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CURCUMIN: A YELLOW MAGICAL SPICE OF KITCHEN FOR TREATMENT OF RHEUMATOID ARTHRITIS

Kapil Kumar[1]*, A.K. Rai[2]
[1]Institute of Pharmacy NIMS University, Jaipur, 303121-Rajasthan, India
[2]Pranveer Singh Institute of Technology, Kanpur, U.P. India

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*Email: kapil5november@gmail.com

ABSTRACT
Over many millennia, natural products were the only means to treat diseases and injuries. With the advances in molecular biology and combinatorial chemistry during the past few decades, natural products have taken a secondary role in drug discovery.
Curcumin is a yellow pigment isolated from the rhizome of perennial herb Curcuma longa family Zingiberaceae and has been popularly used as a food additive in kitchen. It has been extensively used in traditional medicine in India and other parts of the world. Rheumatic diseases have affected mankind since ages and are one of the commonest inflammatory conditions in developing countries. Arthritis is caused by continuous inflammation, which is a result from a complex series of actions and/or reactions triggered by the body's immunological response to tissue damage.
In this review, available treatment and role of Curcumin for its treatment has been explored. The purpose of this review is to provide a brief summary of the current knowledge of the effects of curcumin as reported in basic science publications, clinical trials, and previous reviews.
Curcumin has the potential for the development of modern medicine for the treatment of various diseases.
Key Words: *Curcuma longa*, Rheumatoid Arthritis, perennial herb, Zingiberaceae, Rhizomes.

INTRODUCTION

Plants are nature's remedies and have been used on earth since ancient times by human beings for food and medicine. Today there are global movements towards finding of medicaments in plants; the basic thought behind this is treatment of each disease is hidden in nature. There is only need to find them on lab scale and after successive preclinical and clinical trial to bring it in market in a suitable pharmaceutical dosage form for mankind.

The plant *Curcuma longa linn* (Zingiberaceae) commonly called as Indian saffron. Turmeric in English, Haridra in Sanskrit, Haldi in hindi, paspu in telugu, manjal in Tamail, Halada in Guajarati, Halade in Marathi, Mannal in Malayalam and Arishina in Kannada[1]. Curcumin [(1E, 6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the active ingredient of the spice turmeric, used in cooking in India and other regions of Asia (figure 1). It has a long history as an herbal remedy for a variety of diseases and was used in Indian and Chinese traditional medicine as early as 700 A.D.[2].

The exact origin of turmeric or species is not known but it originates from south or south East Asia, most probably from western India. Turmeric has been used in Asia for thousands of years in food, preservation of food, and as traditional medicine.

It needs a considerable amount of annual rainfall to thrive. Turmeric is a sterile plant and does not produce seed. It is commonly distributed in stream banks in marshy places[3].

The crop cannot stand water logging or alkalinity in the soils.

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. A joint is where two bones meet to allow movement of body parts. Autoimmune diseases are illnesses that occur when the body's tissues are mistakenly attacked by their own immune system. The joint inflammation of rheumatoid arthritis causes swelling, pain, stiffness, and redness in the joints (figure 2). The inflammation of rheumatoid disease can also occur in tissues around the joints, such as the tendons, ligaments, and muscles. In some people with rheumatoid arthritis, chronic inflammation leads to the destruction of the cartilage, bone, and ligaments, causing deformity of the joints. Damage to the joints can occur early in the disease and be progressive. About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men. Onset is most frequent between the ages of 40 and 50, but people of any age can be affected. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated[4].Moreover, studies have shown that the progressive damage to the joints does not necessarily correlate with the degree of pain, stiffness, or swelling present in the joints[5].There are more than 100 different arthritides, however, the 3 most commonly occurring subtypes are gout, osteoarthritis (OS), and RA[6].

Rheumatoid Arthritis

RA is a chronic pro-inflammatory disease that is characterized by hyperplasia of the synovial fibroblasts, which is partly the result of decreased apoptosis, and joint stiffness and swelling, often manifesting in a symmetrical pattern on both sides of the body. RA occurs in women more often than men (75% vs 25%), suggesting the role of hormones in its etiology. There is main roles of inflammatory cytokines, such as TNF (tumor necrosis factor), IL-1 (interleukin-1), IL-6, and chemokines; inflammatory enzymes such as COX-2 (cyclo-oxygenase-2), 5-LOX (lipo-oxygenase), and MMP-9 (Matrix metalloproteinase-9); and adhesion molecules in the pathogenesis of arthritis[7].

This entire process is characterized by inflammation. Mast cells, which secrete pro-inflammatory cytokines, migrate into the synovium, along with by-products of other immune cells, including lymphocytes, macrophages, and fibroblasts. The result is an increase in cytokines, which is responsible for the symptoms of RA. The exact mechanism of bone and cartilage destruction during RA is not completely understood. One theory suggests that the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor-alpha (TNF-alpha) stimulate the production of enzymes that degrade cartilage and inhibit the production of new cartilage and also contribute to the local demineralization of bone by activating osteoclasts[8].

Symptoms

RA usually affects joints on both sides of the body equally. Wrists, fingers, knees, feet, and ankles are the most commonly affected. The disease often begins slowly, usually with only minor joint pain, stiffness, and fatigue.

Joint symptoms may include:

1. Morning stiffness, which lasts more than 1 hour, is common. Joints may feel warm, tender, and stiff when not used for an hour.
2. Joint pain is often felt on the same joint on both sides of the body.
3. Over time, joints may lose their range of motion and may become deformed Chest pain when taking a breath
4. Dry eyes and mouth
5. Eye burning, itching, and discharge
6. Nodules under the skin
7. Numbness, tingling, or burning in the hands and feet.

Modern Therapy for treatment of Rheumatoid Arthritis

RA usually requires lifelong treatment, including medications, physical therapy, exercise, education, and possibly surgery. Early, aggressive treatment for RA can delay joint destruction. The goals of management of patients with RA are to control pain and swelling, delay disease progression, minimize disability, and improve quality of life (figure 3).

1. Drugs and their limitations

I. Disease modifying anti-rheumatic drugs (DMARDs) [9]**-** These drugs are the first drugs usually tried in patients with RA. These drugs modify the body's response to infection and disease. The body naturally produces small amounts of these substances. These drugs are developed in lab scale for treatment. Methotrexate, Leflunomide and sulfasalazine is the most commonly used DMARD for rheumatoid arthritis may also be used. Gold salts are considered second line drug.

Limitations - All these drugs can cause liver and kidney toxicity. Other side effects include rashes, stomach upset, and itching.

II. Anti-inflammatory medications[10]: These include aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, and celecoxib **Limitations** - Over-the-counter NSAIDs, such as naproxen, ibuprofen, and others, operate by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2), which convert arachidonic acid to pro-inflammatory PGE2. Side effects of over-the-counter NSAIDs include gastrointestinal upset because the COX-1 enzyme is also partly responsible for maintaining the mucosal lining of the stomach. These drugs can also cause stomach problems, such as ulcers and bleeding, and possible heart problems. Celecoxib is labeled with strong warnings about heart disease and stroke.

III. Antimalarial medications[11]**:** This group of medicines includes hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine), and is usually used along with methotrexate. **Limitations** -All these drugs can cause liver and kidney toxicity. Other side effects include rashes, stomach upset, and itching. They are sometimes recommended for patients who cannot tolerate NSAIDs.

IV. Corticosteroids[11]**:** Prednisone, a corticosteroid, is used mainly as a treatment for RA. **Limitations**- Corticosteroids have significant side effects and should be used with great caution. Injections should be spaced months apart to avoid joint degeneration. Long-term systemic corticosteroid use is associated with a wide range of metabolic abnormalities, including weight gain, osteoporosis, stress fractures, stretch marks, and adrenal gland failure.

V. Immunosuppressive drugs[12]**-** These drugs are sometimes used in RA to suppress the immune response that causes disease progression. Common immunosuppressive drugs used in RA include azathioprine, leflunomide, cyclosporine, and cyclophosphamide. **Limitations**- These drugs have a variety of toxic side effects, including liver damage and the increased risk of opportunistic infection because of a depressed immune system.

VI. Narcotics[10]**-** Narcotics such as codeine and morphine are sometimes used to control pain in acute flare-ups.

Limitations Use of these drugs may cause drug dependency.

VII.Analgesic[11]**-**

They are pain relievers only for example paracetamol, codeine, aspirin or a combination. **Limitations**-Aspirin (NSAID) may irritate the stomach. Codeine can cause constipation and nausea.

2.Biological Agents[13] Biologic drugs are designed to affect parts of the immune system that play a role in the disease process of rheumatoid arthritis. They may be given when other medicines for rheumatoid arthritis have not worked. At times, your doctor will start biologic drugs sooner, along with other rheumatoid arthritis drugs. Most of them are given either under the skin (subcutaneously) or into a vein (intravenously). There are different types of biologic agents.

I. White blood cell modulators- Abatacept and rituximab

II. Tumor necrosis factor (TNF) inhibitors - Adalimumab, etanercept, infliximab golimumab and certolizumab

III. Interleukin-6 (IL-6) inhibitors- Tocilizumab

Risk factors associated with biological products-Infections from bacteria, viruses, and fungi, leukemia or lymphoma, psoriasis

3. Surgery[14] **-**Occasionally, surgery is needed to correct severely damaged joints .Surgery may include:

- Removal of the joint lining (synovectomy)
- Total joint replacement in extreme cases; may include total knee, hip replacement, ankle replacement, shoulder replacement, and others.

4. Physical Exercises-Physical exercises can delay the loss of joint function and help keep muscles strong. Therapists use special machines to apply deep heat or electrical stimulation to reduce pain and improve joint movement. Joint protection techniques, heat and cold treatments, and splints or orthotic devices to support and align joints may be very helpful. Frequent rest periods between activities, as well as 8 to 10 hours of sleep per night, provide benefit to patient[15].

Curcumin and Rheumatoid Arthritis

Mechanism of Action

Curcumin has substantial anti-inflammatory activity. It inhibits several enzymes involved in the onset of inflammation, including cyclooxygenase-2, or COX-2. By suppressing this enzyme, curcumin reduces production of prostaglandins, compounds that trigger inflammation and cause swelling and pain. Curcumin has been shown in the test tube to inhibit the COX-2, PLA2 and 5-LOX enzymes involved in the inflammatory response (figure 4). In a study to report anti-rheumatic activity of curcumin in human subjects' short-term double blind crossover study was performed on 18 patients with "definite" rheumatoid arthritis to compare the anti-rheumatic activity of curcumin (1200 mg/day) with phenylbutazone (300 mg/day). Subjective and objective assessment in patients who were taking corticosteroids just prior to the study showed significant improvements in morning stiffness, walking time, and joint swelling, following two weeks of curcumin therapy[16]. In another study the effect of curcumin in articular chondrocytes was examined. IL-1, the main cytokine instigator of cartilage degeneration in arthritis, induces MMP-3 and MMP-13 RNA and protein in chondrocytes through the activation of mitogen-activated protein kinase (MAPK), AP- 1, and NF-κB transcription factors. Curcumin achieved 48 to 99% suppression of MMP-3 and 45 to 97% of MMP-13 in human and 8 to 100% (MMP-3) and 32 to 100% (MMP-13) in bovine chondrocytes. Inhibition of IL-1 signal transduction by these agents could be useful for reducing cartilage resorption by MMPs in arthritis[17]. Another studies performed on lab scale have shown that curcumin can downregulate activation of the transcription factor NF-kB thus leading to downregulation of the expression of TNF-a [19], adhesion molecules, MMPs, COX-2, 5 – LOX and other inflammatory intermediates, all of which are associated with arthritis[18]. Curcumin has also been shown to

suppress the expression of TNF-a-induced MMP-13 in primary chondrocytes. It has been found that curcumin inhibit neutrophil activation, synoviocyte proliferation, angiogenesis, and collagenase and stromelysin expression, thus suggesting that curcumin has therapeutic potential in arthritis. It has also been reported to potentiate the growth-inhibitory and pro-apoptotic effects of the COX-2 inhibitor celecoxib in osteoarthritis synovial adherent cells. A recent study showed that the suppression of NF-kB activation by curcumin leads to inhibition of the expression of COX- 2 and MMP-9 in human articular chondrocytes[19].

Dosing and Safety

The recommended dosage of curcumin is 400 to 600 mg of a turmeric extract containing 95% curcuminoids taken three to four times daily, for a total dosage of 1,200 to 2,400 mg daily. Curcumin may be better absorbed when taken with dietary fats and piperine, an extract from black pepper commonly included in curcumin supplements. Both curcumin and piperine may interfere with other medications and should only be taken under the supervision of a doctor if you are taking any prescription medication.

Turmeric is generally safe. However, in high doses it can cause side effects such as diarrhea, indigestion and nausea. Curcumin should not be prescribed to patient having gall bladder disease.

CONCLUSION

Rheumatoid arthritis is affecting the mankind since ancient times. Current treatments for arthritis are inefficient, produce side effects, and tend to be expensive there is need to open new doors for research that is related to natural products, which are devoid of such disadvantages, and thus offer a novel treatment opportunities. However there is need of more work on lab scale on Curcumin to justify it's role in treatment of rheumatoid arthritis.

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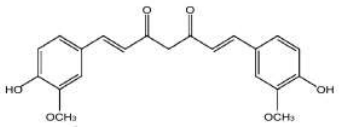


Figure: 1. Structure of Curcumin

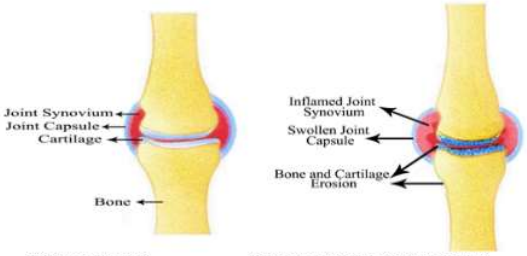


Figure: 2. Normal and Rheumatoid Arthritic Joints

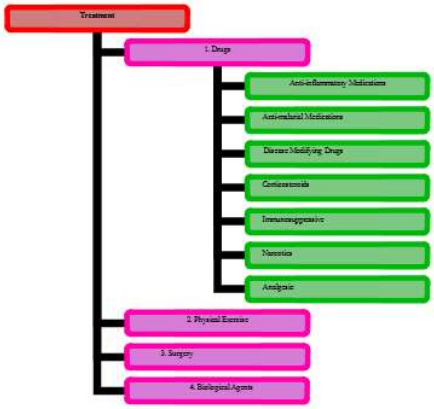


Figure: 3. Modern Therapy for treatment of Rheumatoid Arthritis

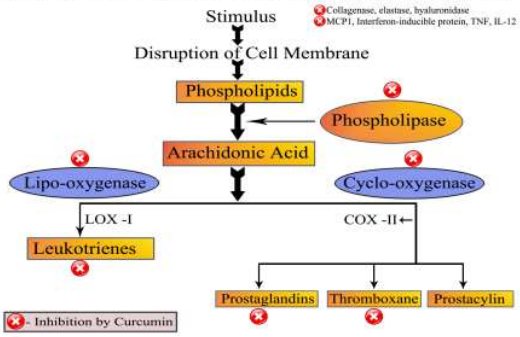


Figure: 4. Pathway of Inflammation and site of action of Curcumin