the curcumin usage.

New advancements

Poor bioavailability has been stated as major hurdle in the usage of the curcumin. Various strategies have been implicated in order to improve the oral bioavailability of curcumin.

Different strategies have been pursued to improve the absorption of curcumin including nanocrystals, emulsions, liposomes, self-assemblies and nanogels.[45] When curcumin was administered in animals along with Piperine, it was shown to increase the absorption of curcumin by 1.5 folds. When curcumin was administered in a complex form with phospholipid molecules, it increased the absorption by 3.4 folds.[46] 9 folds increase in absorption of curcumin was observed in mice when it was given in a formulation with a micellar surfactant.[47] A micro emulsion system of curcumin has been shown to increase the relative absorption in rats by 22.6 folds.[48] PLGA (polylactic co-glycolic acid) and PLGA – polyethylene glycol (PEG) blend nanoparticles increased the curcumin absorption by 15.6 and 55.4 fold respectively in rats.[49]

Benerjee R et al[37] used a new self-emulsifying formulation (SMEDDs – Self Micro Emulsifying Drug Delivery System) of the curcumin which converts it in to nano-sized particle, for the treatment of UC. This change in the formulation increased the bioavailability of the curcumin to many folds, even after giving at lower doses (100mg BD).

Safety evaluation

Use of curcumin as a pharmacological agent has been found to be overall safe in profile. Given in doses as high as 8 gm/day has not been associated with toxicity. Common side effects found in association with the use of curcumin are dryness of mouth and throat, nausea, gastric irritation and diarrhea. These gastro intestinal side effect may be the result of the higher doses of the traditional curcumin used commonly. The supplemental doses of curcumin (2gm/day) have been reported to increase the risk of renal stone.[50] According to JECFA (The Joint United Nations and World Health Organization Expert Committee on Food Additives) and EFSA (European Food Safety Authority) reports, the Allowable Daily Intake (ADI) value of curcumin is 0–3 mg/kg body weight.[18] Piperine, used along with curcumin to increase its bioavailability, has been shown to inhibit the hepatic AHH, UDP-glucuronyltransferase, P-glycoprotein and CYP3A4 activities which may in turn affect the metabolism of several drugs.[51,52]

Conclusion

In conclusion, multiple pharmacological actions of curcumin have already been established in various literature proving its role for the treatment of different chronic inflammatory conditions. Various mechanisms and target sites have been proposed in literatures regarding the execution of the claimed effects of curcumin. There are abundance of evidences supporting the effects of curcumin on inhibition of NFkB in inflammatory process.

As it has been established in multiple clinical studies, curcumin has shown satisfactory results for the improvement in the various disease condition. For IBD, curcumin effectively reduced the duration of treatment for the induction of remission as well as it significantly reduced the chances of relapses. Studies carried out in arthritis patients established that curcumin effectively reduced the overall symptoms of the disease and improved the quality of life of the patients. The overall safety profile of the use of curcumin was also found to be very satisfactory. Due to the proven poor bioavailability of the curcumin, in most of the trials, the dose of curcumin used was very high. This may be the reason for GI intolerability associated with curcumin usage. However, newer formulations of curcumin are available in order to overcome the poor bioavailability of the traditional curcuminoids.

There is a need of large scale, double blind trials comparing the efficacy of curcumin to the standard of care treatment as well as the effectiveness of newer formulations of curcumin. These features make curcumin very promising molecule for the treatment of various chronic inflammatory diseases for which current therapies are unsatisfactory.

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