Curcumin’s therapeutic story: Facts findings in the light of clinical studies

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ABSTRACT: Curcumin, a bright yellow phytochemical derived from Curcuma longa L., has been extensively studied for its health-promoting, disease-preventing, and treatment properties, and has been gaining popularity among medical researchers since its extraction. Unani and Ayurvedic medicine use it to treat a variety of conditions, including hepatic, lung, skin, and GIT disorders. It has diverse biological effects, including antimicrobial, antiproliferative, antioxidant, anti-inflammatory, antidiabetic, and neuroprotective properties, make it a promising lead compound for the development of new derivatives to treat diseases such as cancer, diabetes, and Alzheimer’s disease. Despite its low cost, extensive potency, and its multitargeted approach of pathways, available data on its efficacy in multiple studies is still questioning, and more studies are required for this potential gap. Clinical trials assessing its biological effects revealed significant disproportionality however this review provides a comprehensive overview of recent clinical studies of curcumin, and summarizes its efficacy, biological properties, therapeutic potential, and safety. Moreover, this review provides a more special focus on its anti-inflammatory, antioxidant, anticancer, and neuroprotective properties.

Keywords: Curcumin phytosome; Pharmacology; Therapeutic use; Biological availability; Clinical trial

1. Introduction

Curcumin’s effects on various conditions are primarily attributed to its antioxidant and anti-inflammatory properties (Marchiani et al., 2014). It enhances systemic indicators of oxidative stress and raises serum antioxidant activities such as superoxide dismutase (SOD). The plasma activities of SOD, catalase, glutathione peroxidase (GSH), and lipid peroxides were
among the oxidative stress parameters on which a recent meta-analysis revealed a significant effect of curcuminoids supplementation (Sahebkar et al., 2015). Curcumin scavenges reactive oxygen and nitrogen species, inhibits ROS-generating enzymes, and modifies enzymes involved in neutralizing free radicals (Lin et al., 2007; Marchiani et al., 2014; Menon and Sudheer, 2007).

The World Health Organization considers curcumin to be a safe food additive, with an acceptable daily intake (ADI) of 0–3 mg/kg. Moreover, United States Food and Drug Administration (USFDA) has declared curcumin ‘generally regarded as safe’. Curcumin is generally safe for both humans and animals, and it has a variety of pharmacological qualities. High dosages, however, may have unfavorable effects and raise safety issues. If curcumin’s bioavailability is successfully increased, it may be possible to treat or even cure diseases (Hsu et al., 2023). In developing nations where controlling Staphylococcus aureus infections is challenging, antibiotic resistance is an increasingly pressing global concern. The combination of curcumin with other antibiotics can have synergistic effects.

Curcumin has been found to have potential antibacterial effects against methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-sensitive Staphylococcus aureus (MSSA) (Ribeiro et al., 2013; Wang et al., 2016). Curcumin’s anti-inflammatory and antioxidant properties can be used therapeutically, but its main uses in medicine are restricted by its poor water solubility, low oral absorbability, and rapid metabolic rate, all of which contribute to its low bioavailability. However, many strategies, including the nanoencapsulation of curcumin, the use of an adjuvant that prevents its glucuronidation, and structural modification, have been used to address these shortcomings (He et al., 2018; Sheikhzadeh et al., 2015).

Following a thorough review of the literature, curcumin was found to be one of the best natural substances with analgesic, anti-inflammatory, hypoglycemic, hypolipidemic, hepatoprotective, nephron protective, pulmonoprotective, and cardioprotective properties (Hegde et al., 2023). Additionally, curcumin has been demonstrated upregulate p53, p21, and p27, and downregulate cell survival gene products, induce apoptosis, and modulate several cells signalling pathways in vitro. It is presently marketed as a dietary supplement in several nations around the world due to numerous clinical studies that have shown its exceptional safety, tolerability, and effectiveness even at higher oral dosages (Gbolahan et al., 2022; Girisa et al., 2021; Kumar et al., 2021; Kunnumakkara, Ajaikumar B. et al., 2017).

Curcumin has been proven to have therapeutic benefits for digestive issues, its anti-inflammatory action has been established in preclinical studies, potentially protecting the gastrointestinal tract. Curcumin's anti-helminthic properties have been demonstrated in treating gastrointestinal illnesses like dyspepsia, Helicobacter pylori infection, Crohn's disease, gastric ulcer, acidity, and ulcerative colitis (Thong-Ngam et al., 2012). The relaxing effect of C. longa and its constituents on the smooth muscles of the trachea raises the possibility of a bronchodilatory effect in patients suffering from obstructive lung disease. Additionally, protective effect in an animal model of respiratory disorders was evident which involved improvements in lung pathology, airway responsiveness, immunomodulatory responses, and inflammatory cells and mediators (Boskabady et al., 2020).

The active ingredients in C. longa that prevent TNF-induced NF-κB activation are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Their actions were found to be produced by the methoxy groups on the phenyl ring. In healthy overweight participants, the effects of C. longa extract on serum inflammatory markers, mental health, and mood disturbance were improved (Uchio et al., 2021). Cardiovascular diseases are associated with high rates of illness and mortality, making them appear to be a global health concern. Preclinical and clinical trials have demonstrated curcumin’s anti-hypercholesterolemic, antiatherosclerotic, and protective properties against cardiac ischemia and reperfusion (Cao et al., 2018; Wang et al., 2018). By enhancing patients' lipid profiles, curcumin has the potential to
prevent cardiovascular disease. It can be administered either alone or in addition to conventional cardiovascular medications as a dietary supplement (Qin et al., 2017). Numerous studies have also shown that curcumin has anticoagulant qualities and protects against coronary heart disease (Li et al., 2020).

The study reviews the anti-inflammatory, antioxidant, anti-cancer effects, and its therapeutic potential in chronic diseases. Curcumin modulates multiple molecular targets which provides the treatment and prevention for various diseases. It is a non-toxic, promising natural anti-inflammatory compound with a long history of use.

Table 1: Therapeutic findings of curcumin: (Urošević et al., 2022)

<table>
<thead>
<tr>
<th>Year</th>
<th>Discovery</th>
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</thead>
<tbody>
<tr>
<td>1815</td>
<td>Curcumin was initially identified as the &quot;Orange-yellow Substance&quot; that was isolated from the rhizome of Curcuma longa by Vogel and Pelletier.</td>
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<tr>
<td>1842</td>
<td>Vogel obtained a pure curcumin preparation but did not provide the formula.</td>
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<tr>
<td>1910</td>
<td>Curcumin’s chemical structure was determined by Milobedzka and Lampe and was identified as diferuloylmethane, also known as 1,6-heptadiene-3,5-dione-1,7-bis-(4-hidroxy-3-methoxyphenyl) - (1E, 6E).</td>
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<tr>
<td>1913</td>
<td>Publication of curcumin’s synthesis was made.</td>
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<td>1949</td>
<td>Schraufstatter et al., reported curcumin as a biologically active antibacterial compound</td>
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<tr>
<td>1953</td>
<td>Srinivasan used chromatography to separate and quantify the curcumin components.</td>
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<tr>
<td>1971</td>
<td>Curcumin was found to decrease cholesterol levels</td>
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<tr>
<td>1972</td>
<td>Curcumin was found to decrease blood sugar levels.</td>
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<tr>
<td>1973</td>
<td>Curcumin was found to have anti-inflammatory properties.</td>
</tr>
<tr>
<td>1976</td>
<td>Curcumin was found to possess antioxidant properties.</td>
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<tr>
<td>1980</td>
<td>Curcumin’s anticancer activity was shown by Kuttan et al. in both vitro and in vivo settings.</td>
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<tr>
<td>1995</td>
<td>Curcumin was demonstrated to possess’ anti-inflammatory properties through suppression of nuclear factor-kappa B (NF-κB), a transcription factor that promotes inflammation.</td>
</tr>
</tbody>
</table>

2. Overview of clinical studies on Curcumin

Curcuma longa has long been described as herbal remedy that is universally effective due to its diverse pharmacological characteristics in literature review. Because it contains different chemical components, such as starch, essential elements, proteins, vitamins, volatile oils, curcumin, and curcuminoids, it is considered a powerful medicinal plant with a wide range of potent pharmacological properties. Moreover, during the past 50 years, numerous clinical trials have thoroughly investigated the pharmacokinetics, safety, and efficacy of curcumin (Gupta et al., 2013; Subramani et al., 2018). Curcumin’s effectiveness has been the subject of numerous clinical investigations, each of which reveals a distinct biological activity. Nevertheless, Table 2 provides a comprehensive summary of these investigations.

3. Anti-inflammatory effects of Curcumin

Inflammation plays a significant role in the development of many diseases, including cardiovascular, cancer, diabetes, and neurodegenerative disorders. NF-κB is a key mediator in these diseases and curcumin has been shown in studies to reduce inflammation by significantly suppressing NF-κB. Curcumin also suppresses inflammatory cytokines such as TNF, IL-1, IL-6, IL-8, and interferon. Paulino and colleagues discovered that curcumin analogue (DM1) can suppress iNOS and COX2 while inhibiting the production of inflammatory mediators, demonstrating it might serve as a therapeutic target (Oglah et al., 2020)
Table 2: Comprehensive overview of clinical studies of curcumin evaluating its therapeutic effects:

<table>
<thead>
<tr>
<th>Study design</th>
<th>Trial length</th>
<th>Treatment, dose, and formulation of Curcumin</th>
<th>Therapeutic effects of Curcumin</th>
<th>Adverse effects</th>
<th>First Author, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double blind, randomized, placebo controlled, 55 patients with Non alcoholic fatty liver disease</td>
<td>8 weeks</td>
<td>Curcuminoids 1 capsule of 500mg per day or placebo</td>
<td>Decreased body weight, Improved severity of NAFLD, EGF, MCP-1, and TNF-α were also significantly improved</td>
<td>No</td>
<td>(Saberi-Karimian et al., 2020)</td>
</tr>
<tr>
<td>Randomized, double blind, placebo controlled, 60 patients with stage 3 and 4 COPD</td>
<td>3 months</td>
<td>80mg nanocurcumin or placebo</td>
<td>Decrease in IL-6, Increase in FEV1, FVC, FEV1/FVC ratio, Increased body weight and BMI, improvement in systolic blood pressure</td>
<td>No</td>
<td>(Zare'i et al., 2024)</td>
</tr>
<tr>
<td>Double blind randomized clinical trial, placebo controlled, 30 female patients with Osteoarthritis</td>
<td>3 months</td>
<td>80 mg of Sinacurcumin® per day or placebo</td>
<td>Significant declines were observed in the Visual Analog Score (VAS), C-reactive protein (CRP), Immunomodulatory effect was also observed by curcumin</td>
<td>No</td>
<td>(Atabaki et al., 2020)</td>
</tr>
<tr>
<td>Randomized, double blind study, placebo controlled, 30 patients with mild to moderate Crohn’s disease</td>
<td>12 weeks</td>
<td>360 mg of Theracurmin® per day or placebo</td>
<td>Reduction in endoscopic severity of Crohn’s disease, healing of anal lesions in curcumin group, Clinical remission rates in curcumin group were slightly higher than placebo</td>
<td>No</td>
<td>(Sugimoto et al., 2020)</td>
</tr>
<tr>
<td>Randomized, single blind, placebo controlled, Longitudinal study, 48 patients with chronic kidney disease undergoing peritoneal dialysis</td>
<td>12 weeks</td>
<td>Curcumin (three 500 mg capsules containing 98.42% total curcuminoids from Curcuma longa extract) or placebo.</td>
<td>Plasma MDA, p-CS plasma levels reduced in curcumin group,</td>
<td>No</td>
<td>(Reis et al., 2024)</td>
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<tr>
<td>Study Type</td>
<td>Duration</td>
<td>Intervention Details</td>
<td>Outcomes</td>
<td>Notes</td>
<td>Reference</td>
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<tr>
<td>Randomized double blind, placebo controlled, 70 patients with symptomatic knee osteoarthritis</td>
<td>12 weeks</td>
<td>2 capsules of Curcuma longa extract or placebo</td>
<td>Improved VAS and WOMAC pain</td>
<td>-</td>
<td>(Wang et al., 2020)</td>
</tr>
<tr>
<td>Randomized clinical trial, 60 patients with knee osteoarthritis</td>
<td>4 weeks</td>
<td>Curcuma longa extract, ginger, and pepper capsules twice a day in one group, Naproxen capsule in second group</td>
<td>PGE2 levels decreased</td>
<td>-</td>
<td>(Heidari-Beni et al., 2020)</td>
</tr>
<tr>
<td>Open-label, nonrandomized clinical trial, 41 patients with Covid-19</td>
<td>2 weeks</td>
<td>Sinacurcumin 2 capsules twice a day</td>
<td>Symptoms resolved, Higher levels of SaO2, PGE2 levels, duration of supplemental oxygen and hospitalization decreased, No post treatment infection was seen</td>
<td>-</td>
<td>(Saber-Moghaddam et al., 2021)</td>
</tr>
<tr>
<td>Double blind, randomized controlled trial, 30 patients with Covid-19</td>
<td>2 weeks</td>
<td>Curcumin 525mg + piperine 2.5mg tablets twice a day</td>
<td>Early symptomatic recovery, improved oxygen saturation, better clinical outcomes, reduced duration of hospitalization</td>
<td>-</td>
<td>(Pawar et al., 2021)</td>
</tr>
<tr>
<td>Open-labelled prospective study, 50 patients with knee osteoarthritis</td>
<td>6 months</td>
<td>Theracurmin® 180mg per day</td>
<td>JOA score was improved, Demonstrated potential of treatment with greater efficacy</td>
<td>-</td>
<td>(Nakagawa et al., 2020)</td>
</tr>
<tr>
<td>Randomized, open-labelled, active controlled clinical trial, 84 patients with osteoarthritis</td>
<td>6 weeks</td>
<td>Curcumagalactomannosides (CGM) 400mg once a day in intervention group, Standard therapy in control group</td>
<td>Improvement in VAS, KPS, WOMAC scores, walking performance, pain, stiffness, physical function, reduction in serum inflammatory markers</td>
<td>-</td>
<td>(Thomas et al., 2021)</td>
</tr>
<tr>
<td>Randomized controlled, placebo controlled clinical trial, 45 patients with oral mucositis</td>
<td>3 weeks</td>
<td>First Mouthwash :0.1% w/v curcumin. Second Mouthwash: Sina curcumin soft gel (SinaCurcumin®40), which contains 40 mg curcuminoids as nano-micelles.</td>
<td>Reduced severity and burning before study termination, Ulcer free oral mucosa in patients utilizing curcumin mouthwashes, in</td>
<td>No</td>
<td>(Ramezani et al., 2023)</td>
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<tr>
<td>Study Design</td>
<td>Duration</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Conclusion</td>
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<td>Randomized, double blind, placebo controlled, 66 patients with metabolic syndrome</td>
<td>12 weeks</td>
<td>Curcumin 500mg capsule or placebo</td>
<td>Decreased body weight, improved PWV, Improvement in arterial stiffness due to reduced oxidative stress and inflammation</td>
<td>No (Alidadi et al., 2021)</td>
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<tr>
<td>Randomized, double blind, placebo controlled, 50 patients with metabolic syndrome</td>
<td>12 weeks</td>
<td>Nano-curcumin 80mg or placebo</td>
<td>Reduced TG levels</td>
<td>No (Bateni et al., 2021)</td>
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<tr>
<td>Randomized clinical trial, 44 female patients with metabolic syndrome</td>
<td>6 weeks</td>
<td>Four groups were assigned as follows; MetS control (MC), MetS exercise (ME), MetS exercise + Nano-Curcumin (MENC), and MetS Nano-Curcumin (MNC).</td>
<td>IL-6, MDA, and Hs-CRP levels decreased, BDNF, IL-10 levels and total antioxidant capacity (TAC) increased in curcumin interventions as compared to control</td>
<td>- (Osali, 2020)</td>
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<tr>
<td>Randomized, double blind, placebo controlled clinical trial, 50 patients with metabolic syndrome</td>
<td>12 weeks</td>
<td>Nano-curcumin 80mg or placebo</td>
<td>MDA levels decreased, adiponectin levels improved, total antioxidant capacity (TAC) increased</td>
<td>No (Bateni et al., 2022)</td>
<td></td>
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<tr>
<td>Randomized, double blind, placebo controlled, 60 patients with migraine</td>
<td>8 weeks</td>
<td>Phytosomal curcumin 250mg or placebo</td>
<td>Decreased oxidative stress, neuroinflammation, neurotoxicity</td>
<td>No (Shojaei et al., 2023)</td>
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<tr>
<td>Randomized, triple blind, placebo controlled clinical trial, 124 women with 10 days over 3 menstrual cycles</td>
<td>Curcuminoid 500mg capsule or placebo</td>
<td>Significant improvements in memory, inhibitory control, selective attention, and overall cognitive abilities were</td>
<td>No (Bahrami et al., 2023)</td>
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<tr>
<td>Procedure</td>
<td>Duration</td>
<td>Treatment Description</td>
<td>Outcome/Result</td>
<td>Reference</td>
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<tr>
<td>Postmenstrual syndrome and dysmenorrhea</td>
<td></td>
<td>observed in curcumin group</td>
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<tr>
<td>Double-blind, randomized controlled clinical trial of 68 patients.</td>
<td>12 weeks</td>
<td>Capsules 1000 mg/day</td>
<td>Reduce MDA, total and direct bilirubin levels and boost total antioxidant capacity. Hb, serum iron, ferritin, catalase, and vitamin E levels remained unchanged.</td>
<td>(Nasseri et al., 2018)</td>
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<td>Anticancer</td>
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<tr>
<td>Randomized, double blind clinical trial, Phase II, 22 patients with advanced rectal cancer</td>
<td>13 years</td>
<td>Curcumin 4g/day with chemotherapy</td>
<td>No significant improvements were seen</td>
<td>(Gunther et al., 2022)</td>
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<tr>
<td>Randomized, single blind parallel clinical trial, 33 patients with myeloma</td>
<td>16 weeks</td>
<td>MPC group: Melphalan 4 mg/m2, prednisone 40 mg/m2 for 7 days, and 8 grams of curcumin per day for 28 days were the treatments administered or placebo MP group</td>
<td>Decrease in remission in MPC group due to decrease in VEGF, TNF-α, NF-κB, and IL-6.</td>
<td>(Santosa et al., 2022)</td>
<td></td>
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<tr>
<td>Randomized, double blind, phase II, multicentre study, 50 patients with Metastatic castration-resistant prostate cancer (mCRPC)</td>
<td>18 weeks</td>
<td>Combination of docetaxel and oral curcumin (6 g/d for 7 days every 3 weeks) or placebo</td>
<td>No significant improvements were seen</td>
<td>(Passildas-Jahanmohan et al., 2021)</td>
<td></td>
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<tr>
<td>Randomized, double blind, placebo controlled, Phase II, 150 women with advanced and metastatic breast cancer</td>
<td>23 weeks</td>
<td>Paclitaxel + curcumin 300mg, Paclitaxel + placebo (IV)</td>
<td>Improved physical performance, Stable disease was registered in approx. 30% of patients</td>
<td>(Saghatelyan et al., 2020b)</td>
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<tr>
<td>Study Description</td>
<td>Duration</td>
<td>Intervention</td>
<td>Findings</td>
<td>Result</td>
<td>Reference(s)</td>
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<tr>
<td>Randomized, Phase IIa open labelled clinical trial, 28 patients with metastatic colorectal cancer</td>
<td>24 weeks</td>
<td>CUFOX + 2 g/d of oral curcumin (FOLFOX).</td>
<td>Curcumin glucuronide was detected in 15 of 18 CUFOX-treated patients, and curcumin had no significant effect on CXCL1 over time.</td>
<td>Yes</td>
<td>(Howells et al., 2019)</td>
</tr>
<tr>
<td>Randomized, double blind, placebo controlled, 97 patients with prostate cancer</td>
<td>3 years</td>
<td>Oral curcumin 1440mg/day or placebo</td>
<td>The percentage of patients with PSA progression was lower in the curcumin group.</td>
<td>No</td>
<td>(Choi et al., 2019)</td>
</tr>
<tr>
<td>Randomized, double blind, placebo controlled clinical trial, 44 patients with familial adenomatous polyposis</td>
<td>1 year</td>
<td>Curcumin 1500mg twice a day or placebo</td>
<td>No significant difference was seen among groups in number and size of adenomas</td>
<td>Yes</td>
<td>(Cruz-Correa et al., 2018)</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled, phase II presurgical trial in patients with colon Adenomatous polyps.</td>
<td>6 weeks</td>
<td>Combined curcumin and supplements containing anthocyanins.</td>
<td>There was a noteworthy decrease in the expression of NF-κB immunohistochemistry (IHC) and a tendency towards a decrease in Ki-67 in adenoma tissue. However, there was no noticeable shift in biomarkers in the adjacent normal mucosa.</td>
<td>No</td>
<td>(Briata et al., 2021)</td>
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<td>Neuroprotective</td>
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<tr>
<td>Prospective randomized, placebo controlled, parallel group clinical trial, 70 patients with carpal tunnel syndrome</td>
<td>8 weeks</td>
<td>Night wrist splint with topical curcumin gel or placebo gel</td>
<td>Improvement in symptom severity and daily activity</td>
<td>-</td>
<td>(Sharifi Razavi et al., 2024)</td>
</tr>
<tr>
<td>Study Type</td>
<td>Duration</td>
<td>Intervention</td>
<td>Findings</td>
<td>Side Effects</td>
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<tr>
<td>Randomized, double-blind, two-group</td>
<td>18 months</td>
<td>Theracurmin® containing 90 mg of curcumin twice daily (Curcumin treated group N = 21), (Placebo N = 19)</td>
<td>Significant improvement in the curcumin-treated group, including improved memory performance and less neuropathological accumulation in the amygdala and hypothalamus.</td>
<td>Yes: GI symptoms, Temporary feeling of heat and pressure in chest.</td>
<td>(Small et al., 2018)</td>
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<td>parallel design, 40 non-demented adults aged 51-84 years</td>
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<td>Randomized, double blind, placebo</td>
<td>7 months</td>
<td>Two groups of subjects were assigned, and between chemotherapy cycles, the subjects were given placebo caplets and curcumin at varying doses (escalating from 240 to 400 mg every 14 days).</td>
<td>Improvement in cognitive function in curcumin group</td>
<td>-</td>
<td>(Putri Laksmidewi et al., 2024)</td>
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<tr>
<td>controlled clinical trial, 78 patients with chemotherapy induced cognitive impairment</td>
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<tr>
<td>Randomized, triple blind, placebo</td>
<td>9 months</td>
<td>Curcumin 80mg/day or placebo</td>
<td>Curcumin was well tolerated; however, no efficacy was seen in quality of life and clinical symptoms</td>
<td>Yes, GI symptoms</td>
<td>(Ghodsi et al., 2022)</td>
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<td>controlled clinical trial, 60 patients with Parkinson’s disease</td>
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<tr>
<td>Comparative, cross-sectional study, 68 patients with mild depression</td>
<td>8 weeks</td>
<td>Curcumin supplementation, sunlight exposure, and mindfulness meditation (MCS)</td>
<td>Lower depression scores, and related biomarkers</td>
<td>-</td>
<td>(Taworntawat et al., 2022)</td>
</tr>
<tr>
<td>Randomized, double blind, placebo</td>
<td>16 weeks</td>
<td>Curcumin (160 mg/day), or Fish oil (2000 mg docosahexaenoic acid + 400 mg eicosapentaenoic acid)</td>
<td>Fish oil supplementation improved cerebrovascular function; Curcumin had no significant outcomes</td>
<td>No</td>
<td>(Kuszewski et al., 2020)</td>
</tr>
<tr>
<td>Study Design</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Significance</td>
<td>Reference</td>
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<tr>
<td>Randomized, double blind, placebo controlled</td>
<td>Curcumin Nano micelle soft gelatin capsule 40mg/day + sodium valproate</td>
<td>No significant difference was seen among groups</td>
<td>No</td>
<td>(Akbarzadeh et al., 2023)</td>
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<tr>
<td>clinical trial, 78 patients with bipolar disorder in acute phase of mania</td>
<td>(600mg/day + 20mg/kg)</td>
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<tr>
<td>Randomized, double blind, placebo controlled, 80 patients with diabetic polyneuropathy, anxiety, depression, and stress</td>
<td>Nano-curcumin 80mg/day or placebo</td>
<td>Reduction in depression and anxiety in curcumin groups; however no significant difference in stress was seen between groups</td>
<td>-</td>
<td>(Asadi et al., 2020)</td>
<td></td>
</tr>
<tr>
<td>Pseudo randomized, crossover trial, placebo controlled, 20 men with gulf war illness</td>
<td>Curcumin phytosome Meriva: (Low dose: 100 mg; high dose: 4000 mg per day) Boswellia products: (400 mg and 800 mg per day) Pycnogenol pine bark extract: (200 and 400 mg daily)</td>
<td>At both the lower and higher doses, curcumin significantly lessened the severity of GWI symptoms compared to placebo. At the higher dosage, maritime pine proved to be more effective than a placebo.</td>
<td>Yes, GI symptoms</td>
<td>(Donovan et al., 2021)</td>
<td></td>
</tr>
</tbody>
</table>

**Chronic diseases**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, triple blind, placebo controlled</td>
<td>Curcumin capsules 500mg or placebo</td>
<td>Curcumin didn’t improve symptoms or quality of life</td>
<td>-</td>
<td>(Gudarzi et al., 2024)</td>
</tr>
<tr>
<td>clinical trial, 68 women with endometriosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, double blind, placebo controlled</td>
<td>Curcumin 80mg/day or placebo</td>
<td>Curcumin had no effect on the maximum, mean, or pulse wave velocity (PWV) levels of left or right carotid intima media thickness (CIMT)</td>
<td>No</td>
<td>(Ghasemiadl et al., 2024)</td>
</tr>
<tr>
<td>clinical trial, 39 diabetic patients undergoing hemodialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Randomized, placebo-controlled, double blind, 40 individuals with scalp psoriasis, two parallel groups in a prospective clinical trial.

9 weeks  
Twice daily use of a turmeric tonic  
Improved quality of life for patients; decreased erythema, scaling, and induration of lesions (PASI score)  
(Bahraini et al., 2018)

Randomized, double blind, placebo controlled clinical trial, 60 patients with non-atopic asthma

60 days  
Nano-curcumin soft gel 40mg thrice a day or placebo  
FEV1 improved in patients; however, no significant differences were seen among groups  
(Lari et al., 2024)

Nitric oxide synthase (iNOS), a crucial enzyme in macrophages, produces nitric oxide (NO), which lowers blood pressure and has antibacterial qualities. However, overproduction of it can lead to tissue damage. Here, haemoglobin oxygenase 1 (HO-1) breaks down haemoglobin into bilirubin, carbon monoxide, and iron ions to regulate the levels. Additionally, HO-1 and CO deactivate nuclear factor-kappa B (NF-κB) to suppress NO production and iNOS expression in activated macrophages. This is the same mechanism by which curcumin acts, in that it indirectly inhibits NO production, while HO-1 and CO suppress NO and iNOS production in activated macrophages (Hsu et al., 2023; Manikandan et al., 2011; Morales et al., 2015).

The four components of the inflammatory pathway are effectors, mediators, sensors, and inducers. There are differences and unclear physiological and pathological mechanisms underlying inflammation brought on by various inflammatory triggers (Medzhitov, 2008). Anti-inflammatory effects of drugs generally involve mechanisms which includes, acting on receptors and signalling pathways; control target tissues response to inflammatory mediators; reverse medium effect on target tissue; generate anti-inflammatory mediators (Medzhitov, 2010), however, curcumin inhibits inflammatory signalling pathways to produce anti-inflammatory effects. Figure 1 explains the modulation of pathways by curcumin that produces anti-inflammatory effects.
Curcumin is a natural treatment for inflammatory diseases which acts by modulating multiple signaling pathways, such as NF-κB, MAPK, AP-1, and JAK/STAT. Additionally, curcumin can limit the NLRP3 inflammasome assembly and prevent its activation by blocking the NF-κB pathway. According to studies, curcumin lowers levels of pro-inflammatory mediators like TNF-α, iNOS, NO, G-CSF, IL-1, IL-1β, IL-6, IL-8, IL-17, and IL-27 (Peng et al., 2021).

Curcumin inhibit the expression of TNF-α, IL-1β, and IL-6 that is mediated by lipopolysaccharide (LPS), and reduce inflammation by means of the nuclear factor-E2-related factor 2 (Nrf2)/OH-1 pathway (Liu et al., 2015). Two transcription factor genes, NF-κB and AP-1, are frequently overexpressed in cancer cells and are essential to the LPS-induced inflammatory response (Perrone et al., 2015). In this instance, curcumin therapy causes the death of cancerous cells and reduces inflammation by blocking NF-κB. Notably, a study found that curcumin functions in the inflammatory system similarly to a pro-drug that needs to be activated by oxidation to become a reactive metabolite to have anti-inflammatory effects (Edwards et al., 2017).

Curcumin has demonstrated its therapeutic potential in various inflammatory diseases in clinical studies, which includes obesity, diabetes, CVS diseases, cerebral edema, neurodegenerative diseases, inflammatory bowel disease, allergy, bronchial asthma, rheumatoid arthritis, renal ischemia, psoriasis, and scleroderma (Shehzad et al., 2013). Moreover, an overview of curcumin targets in inflammatory processes is shown in Table 3.

4. Anti-inflammatory effects of Curcumin

Inflammation plays a significant role in the development of many diseases, including cardiovascular, cancer, diabetes, and neurodegenerative disorders. NF-κB is a key mediator in these diseases and curcumin has been shown in studies to reduce inflammation by significantly suppressing NF-κB. Curcumin also suppresses inflammatory cytokines such as TNF, IL-1, IL-6, IL-8, and interferon. Paulino and colleagues discovered that curcumin analogue (DM1) can suppress iNOS and COX2 while...
inhibiting the production of inflammatory mediators, demonstrating it might serve as a therapeutic target (Oglah et al., 2020). Nitric oxide synthase (iNOS), a crucial enzyme in macrophages, produces nitric oxide (NO), which lowers blood pressure and has antibacterial qualities. However, overproduction of it can lead to tissue damage. Here, haemoglobin oxygenase 1 (HO-1) breaks down haemoglobin into bilirubin, carbon monoxide, and iron ions to regulate the levels. Additionally, HO-1 and CO deactivate nuclear factor-kappa B (NF-κB) to suppress NO production and iNOS expression in activated macrophages.

Table 3: A summary of current research on curcumin's anti-inflammatory properties.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Target</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>ROS, COX-2, NF-κB, p-IκB</td>
<td>Reduces the neurotoxicity caused by colistin in N2a cells by inhibiting oxidative stress, promoting apoptosis, and having anti-inflammatory properties.</td>
<td>(Dai, C. et al., 2018)</td>
</tr>
<tr>
<td>Curcumin + Rutin</td>
<td>COX-2</td>
<td>Reduces inflammation linked to tumours in HPV16-transgenic mice.</td>
<td>(Moutinho et al., 2018)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>NFκB, COX-2</td>
<td>Reduces airway remoulding and inflammation in mice with COPD induced by cigarette smoke.</td>
<td>(Yuan et al., 2018)</td>
</tr>
<tr>
<td>Curcumin + capsaicin</td>
<td>COX-2, IL-6, TGF-β</td>
<td>In peripheral blood mononuclear cells, lipopolysaccharide-induced expression of proinflammatory cytokines was effectively inhibited.</td>
<td>(Vasanthkumar et al., 2019)</td>
</tr>
</tbody>
</table>

5. **Antioxidant and Anti-cancer properties**

Reactive oxygen and nitrogen species can start an intracellular signaling cascade that increases the expression of genes that promote inflammation. Numerous chronic diseases have been linked to inflammation in their development (Panahi et al., 2016; Recio and Andujar, 2012). Inflammation plays an important role in the development of chronic diseases such as Alzheimer’s, Parkinson’s, multiple sclerosis, epilepsy, asthma, allergy, psoriasis, and diabetes. TNF-α is a major inflammatory mediator which is regulated by NF-κB activation. NF-κB is activated by various factors such as inflammatory cytokines, bacteria, viruses, environmental pollutants, stress, and cigarette smoke. Agents that inhibit NF-κB and its products may be effective in treating these diseases. Curcumin has been shown to inhibit NF-κB activation and suppress inflammation through multiple mechanisms, indicating its potential as an anti-inflammatory agent (Panahi et al., 2016).

Curcumin provides neuroprotection in Alzheimer’s disease by producing anti-inflammatory and antioxidant effects through the upregulation and downregulation of the transcription factors Nrf2 and NF-κB, respectively. While the downregulation of NF-κB inhibits the production of proinflammatory cytokines like IL-6, the upregulation of Nrf2 triggers the transcription of genes involved in controlling oxidative stress, this mechanism is
An imbalance between endogenous antioxidants and reactive oxygen species (ROS) that are produced naturally in the body leads to oxidative stress. Singlet oxygen, hydrogen peroxide, superoxide radicals, and hydroxyl radicals are examples of ROS that are produced during cellular functions like respiration (Gülcin, 2012). Cellular oxidation triggered by an excess of reactive oxygen species (ROS) may damage tissue. The body's natural antioxidant defence mechanisms, including reduced glutathione, catalase, and superoxide dismutase, help protect cells from reactive oxygen species (ROS) damage (Batinić-Haberle et al., 2010). Sankar et al., found curcumin in it’s both free and encapsulated form to indirectly activate antioxidant enzymes such as SOD, CAT, and glutathione reductase (Sankar et al., 2015). It also demonstrated synergistic antioxidant properties when combined with other antioxidants (Aftab and Vieira, 2010).

Several recent studies have demonstrated antioxidant properties of curcumin in clinical trials i.e., recent meta-analysis of clinical trials revealed pure curcumin, and nano-curcumin to have antioxidant properties (Hassanizadeh et al., 2023; Jakubczyk et al., 2020). Further, potential of curcumin in separate diseases reporting its antioxidant potential are as follows, Non-alcoholic fatty liver disease (NAFLD) (Ebrahimzadeh et al., 2024), anxiety and stress disorders (Spanoudaki et al., 2024), premenstrual syndrome and dysmenorrhea (Shabanian Boroujeni et al., 2024), hypertension (Ghaeini Hesaroeeyeh et al., 2024), cholesterol management (Boretti, 2024), and Alzheimer’s disease (AD) (Abdul-Rahman et al., 2024).

Many biochemical pathways and mediators, such as proliferative enhancers, growth factors, growth factor receptors, cytokines, transcription factors, apoptosis inhibitors, and enzymes, are
involved in the development of cancer. These molecules have been found to be targeted by curcumin, which controls both apoptosis and cell proliferation (Kunnumakkara et al., 2008).

Figure 3 below underscores the mechanisms of curcumin and curcumin delivery systems (CDSs) in anti-cancer cell proliferation.

**Figure 3:** Mechanisms exhibited by curcumin and curcumin delivery systems (CDSs) to produce anticancer effects.

Curcumin has been demonstrated to induce apoptosis and suppress proliferation in numerous cancers e.g., In breast cancer, development and progression is significantly influenced by estrogen and its receptors i.e., alpha and beta. Shao et al. found that curcumin’s antiproliferative effects are estrogen-dependent in estrogen receptor-positive breast cancer cell lines. This study also found that curcumin has strong anti-invasive properties in estrogen-negative MCF-7 cells. The action appears to be mediated by downregulation of MMP-2 (matrix metalloproteinase) and upregulation of TIMP-1 (tissue inhibitor of metalloproteinase), both of which play a critical role in tumour cell metastasis (Oglah et al., 2020). Calaf and colleagues discovered that curcumin inhibits microtubule assembly dynamics and activates the mitotic checkpoint, thereby inducing apoptosis and suppressing cell proliferation in MCF-7 cells, moreover higher apoptosis levels were observed when paclitaxel and curcumin were combined (Calaf et al., 2018).

Curcumin is shown as a potential candidate for non-small cell lung cancer (NSCLC) by inhibiting NF-κB activation, which can cause inflammation, chemotherapy resistance, invasion, metastasis, and cellular transformation. This could lessen negative effects and strengthen current management protocols (Tsai et al., 2015). JZ534 is a novel curcumin analogue which has been synthesized and examined for its potential antitumor effects on lung cancer cell lines. It demonstrated excellent activity through apoptosis induction, growth inhibition, and upregulation of apoptosis-related proteins.
Moreover, JZ534 exhibited greater antitumor activity at the same concentration as curcumin (Wu et al., 2015). Curcumin has been observed to impede the migration and invasion of cancer cells in vitro by reducing the expression and activity of enzymes like matrix metalloproteinases (MMP-2) and (MMP-9) that promote metastasis and invasion. In cervical cancer, it has also been demonstrated to inhibit telomerase activity (Clarke et al., 2012; Momtazi-Borojeni et al., 2019; Singh and Singh, 2011).

In a clinical trial involving patients with castration-resistant prostate cancer CRPC, it was discovered that more than half of the patients experienced a prostate-specific antigen (PSA) response when curcumin and docetaxel were administered together (Mahammedi et al., 2016). Furthermore Chen et al.’s investigation also discovered that the novel curcumin analogues RL118 and RL121 exhibit strong cytotoxicity against CRPC through inducing apoptosis, increasing the number of cells in the G2/M phase, and suppressing nuclear factor (NF)-expression (Chen et al., 2018). Moreover, Figure 4 below demonstrates the mechanisms of curcumin in anticancer cell invasion, and metastasis.

Figure 4: Inhibition of invasion and metastasis by Curcumin through multiple pathways.

Two derivatives of curcumin, EF31 and UBS109, have been shown in a recent study by Rajitha et al. to significantly suppress colorectal cancer cell lines by interfering with mechanisms such as the inhibition of COX-2, STAT-3, and NF-κB. These derivatives also have improved aqueous solubility, potency, and pharmacokinetic profile compared to curcumin (Rajitha et al., 2016). Although there is plenty evidence on curcumin anticancer effect in preclinical studies, several recent clinical studies on curcumin treating various cancers are as follows; prostate cancer (Mofid et al., 2018), colon cancer, breast cancer (Wang et al., 2024), brain cancer (Verma et al., 2024), colorectal cancer (Liu et al., 2024).

6. Neuroprotective benefits of Curcumin:

In neurodegenerative diseases, misfolded amyloid protein accumulation causes synaptic damage and neuronal impairment. Natural polyphenol curcumin has demonstrated potential as an anti-inflammatory, anti-amyloid,
and neuroprotective substance. In animal models, its molecular targeting could reduce the amount of amyloid plaque, repair neuronal damage, and reestablish sensory motor and cognitive functions (Maiti and Dunbar, 2018). Most neurodegenerative diseases are as a result of inflammation, oxidative stress, and amyloid aggregates, and curcumin has shown its protective effect on nervous system by halting all these processes (Abdul-Rahman et al., 2024). Some of the major processes that curcumin exhibit in providing neuroprotection is illustrated in Figure 5 below.

Curcumin, possessing anti-amyloid characteristics, has demonstrated potential in addressing neurodegenerative illnesses by binding to multiple forms of amyloid proteins, such as Aβ-oligomers and fibrils in Alzheimer Disease (Yanagisawa et al., 2011), α-synuclein in Parkinson Disease (Singh et al., 2013), huntingtin in Huntington Disease (Chongtham and Agrawal, 2016), phosphorylated tau in tauopathies and AD (Mohorko et al., 2010), and prion proteins in prion disorders (Hafner-Bratkovič et al., 2008). Brain tissue contains a high amount of lipids therefore curcumin molecules can pass through the blood-brain barrier and prevent aggregation of amyloid proteins. Central nervous system is particularly vulnerable to oxidative damage because of its high metabolic rate, elevated oxygen consumption, high membrane phospholipid and PUFA content, and reduced levels of antioxidants. These elements raise the amounts of reactive oxygen species and peroxynitrite, which cause inflammation, malfunctioning mitochondria, and death of neurons. Inflammation, lipid peroxidation, DNA damage, and oxidized protein products are the results of chronic, progressive neurological diseases (Mosley et al., 2006). Misfolded protein aggregates have also been linked to the induction of chronic oxidative stress in brain tissues (Gregersen and Bross, 2010), however curcumin’s

![Figure 5: Proposed mechanisms of curcumin in modulating neurodegenerative diseases.](image-url)
strong antioxidant properties allow it to scavenge superoxide anions (O2–) and hydroxyl radicals (OH–) as well as raise antioxidant levels like glutathione (GSH) (Lin et al., 2022). Moreover, curcumin can activate the brain’s antioxidant enzyme systems, such as glutathione peroxidase, superoxide dismutase, and glutathione S-transferase (Hassani and Esmaeili, 2024). Furthermore, it guards against DNA deterioration, lipid peroxidation, and protein oxidation or carbonylation (Jat et al., 2013). Figure 6 below shows how curcumin protects CNS from oxidative damage.

Curcumin’s capacity to lessen neuroinflammation is the second most significant factor attracting attention as a potential treatment for neurological disorders, after its anti-oxidant qualities (He et al., 2015a). According to multiple reports, curcumin can effectively reduce inflammation by downregulating numerous neuroinflammatory marker proteins, including nuclear factor kappa beta (NF-κB) (Huang et al., 2018), phospholipases and the metabolic enzymes of arachidonic acid, including 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) (Razavi et al., 2021). Furthermore, it lowers the concentrations of several cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor (TNF). Similarly, curcumin inhibits pro-inflammatory pathways by acting as an agonist for peroxisome proliferator-activated receptor gamma (PPARγ) (Maiti and Dunbar, 2018), moreover a neuroprotective effect exerted by curcumin is shown in Figure 7.

Curcumin has demonstrated clinical potential as a neuroprotective agent in humans through several clinical trials. Early controlled trials with mild-to-moderate AD participants yielded no evidence of efficacy (Baum et al., 2008; Ringman et al., 2012), probably due to trial’s brief duration i.e., 6 months or the limited bioavailability of the curcumin used (despite the high dose of up to 4 g/day). However, the use of Longvida, a solid lipid formulation of curcumin that contains about 80 mg of curcumin, after acute (1 hour) administration in elderly, healthy subjects showed improvements in mood, working memory, and attention (Cox et al., 2015; Cox et al., 2020).
7. **Potential applications of curcumin in the treatment of chronic diseases**

The occurrence rate of complex, multigenic, and chronic human diseases has increased significantly in recent times, despite significant advancements in their treatment (Gupta et al., 2011). Smart drugs also known as mono-targeted therapies, have been developed over the years to treat chronic conditions such as cancer, metabolic, cardiovascular, and neurological disorders. However, because these complex diseases involve multiple signalling pathways, focusing on one of the many involved pathways is unlikely to be effective in treating and preventing these diseases (Bordoloi et al., 2016), however the high cost and unfavourable side effects of these smart drugs have created a need for multi-targeted, affordable, easily accessible, safe, and extremely effective agents to treat a range of human diseases (Gupta et al., 2012).

Chronic inflammation is closely related to oxidative stress and oxidative damage, and is a major factor in many chronic diseases, including cancer, diabetes, cardiovascular, neurological, inflammatory bowel disease, and pulmonary diseases. Since oxidative stress and most chronic diseases are closely related, curcumin, with its potent antioxidant qualities, can be beneficial in both preventing and treating such diseases (He et al., 2015b). Both in vitro and clinical trials have shown that curcumin is a highly pleiotropic molecule that interacts with a variety of inflammatory targets, suggesting potential therapeutic potential in chronic diseases (Jurenka, 2009).

Chronic inflammatory and degenerative disorders are exacerbated by oxidative stress, which affects health and raises the risk of chronic diseases like cancer, atherosclerosis, Alzheimer’s, and metabolic disorders. Increased levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, which are genes encoded by activation of NF-kB, suggest that these disorders are likely caused by low-grade inflammation (Sikora et al., 2010).

Curcumin was therapeutically potent against wide variety of chronic diseases in clinical trials which includes, inflammatory bowel disease (Atreya et al., 2008; Fallahi et al., 2021), cardiovascular diseases (Cox et al., 2022; Li et al., 2020; Pourbagher-Shahri et al., 2021), neurodegenerative diseases (Maiti and Dunbar, 2018; Mohseni et al., 2021), allergic diseases (Haftcheshmeh et al., 2022; Memarzia et al., 2022), rheumatoid arthritis (Bagherniya et al., 2021; Dai, Q. et al., 2018; Makuch et al., 2021), chronic kidney disease (Ali et al., 2018; de
Almeida Alvarenga et al., 2018; Emami et al., 2022; He et al., 2020), diabetes (Den Hartogh et al., 2020; Parsamanesh et al., 2018; Pivari et al., 2019; Zheng et al., 2018), psoriasis (Kang et al., 2016; Zhang et al., 2021; Zhang et al., 2022), and cancer (Arslan et al., 2022).

8. Safety and side effects of curcumin supplementation

Curcumin’s safety, tolerability, and effectiveness against a variety of chronic diseases have all been thoroughly demonstrated by clinical trials (Kunnumakkara, A.B. et al., 2017). Despite its exceptional safety and efficacy, curcumin has not yet received FDA approval as a medication. One major reason for this is curcumin’s relative bioavailability. Over the past three decades, research has shown that curcumin’s fast metabolism, poor gut absorption, and systemic elimination greatly limit its bioavailability (Lee et al., 2014; Pancholi et al., 2021; Yallapu et al., 2012). Furthermore, curcumin has an octanol-water partition coefficient of approximately 3.2, which indicates that it is a hydrophobic molecule with a water solubility of only 30 nM (Hegde et al., 2023).

In clinical trials, oral administration of 6 g/day of curcumin for a period of 4–7 weeks did not result in any harmful effects (Soleimani et al., 2018). Greil et al. studied the safety, tolerability, and efficacy of liposomal curcumin (LipocurcTM) in patients with metastatic or locally advanced cancer. Research showed that the highest safe dosage of liposomal curcumin for cancer patients receiving treatment was 300 mg/m2 (Greil et al., 2018). Furthermore, Saghateleryan et al. evaluated the safety and effectiveness of intravenous curcumin infusion combined with paclitaxel in patients suffering from advanced and metastatic breast cancer. After a 12-week course of treatment, intravenous curcumin did not result in any major health problems or a decline in quality of life (Saghateleryan et al., 2020a). Toxicity studies conducted in-vivo have validated the safety of the drug’s formulation at tested doses (Busari et al., 2017). Additionally, a thorough summary of the insignificant or absent adverse outcomes in the most recent studies is given in Table 2.

Curcumin has been a staple of diet of numerous nations for hundreds of years which demonstrates its safety profile (Alrawaiq and Abdullah, 2014). However, it is crucial to determine curcumin’s pharmacokinetics or pharmacodynamics after human administration to understand its advantageous effects. Clinical studies reported that short-term curcumin therapy of 8 g/day has no significant adverse reactions (Gupta et al., 2013). Similarly, no harmful effects were seen in a different phase-1 human trial that used 8 g of curcumin daily for three months (Mishra and Palanivelu, 2008). On the contrary, few studies have demonstrated that higher dosages of curcumin may result in numerous adverse reactions, such as dermatitis, rashes, chest tightness, and gastrointestinal distress (Liddle et al., 2006). However, some side effects of curcumin reported at high dosages with oral administration is highlighted in Table 4.

Table 4: Side effects of curcumin at higher dosages

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Side effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>General effects</td>
<td>Chest tightness, GI discomfort, nausea, diarrhea, allergic reactions, dermatitis, skin rashes, swollen skin,</td>
<td>(Burgos-Morón et al.)</td>
</tr>
<tr>
<td>Blood clotting</td>
<td>Prolonged clotting process</td>
<td>(Kim et al., 2012)</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>Increased bile duct blockage and gallstone contraction</td>
<td>(Burgos-Morón et al.)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Induce menstruation or stimulate the uterus</td>
<td>(Prasad and Aggarwal, 2011)</td>
</tr>
<tr>
<td>Stomach</td>
<td>Increased acidity when taken with antacids</td>
<td>(Prasad and Aggarwal, 2011)</td>
</tr>
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</table>
9. Conclusion: Future directions for Curcumin research

Curcumin’s biological activities against a wide range of molecular targets have been shown to have therapeutic effects in clinical use. Variety of research has produced important data regarding the therapeutic potential of curcumin, which will form the basis for further investigation and clinical application of these extraordinarily potent drugs. As problems with curcumin’s metabolism, elimination, biodistribution, and absorption are being addressed to improve its bioavailability, several diseases will become obvious candidates for curcumin therapy. However, further human studies are needed to validate its clinical use for treating various cancers and chronic diseases, as there are still conflicting findings from a small number of studies. In the future, curcumin-derived tailored agents or combinations with other medications might provide better results.

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