PN
PHYTONUTRIENTS

Information available at: infor@phytonutrients.pk
PHYTONutrients
Journal home page: https://phytonutrients.pk/index.php/pn

Lyceum Publisher

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

Sumbal Bibi [1], Huma Hussain [1], Yaseen Hussain[2*], Menahil Rauf [3*]

Received: May 24, 2024
Accepted: May 29, 2024
Published: July 19, 2024
Volume: 03: 2024
Article ID: pn.v3i.25
https://doi.org/10.62368/pn.v3i.25

[1] Department of Chemistry, Shaheed Benazir Bhutto University, Sheringal, Pakistan
[2] Lab of controlled release and drug delivery system, College of pharmaceutical sciences, Soochow University, Jiangsu, Suzhou, China
[3] Department of Allied Health Sciences, Bashir institute of health sciences, Islamabad, Pakistan

*Correspondence: Menahil Rauf; menahilrauf1@gmail.com; Yaseen Hussain; pharmycc@gmail.com

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, antirheumatic, 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, anti-atherosclerotic, 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)

Year	Discovery
1815	Curcumin was initially identified as the "Orange-yellow Substance" that was isolated from the rhizome of Curcuma longa by Vogel and Pelletier.
1842	Vogel obtained a pure curcumin preparation but did not provide the formula.
1910	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).
1913	Publication of curcumin's synthesis was made.
1949	Schraufstatter et al., reported curcumin as a biologically active antibacterial compound
1953	Srinivasan used chromatography to separate and quantify the curcumin components.
1971	Curcumin was found to decrease cholesterol levels
1972	Curcumin was found to decrease blood sugar levels.
1973	Curcumin was found to have anti-inflammatory properties.
1976	Curcumin was found to possess antioxidant properties.
1980	Curcumin's anticancer activity was shown by Kuttan et al. in both vitro and in vivo settings.
1995	Curcumin was demonstrated to posses' anti-inflammatory properties through suppression of nuclear factor-kappa B (NF-κB), a transcription factor that promotes inflammation.

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:

Study design	Trial length	Treatment, dose, and formulation of Curcumin	Therapeutic effects of Curcumin	Adverse effects	First Author, Year
Anti-inflammatory					
Double blind, randomized, placebo controlled, 55 patients with Non alcoholic fatty liver disease	8 weeks	Curcuminoids 1 capsule of 500mg per day or placebo	Decreased body weight, Improved severity of NAFLD, EGF, MCP-1, and TNF-α were also significantly improved	No	(Saberi-Karimian et al., 2020)
Randomized, double blind, placebo controlled, 60 patients with stage 3 and 4 COPD	3 months	80mg nanocurcumin or placebo	Decrease in IL-6, Increase in FEV1, FVC, FEV1/FVC ratio, Increased body weight and BMI, improvement in systolic blood pressure	No	(Zare'i et al., 2024)
Double blind randomized clinical trial, placebo controlled, 30 female patients with Osteoarthritis	3 months	80 mg of Sinacurcumin® per day or placebo	Significant declines were observed in the Visual Analog Score (VAS), C-reactive protein (CRP), Immunomodulatory effect was also observed by curcumin	No	(Atabaki et al., 2020)
Randomized, double blind study, placebo controlled, 30 patients with mild to moderate Crohn's disease	12 weeks	360 mg of Theracurmin® per day or placebo	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	No	(Sugimoto et al., 2020)
Randomized, single blind, placebo controlled, Longitudinal study, 48 patients with chronic kidney disease undergoing peritoneal dialysis	12 weeks	Curcumin (three 500 mg capsules containing 98.42% total curcuminoids from Curcuma longa extract) or placebo.	Plasma MDA, p-CS plasma levels reduced in curcumin group,	No	(Reis et al., 2024)

Randomized double blind, placebo controlled, 70 patients with symptomatic knee osteoarthritis	12 weeks	2 capsules of Curcuma longa extract or placebo	Improved VAS and WOMAC pain	-	(Wang et al., 2020)
Randomized clinical trial, 60 patients with knee osteoarthritis	4 weeks	Curcuma longa extract, ginger, and pepper capsules twice a day in one group, Naproxen capsule in second group	PGE_2 levels decreased	-	(Heidari-Beni et al., 2020)
Open-label, nonrandomized clinical trial, 41 patients with Covid-19	2 weeks	Sinacurcumin 2 capsules twice a day	Symptoms resolved, Higher levels of SaO_2 levels, duration of supplemental oxygen and hospitalization decreased, No post treatment infection was seen	-	(Saber-Moghaddam et al., 2021)
Double blind, randomized controlled trial, 30 patients with Covid-19	2 weeks	Curcumin 525mg + piperine 2.5mg tablets twice a day	Early symptomatic recovery, improved oxygen saturation, better clinical outcomes, reduced duration of hospitalization	-	(Pawar et al., 2021)
Open-labelled prospective study, 50 patients with knee osteoarthritis	6 months	Theracurmin® 180mg per day	JOA score was improved, Demonstrated potential of treatment with greater efficacy	-	(Nakagawa et al., 2020)
Randomized, open-labelled, active controlled clinical trial, 84 patients with osteoarthritis	6 weeks	Curcumagalactomannosides (CGM) 400mg once a day in intervention group, Standard therapy in control group	Improvement in VAS, KPS, WOMAC scores, walking performance, pain, stiffness, physical function, reduction in serum inflammatory markers	-	(Thomas et al., 2021)
Randomized controlled, placebo controlled clinical trial, 45 patients with oral mucositis	3 weeks	First Mouthwash :0.1% w/v curcumin. Second Mouthwash: Sina curcumin soft gel (SinaCurcumin®40), which contains 40 mg curcuminoids as nano-micelles.	Reduced severity and burning before study termination, Ulcer free oral mucosa in patients utilizing curcumin mouthwashes, in	No	(Ramezani et al., 2023)

		Third Mouthwash: Placebo clear mouthwash. Mouth washing 3 times a day for 1 minute.	comparison to placebo who had oral mucositis		
Antioxidant					
Randomized, double blind, placebo controlled, 66 patients with metabolic syndrome	12 weeks	Curcumin 500mg capsule or placebo	Decreased body weight, improved PWV, Improvement in arterial stiffness due to reduced oxidative stress and inflammation	No	(Alidadi et al., 2021)
Randomized, double blind, placebo controlled, 50 patients with metabolic syndrome	12 weeks	Nano-curcumin 80mg or placebo	Reduced TG levels	No	(Bateni et al., 2021)
Randomized clinical trial, 44 female patients with metabolic syndrome	6 weeks	Four groups were assigned as follows; MetS control (MC), MetS exercise (ME), MetS exercise + Nano-Curcumin (MENC), and MetS Nano-Curcumin (MNC).	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	-	(Osali, 2020)
Randomized, double blind, placebo controlled clinical trial, 50 patients with metabolic syndrome	12 weeks	Nano-curcumin 80mg or placebo	MDA levels decreased, adiponectin levels improved, total antioxidant capacity (TAC) increased	No	(Bateni et al., 2022)
Randomized, double blind, placebo controlled, 60 patients with migraine	8 weeks	Phytosomal curcumin 250mg or placebo	Decreased oxidative stress, neuroinflammation, neurotoxicity	No	(Shojaei et al., 2023)
Randomized, triple blind, placebo controlled clinical trial, 124 women with	10 days over 3 menstrual cycles	Curcuminoid 500mg capsule or placebo	Significant improvements in memory, inhibitory control, selective attention, and overall cognitive abilities were	No	(Bahrami et al., 2023)

postmenstrual syndrome and dysmenorrhea			observed in curcumin group		
Double-blind, randomized controlled clinical trial of 68 patients.	12 weeks	Capsules 1000 mg/day	Reduce MDA, total and direct bilirubin levels and boost total antioxidant capacity. Hb, serum iron, ferritin, catalase, and vitamin E levels remained unchanged.	-	(Nasseri et al., 2018)
Anticancer					
Randomized, double blind clinical trial, Phase II, 22 patients with advanced rectal cancer	13 years	Curcumin 4g/day with chemotherapy	No significant improvements were seen	-	(Gunther et al., 2022)
Randomized, single blind parallel clinical trial, 33 patients with myeloma	16 weeks	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	Decrease in remission in MPC group due to decrease in VEGF, TNF-α, NF-κB, and IL-6.	-	(Santosa et al., 2022)
Randomized, double blind, phase II, multicentre study, 50 patients with Metastatic castration-resistant prostate cancer (mCRPC)	18 weeks	Combination of docetaxel and oral curcumin (6 g/d for 7 days every 3 weeks) or placebo	No significant improvements were seen	-	(Passildas-Jahanmohan et al., 2021)
Randomized, double blind, placebo controlled, Phase II, 150 women with advanced and metastatic breast cancer	23 weeks	Paclitaxel + curcumin 300mg, Paclitaxel + placebo (IV)	Improved physical performance, Stable disease was registered in approx. 30% of patients	No	(Saghatelyan et al., 2020b)

Randomized, Phase IIa open labelled clinical trial, 28 patients with metastatic colorectal cancer	24 weeks	CUFOX + 2 g/d of oral curcumin (FOLFOX).	Curcumin glucuronide was detected in 15 of 18 CUFOX-treated patients, and curcumin had no significant effect on CXCL1 over time.	Yes	(Howells et al., 2019)
Randomized, double blind, placebo controlled, 97 patients with prostate cancer	3 years	Oral curcumin 1440mg/day or placebo	The percentage of patients with PSA progression was lower in the curcumin group.	No	(Choi et al., 2019)
Rnadomized, double blind, placebo controlled clinical trial, 44 patients with familial adenomatous polyposis	1 year	Curcumin 1500mg twice a day or placebo	No significant difference was seen among groups in number and size of adenomas	Yes	(Cruz-Correa et al., 2018)
Randomized, double-blind, placebo-controlled, phase II presurgical trial in patients with colon Adenomatous polyps.	6 weeks	Combined curcumin and supplements containing anthocyanins.	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.	No	(Briata et al., 2021)
Neuroprotective					
Prospective randomized, placebo controlled, parallel group clinical trial, 70 patients with carpel tunnel syndrome	8 weeks	Night wrist splint with topical curcumin gel or placebo gel	Improvement in symptom severity and daily activity	-	(Sharifi Razavi et al., 2024)

Randomized, double-blind, two-group parallel design, 40 non-demented adults aged 51-84 years	18 months	Theracurmin® containing 90 mg of curcumin twice daily (Curcumin treated group N = 21), (Placebo N = 19)	Significant improvement in the curcumin-treated group, including improved memory performance and less neuropathological accumulation in the amygdala and hypothalamus.	Yes: GI symptoms, Temporary feeling of heat and pressure in chest.	(Small et al., 2018)
Randomized, double blind, placebo controlled clinical trial, 78 patients with chemotherapy induced cognitive impairment	7 months	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).	Improvement in cognitive function in curcumin group	-	(Putri Laksmidewi et al., 2024)
Randomized, triple blind, placebo controlled clinical trial, 60 patients with Parkinson's disease	9 months	Curcumin 80mg/day or placebo	Curcumin was well tolerated; however, no efficacy was seen in quality of life and clinical symptoms	Yes, GI symptoms	(Ghodsi et al., 2022)
Comparative, cross-sectional study, 68 patients with mild depression	8 weeks	Curcumin supplementation, sunlight exposure, and mindfulness meditation (MCS)	Lower depression scores, and related biomarkers	-	(Taworntawat et al., 2022)
Randomized, double blind, placebo controlled clinical trial, 152 sedentary obese adults	16 weeks	Curcumin (160 mg/day), or Fish oil (2000 mg docosahexaenoic acid + 400 mg eicosapentaenoic acid)	Fish oil supplementation improved cerebrovascular function; Curcumin had no significant outcomes	No	(Kuszewski et al., 2020)

Randomized, double blind, placebo controlled clinical trial, 78 patients with bipolar disorder in acute phase of mania	4 weeks	Curcumin Nano micelle soft gelatin capsule 40mg/day + sodium valproate (600mg/day + 20mg/kg)	No significant difference was seen among groups	No	(Akbarzadeh et al., 2023)
Randomized, double blind, placebo controlled, 80 patients with diabetic polyneuropathy, anxiety, depression, and stress	8 weeks	Nano-curcumin 80mg/day or placebo	Reduction in depression and anxiety in curcumin groups; however no significant difference in stress was seen between groups	-	(Asadi et al., 2020)
Pseudo randomized, crossover trial, placebo controlled, 20 men with gulf war illness	1 month	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)	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.	Yes, GI symptoms	(Donovan et al., 2021)
Chronic diseases					
Randomized, triple blind, placebo controlled clinical trial, 68 women with endometriosis	8 weeks	Curcumin capsules 500mg or placebo	Curcumin didn't improve symptoms or quality of life	-	(Gudarzi et al., 2024)
Randomized, double blind, placebo controlled clinical trial, 39 diabetic patients undergoing hemodialysis	24 weeks	Curcumin 80mg/day or placebo	Curcumin had no effect on the maximum, mean, or pulse wave velocity (PWV) levels of left or right carotid intima media thickness (CIMT)	No	(Ghasemiadl et al., 2024)

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.

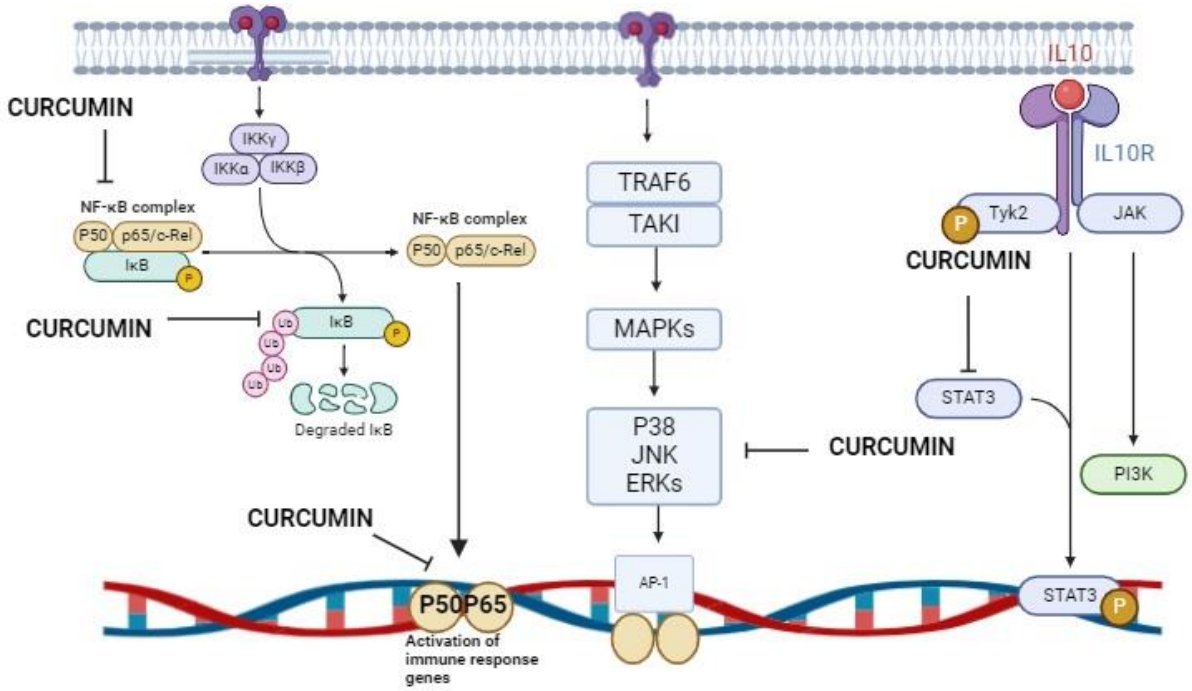

Figure 1: Curcumin's inhibitory action on the inflammatory signaling pathways

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.

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

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-kB, respectively, While the downregulation of NF-kB 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

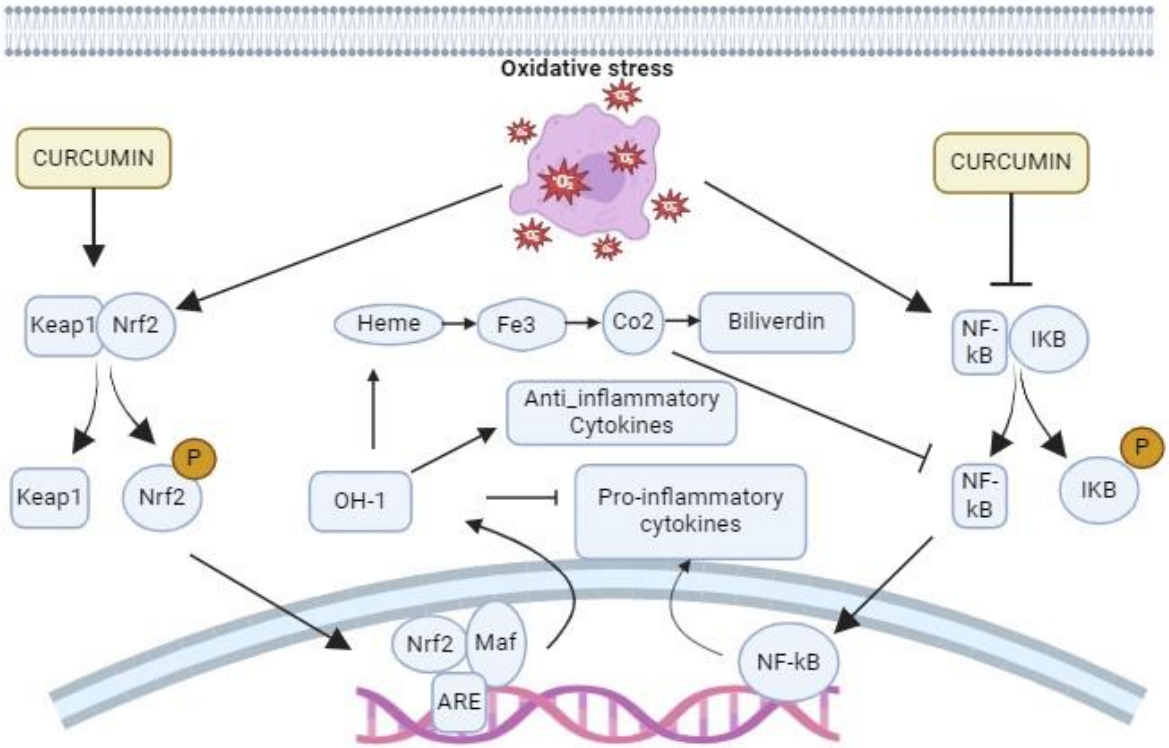

Figure 2: Curcumin exerting antioxidant and anti-inflammatory effect by upregulation and downregulation of Nrf2 and NF-kB.

illustrated in schematic diagram in **Figure 2.**

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 on 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 anti-oxidant 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 Hesarooeyeh 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). **Figure3** below underscores the mechanisms of curcumin and curcumin delivery systems (CDSs) in anti-cancer cell proliferation.

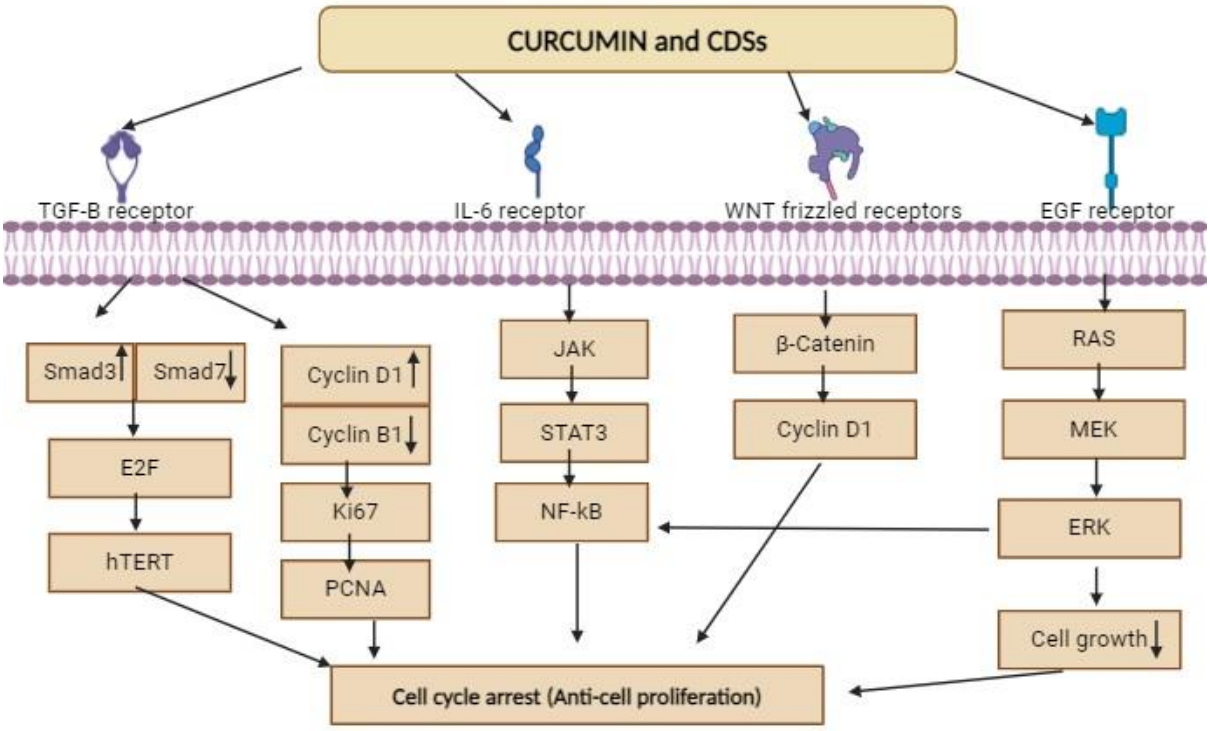

Figure 3: Mechanisms exhibited by curcumin and curcumin delivery systems (CDSs) to produce anticancer effects.

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.

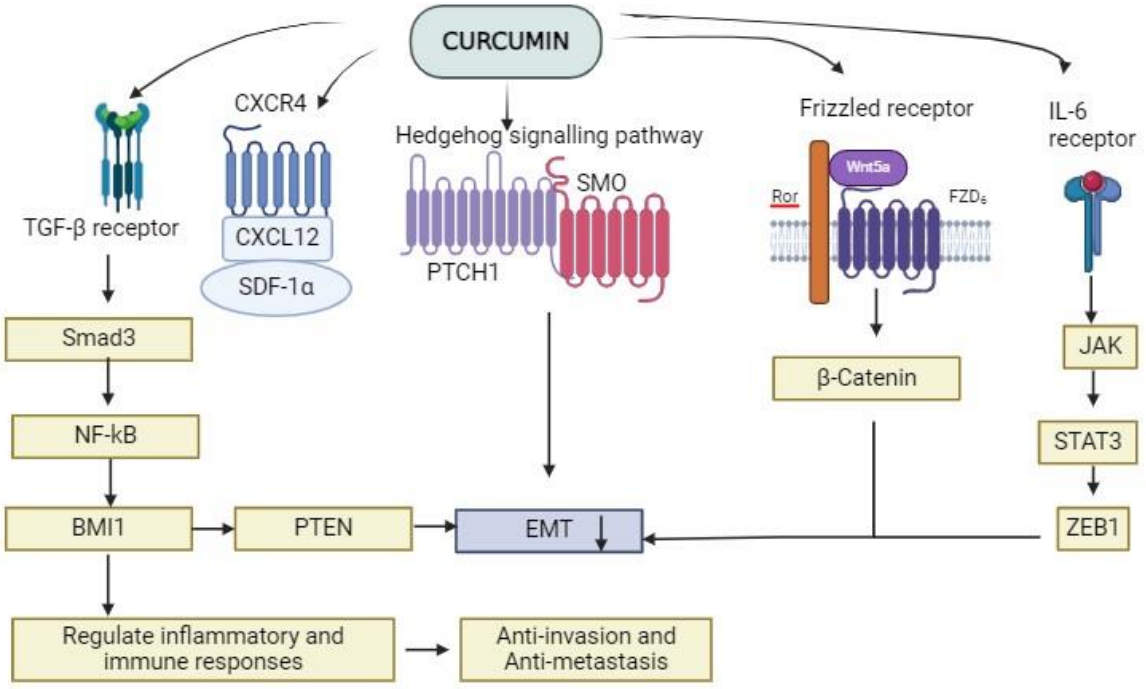

Figure 4: Inhibition of invasion and metastasis by Curcumin through multiple pathways.

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.

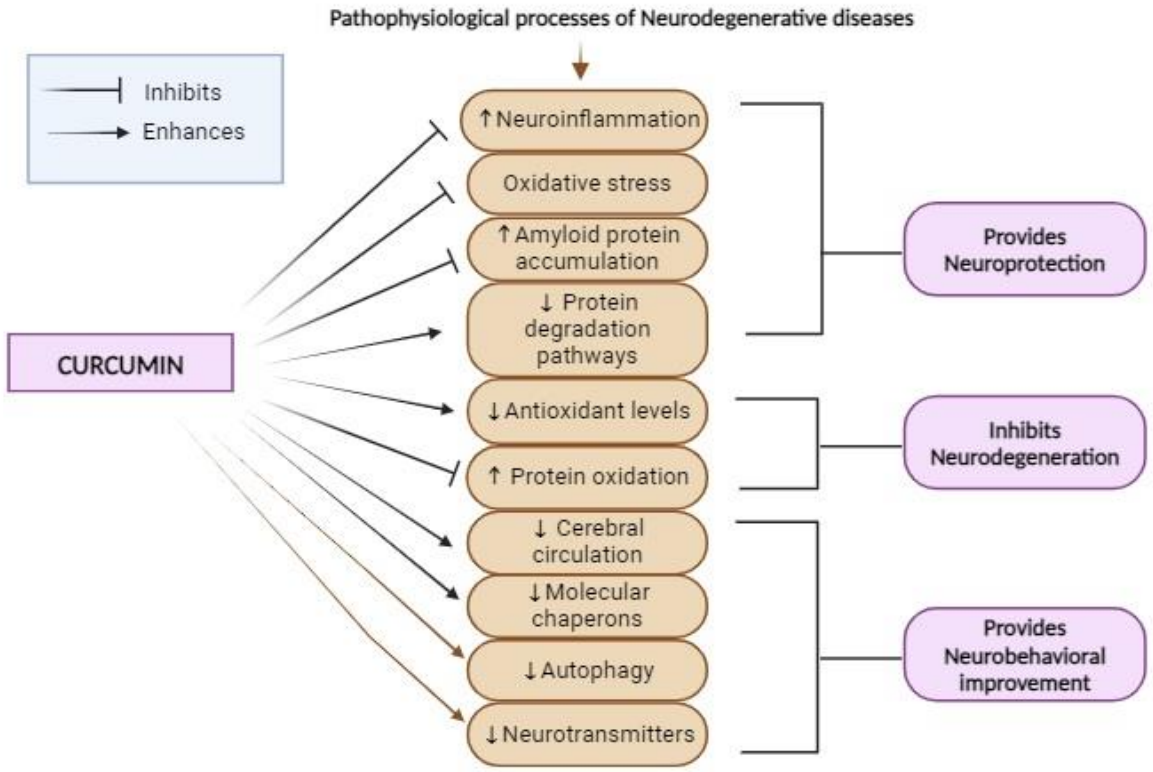

Figure 5: Proposed mechanisms of curcumin in modulating neurodegenerative diseases.

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

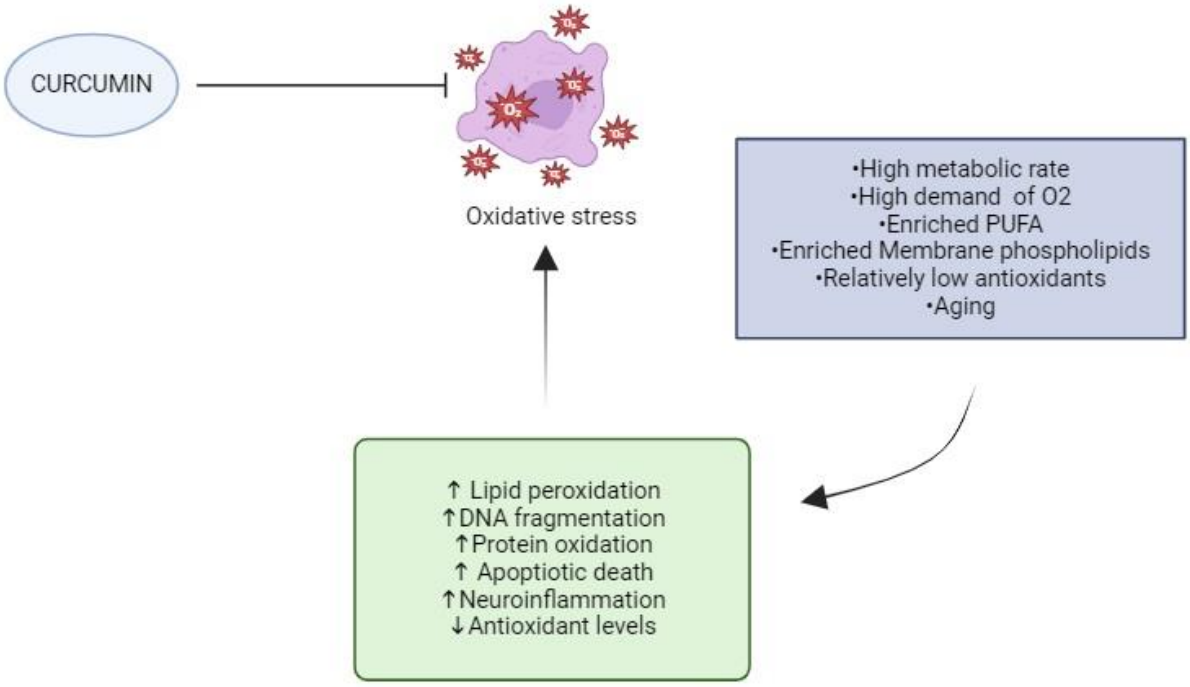

Figure 6: Curcumins influence on oxidative stress in CNS.

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).

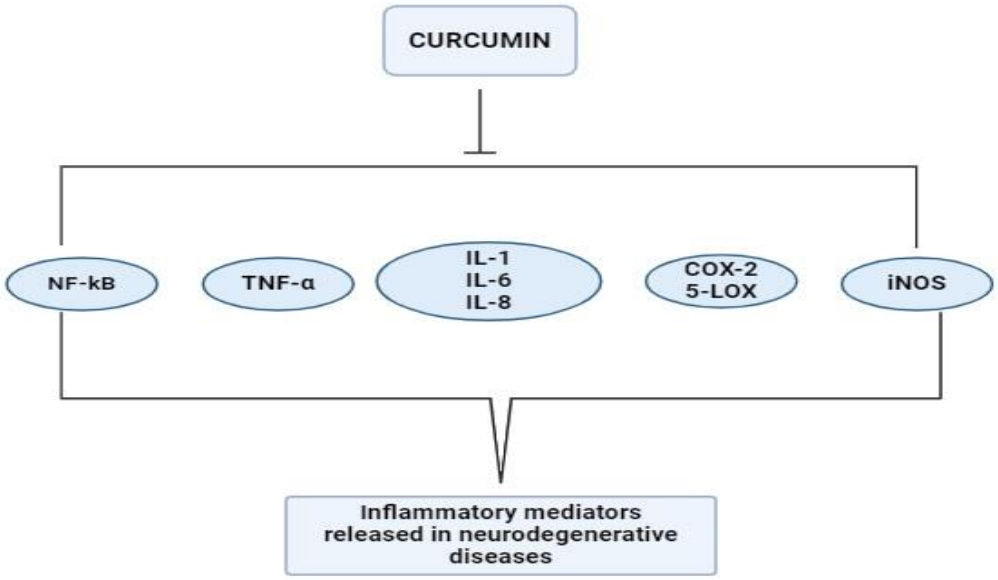

Figure 7: Curcumin's interaction with inflammatory mediators to provide neuroprotective effect.

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-κB, 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, Saghatelyan 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 (Saghatelyan 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

Parameter	Side effects	References
General effects	Chest tightness, GI discomfort, nausea, diarrhea, allergic reactions, dermatitis, skin rashes, swollen skin,	(Burgos-Morón et al.)
Blood clotting	Prolonged clotting process	(Kim et al., 2012)
Gall bladder	Increased bile duct blockage and gallstone contraction	(Burgos-Morón et al.)
Pregnancy	Induce menstruation or stimulate the uterus	(Prasad and Aggarwal, 2011)
Stomach	Increased acidity when taken with antacids	(Prasad and Aggarwal, 2011)

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.

Author Contributions: Conceptualization and final revision by YH and MR; initial data search and manuscript draft by SB and HH.

Conflicts of Interest: The authors declare no conflict of interest.

Funding: This article not received any external funding.

References

Abdul-Rahman, T., Awuah, W.A., Mikhailova, T., Kalmanovich, J., Mehta, A., Ng, J.C., Coghlan, M.A., Zivcevska, M., Tedeschi, A.J., de Oliveira, E.C., 2024. Antioxidant, anti-inflammatory and epigenetic potential of curcumin in Alzheimer's disease. BioFactors.

Aftab, N., Vieira, A., 2010. Antioxidant activities of curcumin and combinations of this curcuminoid with other phytochemicals. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 24(4), 500-502.

Aggarwal, B.B., Kumar, A., Bharti, A.C., 2003. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer research 23(1/A), 363-398.

Akbarzadeh, F., Niksun, N., Behravan, G., Behdani, F., Mohammadpour, A.H., Jaafari, M., Hosseini, T., Rajai, Z., Ebrahimi, A., Eslamzadeh, M., 2023. The effect of adding curcumin to sodium valproate in treatment of patients with bipolar disorder in the acute phase of mania: A randomized double-blind clinical trial. Frontiers in Psychiatry 14.

Ali, B.H., Al-Salam, S., Al Suleimani, Y., Al Kalbani, J., Al Bahlani, S., Ashique, M., Manoj, P., Al Dhahli, B., Al Abri, N., Naser, H.T., 2018. Curcumin ameliorates kidney function and oxidative stress in experimental chronic kidney disease. Basic & Clinical Pharmacology & Toxicology 122(1), 65-73.

Alidadi, M., Sahebkar, A., Eslami, S., Vakilian, F., Jarahi, L., Alinezhad-Namaghi, M., Arabi, S.M., Vakili, S., Tohidinezhad, F., Nikooiyan, Y., 2021. The effect of curcumin supplementation on pulse wave velocity in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. Pharmacological properties of plant-derived natural products and implications for human health, 1-11.

Alrawaiq, N.S., Abdullah, A., 2014. A review of antioxidant polyphenol curcumin and its role in detoxification. Int J Pharm Tech Res 6(1), 280-289.

Arslan, A.K.K., Uzunhisarcıklı, E., Yerer, M.B., Bishayee, A., 2022. The golden spice curcumin in cancer: A perspective on finalized clinical trials during the last 10 years. Journal of Cancer Research and Therapeutics 18(1), 19-26.

Asadi, S., Gholami, M.S., Siassi, F., Qorbani, M., Sotoudeh, G., 2020. Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, double-blind, placebo-controlled clinical trial. Phytotherapy Research 34(4), 896-903.

Atabaki, M., Shariati-Sarabi, Z., Tavakkol-Afshari, J., Mohammadi, M., 2020. Significant immunomodulatory properties of curcumin

in patients with osteoarthritis; a successful clinical trial in Iran. International Immunopharmacology 85, 106607.

Atreya, I., Atreya, R., Neurath, M.F., 2008. NF-κB in inflammatory bowel disease. Journal of internal medicine 263(6), 591-596.

Bagherniya, M., Darand, M., Askari, G., Guest, P.C., Sathyapalan, T., Sahebkar, A., 2021. The clinical use of curcumin for the treatment of rheumatoid arthritis: A systematic review of clinical trials. Studies on Biomarkers and New Targets in Aging Research in Iran: Focus on Turmeric and Curcumin, 251-263.

Bahraini, P., Rajabi, M., Mansouri, P., Sarafian, G., Chalangari, R., Azizian, Z., 2018. Turmeric tonic as a treatment in scalp psoriasis: a randomized placebo-control clinical trial. Journal of Cosmetic Dermatology 17(3), 461-466.

Bahrami, A., Jafari-Nozad, A.M., Karbasi, S., Ayadilord, M., Ferns, G.A., 2023. Efficacy of curcumin on cognitive function scores in women with premenstrual syndrome and dysmenorrhea: a triple-blind, placebo-controlled clinical trial. Chinese journal of integrative medicine 29(5), 387-393.

Bateni, Z., Behrouz, V., Rahimi, H.R., Hedayati, M., Afsharian, S., Sohrab, G., 2022. Effects of nano-curcumin supplementation on oxidative stress, systemic inflammation, adiponectin, and NF-κB in patients with metabolic syndrome: A randomized, double-blind clinical trial. Journal of Herbal Medicine 31, 100531.

Bateni, Z., Rahimi, H.R., Hedayati, M., Afsharian, S., Goudarzi, R., Sohrab, G., 2021. The effects of nano-curcumin supplementation on glycemic control, blood pressure, lipid profile, and insulin resistance in patients with the metabolic syndrome: A randomized, double-blind clinical trial. Phytotherapy Research 35(7), 3945-3953.

Batinić-Haberle, I., Rebouças, J.S., Spasojević, I., 2010. Superoxide dismutase mimics: chemistry, pharmacology, and therapeutic potential. Antioxidants & redox signaling 13(6), 877-918.

Baum, L., Lam, C.W.K., Cheung, S.K.-K., Kwok, T., Lui, V., Tsoh, J., Lam, L., Leung, V., Hui, E., Ng, C., 2008. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. Journal of clinical psychopharmacology 28(1), 110-113.

Bordoloi, D., K Roy, N., Monisha, J., Padmavathi, G., B Kunnumakkara, A., 2016. Multi-targeted agents in cancer cell chemosensitization: what we learnt from curcumin thus far. Recent patents on anti-cancer drug discovery 11(1), 67-97.

Boretti, A., 2024. Curcumin-Based Fixed Dose Combination Products for Cholesterol Management: A Narrative Review. ACS Pharmacology & Translational Science 7(2), 300-308.

Boskabady, M.H., Shakeri, F., Naghdi, F., 2020. The effects of Curcuma Longa L. and its constituents in respiratory disorders and molecular mechanisms of their action. Studies in Natural Products Chemistry 65, 239-269.

Briata, I.M., Paleari, L., Rutigliani, M., Petrera, M., Caviglia, S., Romagnoli, P., Libera, M.D., Oppezzi, M., Puntoni, M., Siri, G., Lazzeroni, M., Howells, L., Singh, R., Brown, K., DeCensi, A., 2021. A Presurgical Study of Curcumin Combined with Anthocyanin Supplements in Patients with Colorectal Adenomatous Polyps, International Journal of Molecular Sciences.

Burgos-Morón, E., Calderón-Montano, J.M., Salvador, J., Robles, A., L ópez-Lázaro, M., 2010. The dark side of curcumin. Int. J. Cancer 126, 177.

Busari, Z.A., Dauda, K.A., Morenikeji, O.A., Afolayan, F., Oyeyemi, O.T., Meena, J., Sahu, D., Panda, A.K., 2017. Antiplasmodial activity and toxicological assessment of curcumin PLGA-encapsulated nanoparticles. Frontiers in pharmacology 8, 622.

Calaf, G.M., Ponce-Cusi, R., Carrión, F., 2018. Curcumin and paclitaxel induce cell death in breast cancer cell lines. Oncology Reports 40(4), 2381-2388.

Cao, Q., Zhang, J., Gao, L., Zhang, Y., Dai, M., Bao, M., 2018. Dickkopf-3 upregulation mediates the cardioprotective effects of curcumin on chronic heart failure. Molecular medicine reports 17(5), 7249-7257.

Chen, S., Nimick, M., Cridge, A.G., Hawkins, B.C., Rosengren, R.J., 2018. Anticancer

potential of novel curcumin analogs towards castrate-resistant prostate cancer. International Journal of Oncology 52(2), 579-588.

Choi, Y.H., Han, D.H., Kim, S.-w., Kim, M.-J., Sung, H.H., Jeon, H.G., Jeong, B.C., Seo, S.I., Jeon, S.S., Lee, H.M., Choi, H.Y., 2019. A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent androgen deprivation. The Prostate 79(6), 614-621.

Chongtham, A., Agrawal, N., 2016. Curcumin modulates cell death and is protective in Huntington's disease model. Scientific Reports 6(1), 18736.

Clarke, M.A., Wentzensen, N., Mirabello, L., Ghosh, A., Wacholder, S., Harari, A., Lorincz, A., Schiffman, M., Burk, R.D., 2012. Human papillomavirus DNA methylation as a potential biomarker for cervical cancer. Cancer Epidemiology, biomarkers & prevention 21(12), 2125-2137.

Cox, F.F., Misiou, A., Vierkant, A., Ale-Agha, N., Grandoch, M., Haendeler, J., Altschmied, J., 2022. Protective effects of curcumin in cardiovascular diseases—Impact on oxidative stress and mitochondria. Cells 11(3), 342.

Cox, K.H.M., Pipingas, A., Scholey, A.B., 2015. Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. Journal of psychopharmacology 29(5), 642-651.

Cox, K.H.M., White, D.J., Pipingas, A., Poorun, K., Scholey, A., 2020. Further evidence of benefits to mood and working memory from lipidated curcumin in healthy older people: a 12-week, double-blind, placebo-controlled, partial replication study. Nutrients 12(6), 1678.

Cruz-Correa, M., Hylind, L.M., Marrero, J.H., Zahurak, M.L., Murray-Stewart, T., Casero, R.A., Montgomery, E.A., Iacobuzio-Donahue, C., Brosens, L.A., Offerhaus, G.J., Umar, A., Rodriguez, L.M., Giardiello, F.M., 2018. Efficacy and Safety of Curcumin in Treatment of Intestinal Adenomas in Patients With Familial Adenomatous Polyposis. Gastroenterology 155(3), 668-673.

Dai, C., Ciccotosto, G.D., Cappai, R., Tang, S., Li, D., Xie, S., Xiao, X., Velkov, T., 2018. Curcumin attenuates colistin-induced neurotoxicity in N2a cells via anti-inflammatory activity, suppression of oxidative stress, and apoptosis. Molecular neurobiology 55, 421-434.

Dai, Q., Zhou, D., Xu, L., Song, X., 2018. Curcumin alleviates rheumatoid arthritis-induced inflammation and synovial hyperplasia by targeting mTOR pathway in rats. Drug design, development and therapy, 4095-4105.

de Almeida Alvarenga, L., de Oliveira Leal, V., Borges, N.A., de Aguiar, A.S., Faxén-Irving, G., Stenvinkel, P., Lindholm, B., Mafra, D., 2018. Curcumin-A promising nutritional strategy for chronic kidney disease patients. Journal of Functional Foods 40, 715-721.

Den Hartogh, D.J., Gabriel, A., Tsiani, E., 2020. Antidiabetic properties of curcumin I: Evidence from in vitro studies. Nutrients 12(1), 118.

Donovan, E.K., Kekes-Szabo, S., Lin, J.C., Massey, R.L., Cobb, J.D., Hodgin, K.S., Ness, T.J., Hangee-Bauer, C., Younger, J.W., 2021. A Placebo-Controlled, Pseudo-Randomized, Crossover Trial of Botanical Agents for Gulf War Illness: Curcumin (Curcuma longa), Boswellia (Boswellia serrata), and French Maritime Pine Bark (Pinus pinaster), International Journal of Environmental Research and Public Health.

Ebrahimzadeh, A., Mohseni, S., Safargar, M., Mohtashamian, A., Niknam, S., Bakhoda, M., Afshari, S., Jafari, A., Ebrahimzadeh, A., Fooladshekan, S., Mohtashami, A., Ferns, G.A., Babajafari, S., Sohrabi, Z., 2024. Curcumin effects on glycaemic indices, lipid profile, blood pressure, inflammatory markers and anthropometric measurements of non-alcoholic fatty liver disease patients: A systematic review and meta-analysis of randomized clinical trials. Complementary Therapies in Medicine 80, 103025.

Edwards, R.L., Luis, P.B., Varuzza, P.V., Joseph, A.I., Presley, S.H., Chaturvedi, R., Schneider, C., 2017. The anti-inflammatory activity of curcumin is mediated by its oxidative

metabolites. Journal of Biological Chemistry 292(52), 21243-21252.
Emami, E., Heidari-Soureshjani, S., Sherwin, C.M.T., 2022. Anti-inflammatory response to curcumin supplementation in chronic kidney disease and hemodialysis patients: A systematic review and meta-analysis. Avicenna Journal of Phytomedicine 12(6), 576.
Fallahi, F., Borran, S., Ashrafizadeh, M., Zarrabi, A., Pourhanifeh, M.H., Mahabady, M.K., Sahebkar, A., Mirzaei, H., 2021. Curcumin and inflammatory bowel diseases: From in vitro studies to clinical trials. Molecular Immunology 130, 20-30.
Gbolahan, O.B., O'Neil, B.H., McRee, A.J., Sanoff, H.K., Fallon, J.K., Smith, P.C., Ivanova, A., Moore, D.T., Dumond, J., Asher, G.N., 2022. A phase I evaluation of the effect of curcumin on dose-limiting toxicity and pharmacokinetics of irinotecan in participants with solid tumors. Clinical and Translational Science 15(5), 1304-1315.
Ghaeini Hesarooeyeh, Z., Basham, A., Sheybani-Arani, M., Abbaszadeh, M., Salimi Asl, A., Moghbeli, M., Saburi, E., 2024. Effect of resveratrol and curcumin and the potential synergism on hypertension: A mini-review of human and animal model studies. Phytotherapy Research 38(1), 42-58.
Ghasemiadl, M., Ghasemi, S., Soleimani, A., Esfahani, M.M., Azadbakht, J., Gilasi, H.R., Talari, H.R., 2024. The Effects of Curcumin Administration on Carotid Intima-Media Thickness and Pulse Wave Velocity in Diabetic Hemodialysis Patients: A Randomized, Double-Blinded, Placebo-Controlled Trial. International Journal of Preventive Medicine 15.
Ghodsi, H., Rahimi, H.R., Aghili, S.M., Saberi, A., Shoeibi, A., 2022. Evaluation of curcumin as add-on therapy in patients with Parkinson's disease: A pilot randomized, triple-blind, placebo-controlled trial. Clinical Neurology and Neurosurgery 218, 107300.
Girisa, S., Kumar, A., Rana, V., Parama, D., Daimary, U.D., Warnakulasuriya, S., Kumar, A.P., Kunnumakkara, A.B., 2021. From Simple Mouth Cavities to Complex Oral Mucosal Disorders—Curcuminoids as a Promising Therapeutic Approach. ACS Pharmacology & Translational Science 4(2), 647-665.
Gregersen, N., Bross, P., 2010. Protein misfolding and cellular stress: an overview. Protein Misfolding and Cellular Stress in Disease and Aging: Concepts and Protocols, 3-23.
Greil, R., Greil-Ressler, S., Weiss, L., Schönlieb, C., Magnes, T., Radl, B., Bolger, G.T., Vcelar, B., Sordillo, P.P., 2018. A phase 1 dose-escalation study on the safety, tolerability and activity of liposomal curcumin (Lipocurc™) in patients with locally advanced or metastatic cancer. Cancer chemotherapy and pharmacology 82, 695-706.
Gudarzi, R., Shabani, F., Mohammad-Alizadeh-Charandabi, S., Naghshineh, E., Shaseb, E., Mirghafourvand, M., 2024. Effect of curcumin on painful symptoms of endometriosis: A triple-blind randomized controlled trial. Phytotherapy Research 38(1), 147-155.
Gülcin, I., 2012. Antioxidant activity of food constituents: an overview. Archives of toxicology 86, 345-391.
Gunther, J.R., Chadha, A.S., Guha, S., Raju, G.S., Maru, D.M., Munsell, M.F., Jiang, Y., Yang, P., Felix, E., Clemons, M., Mathew, G.G., Singh, P.K., Skibber, J.M., Rodriguez-Bigas, M.A., Chang, G.J., Eng, C., Delclos, M.E., Crane, C.H., Das, P., Krishnan, S., 2022. A phase II randomized double blinded trial evaluating the efficacy of curcumin with pre-operative chemoradiation for rectal cancer. Journal of gastrointestinal oncology 13(6), 2938-2950.
Gupta, S.C., Patchva, S., Aggarwal, B.B., 2013. Therapeutic roles of curcumin: lessons learned from clinical trials. The AAPS journal 15, 195-218.
Gupta, S.C., Patchva, S., Koh, W., Aggarwal, B.B., 2012. Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clinical and experimental pharmacology and physiology 39(3), 283-299.
Gupta, S.C., Prasad, S., Kim, J.H., Patchva, S., Webb, L.J., Priyadarsini, I.K., Aggarwal, B.B., 2011. Multitargeting by curcumin as revealed by molecular interaction studies. Natural product reports 28(12), 1937-1955.
Hafner-Bratkovič, I., Gašperšič, J., Šmid, L.M., Bresjanac, M., Jerala, R., 2008. Curcumin binds to the α-helical intermediate and to the

amyloid form of prion protein–a new mechanism for the inhibition of PrPSc accumulation. Journal of neurochemistry 104(6), 1553-1564.

Haftcheshmeh, S.M., Mirhafez, S.R., Abedi, M., Heydarlou, H., Shakeri, A., Mohammadi, A., Sahebkar, A., 2022. Therapeutic potency of curcumin for allergic diseases: A focus on immunomodulatory actions. Biomedicine & Pharmacotherapy 154, 113646.

Hassani, S., Esmaeili, A., 2024. The neuroprotective effects of Ferulic acid in toxin-induced models of Parkinson's disease: a review. Ageing Research Reviews, 102299.

Hassanizadeh, S., Shojaei, M., Bagherniya, M., Orekhov, A.N., Sahebkar, A., 2023. Effect of nano-curcumin on various diseases: A comprehensive review of clinical trials. Biofactors 49(3), 512-533.

He, X., Li, G., Chen, Y., Xiao, Q., Yu, X., Yu, X., Lu, X., Xiang, Z., 2020. Pharmacokinetics and pharmacodynamics of the combination of rhein and curcumin in the treatment of chronic kidney disease in rats. Frontiers in Pharmacology 11, 573118.

He, Y., Li, W., Hu, G., Sun, H., Kong, Q., 2018. Bioactivities of EF24, a novel curcumin analog: a review. Frontiers in Oncology 8, 614.

He, Y., Yue, Y., Zheng, X., Zhang, K., Chen, S., Du, Z., 2015a. Curcumin, inflammation, and chronic diseases: how are they linked? Molecules 20(5), 9183-9213.

He, Y., Yue, Y., Zheng, X., Zhang, K., Chen, S., Du, Z., 2015b. Curcumin, Inflammation, and Chronic Diseases: How Are They Linked?, Molecules. pp. 9183-9213.

Hegde, M., Girisa, S., BharathwajChetty, B., Vishwa, R., Kunnumakkara, A.B., 2023. Curcumin Formulations for Better Bioavailability: What We Learned from Clinical Trials Thus Far? ACS Omega 8(12), 10713-10746.

Heidari-Beni, M., Moravejolahkami, A.R., Gorgian, P., Askari, G., Tarrahi, M.J., Bahreini-Esfahani, N., 2020. Herbal formulation "turmeric extract, black pepper, and ginger" versus Naproxen for chronic knee osteoarthritis: A randomized, double-blind, controlled clinical trial. Phytotherapy Research 34(8), 2067-2073.

Howells, L.M., Iwuji, C.O.O., Irving, G.R.B., Barber, S., Walter, H., Sidat, Z., Griffin-Teall, N., Singh, R., Foreman, N., Patel, S.R., Morgan, B., Steward, W.P., Gescher, A., Thomas, A.L., Brown, K., 2019. Curcumin Combined with FOLFOX Chemotherapy Is Safe and Tolerable in Patients with Metastatic Colorectal Cancer in a Randomized Phase IIa Trial. The Journal of Nutrition 149(7), 1133-1139.

Hsu, K.Y., Ho, C.T., Pan, M.H., 2023. The therapeutic potential of curcumin and its related substances in turmeric: From raw material selection to application strategies. Journal of food and drug analysis 31(2), 194-211.

Huang, L., Chen, C., Zhang, X., Li, X., Chen, Z., Yang, C., Liang, X., Zhu, G., Xu, Z., 2018. Neuroprotective effect of curcumin against cerebral ischemia-reperfusion via mediating autophagy and inflammation. Journal of Molecular Neuroscience 64, 129-139.

Jakubczyk, K., Drużga, A., Katarzyna, J., Skonieczna-Żydecka, K., 2020. Antioxidant potential of curcumin—A meta-analysis of randomized clinical trials. Antioxidants 9(11), 1092.

Jamwal, R., 2018. Bioavailable curcumin formulations: A review of pharmacokinetic studies in healthy volunteers. Journal of Integrative Medicine 16(6), 367-374.

Jat, D., Parihar, P., Kothari, S.C., Parihar, M.S., 2013. Curcumin reduces oxidative damage by increasing reduced glutathione and preventing membrane permeability transition in isolated brain mitochondria. Cellular and Molecular Biology 59(2), 1899-1805.

Jurenka, J.S., 2009. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative medicine review 14(2).

Kang, D., Li, B., Luo, L., Jiang, W., Lu, Q., Rong, M., Lai, R., 2016. Curcumin shows excellent therapeutic effect on psoriasis in mouse model. Biochimie 123, 73-80.

Kim, D.-C., Ku, S.-K., Bae, J.-S., 2012. Anticoagulant activities of curcumin and its derivative. BMB reports 45(4), 221-226.

Kumar, A., Harsha, C., Parama, D., Girisa, S., Daimary, U.D., Mao, X., Kunnumakkara, A.B.,

2021. Current clinical developments in curcumin-based therapeutics for cancer and chronic diseases. Phytotherapy Research 35(12), 6768-6801.

Kunnumakkara, A.B., Anand, P., Aggarwal, B.B., 2008. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer letters 269(2), 199-225.

Kunnumakkara, Ajaikumar B., Bordoloi, D., Harsha, C., Banik, K., Gupta, Subash C., Aggarwal, Bharat B., 2017. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. Clinical Science 131(15), 1781-1799.

Kunnumakkara, A.B., Bordoloi, D., Padmavathi, G., Monisha, J., Roy, N.K., Prasad, S., Aggarwal, B.B., 2017. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. British journal of pharmacology 174(11), 1325-1348.

Kuszewski, J.C., Wong, R.H.X., Wood, L.G., Howe, P.R.C., 2020. Effects of fish oil and curcumin supplementation on cerebrovascular function in older adults: A randomized controlled trial. Nutrition, Metabolism and Cardiovascular Diseases 30(4), 625-633.

Lari, S.M., Mohamadpour, A.H., Attaran, D., Jafari, M., Arasteh, O., Emadzadeh, M., Mozdourian, M., Attaran, S., Javidarabshahi, Z., 2024. Evaluation of oral nano-curcumin efficacy on respiratory function and quality of life in patients with bronchial non-atopic asthma: A randomized controlled trial. Avicenna Journal of Phytomedicine 14(2).

Lee, W.-H., Loo, C.-Y., Young, P.M., Traini, D., Mason, R.S., Rohanizadeh, R., 2014. Recent advances in curcumin nanoformulation for cancer therapy. Expert opinion on drug delivery 11(8), 1183-1201.

Lestari, M.L., Indrayanto, G., 2014. Curcumin. Profiles of drug substances, excipients, and related methodology 39, 113-204.

Li, H., Sureda, A., Devkota, H.P., Pittalà, V., Barreca, D., Silva, A.S., Tewari, D., Xu, S., Nabavi, S.M., 2020. Curcumin, the golden spice in treating cardiovascular diseases. Biotechnology advances 38, 107343.

Liddle, M., Hull, C., Liu, C., Powell, D., 2006. Contact urticaria from curcumin. DERM 17(4), 196-197.

Lin, D., Xiao, L., Qin, W., Loy, D.A., Wu, Z., Chen, H., Zhang, Q., 2022. Preparation, characterization and antioxidant properties of curcumin encapsulated chitosan/lignosulfonate micelles. Carbohydrate Polymers 281, 119080.

Lin, Y.G., Kunnumakkara, A.B., Nair, A., Merritt, W.M., Han, L.Y., Armaiz-Pena, G.N., Kamat, A.A., Spannuth, W.A., Gershenson, D.M., Lutgendorf, S.K., 2007. Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-κB pathway. Clinical Cancer Research 13(11), 3423-3430.

Liu, L., Shang, Y., Li, M., Han, X., Wang, J., Wang, J., 2015. Curcumin ameliorates asthmatic airway inflammation by activating nuclear factor-E2-related factor 2/haem oxygenase (HO)-1 signalling pathway. Clinical and Experimental Pharmacology and Physiology 42(5), 520-529.

Liu, X., Miao, X., Bo, S., Deng, X., Zhang, Z., Zheng, Y., 2024. Macrophage membrane-coated self-assembled curcumin nanoparticle missile for the treatment of colorectal cancer. Journal of Drug Delivery Science and Technology 91, 105237.

Mahammedi, H., Planchat, E., Pouget, M., Durando, X., Curé, H., Guy, L., Van-Praagh, I., Savareux, L., Atger, M., Bayet-Robert, M., 2016. The new combination docetaxel, prednisone and curcumin in patients with castration-resistant prostate cancer: a pilot phase II study. Oncology 90(2), 69-78.

Maiti, P., Dunbar, G.L., 2018. Use of Curcumin, a Natural Polyphenol for Targeting Molecular Pathways in Treating Age-Related Neurodegenerative Diseases, International Journal of Molecular Sciences.

Makuch, S., Więcek, K., Woźniak, M., 2021. The immunomodulatory and anti-inflammatory effect of curcumin on immune cell populations, cytokines, and in vivo models of rheumatoid arthritis. Pharmaceuticals 14(4), 309.

Manikandan, R., Beulaja, M., Thiagarajan, R., Priyadarsini, A., Saravanan, R., Arumugam,

M., 2011. Ameliorative effects of curcumin against renal injuries mediated by inducible nitric oxide synthase and nuclear factor kappa B during gentamicin-induced toxicity in Wistar rats. European journal of pharmacology 670(2-3), 578-585.

Marchiani, A., Rozzo, C., Fadda, A., Delogu, G., Ruzza, P., 2014. Curcumin and curcumin-like molecules: from spice to drugs. Current medicinal chemistry 21(2), 204-222.

Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454(7203), 428-435.

Medzhitov, R., 2010. Inflammation 2010: new adventures of an old flame. Cell 140(6), 771-776.

Memarzia, A., Saadat, S., Behrouz, S., Boskabady, M.H., 2022. Curcuma longa and curcumin affect respiratory and allergic disorders, experimental and clinical evidence: A comprehensive and updated review. BioFactors 48(3), 521-551.

Menon, V.P., Sudheer, A.R., 2007. Antioxidant and anti-inflammatory properties of curcumin. The molecular targets and therapeutic uses of curcumin in health and disease, 105-125.

Mishra, S., Palanivelu, K., 2008. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Annals of Indian Academy of Neurology 11(1), 13-19.

Mofid, B., Razzaghdoust, A., Sadipour, A., Bakhshandeh, M., Mahdavi, A., Simforoush, N., 2018. Lack of radioprotective efficacy of nanocurcumin in prostate cancer patients undergoing radiotherapy. Radiother Oncol 127, S835-S836.

Mohorko, N., Repovš, G., Popović, M., Kovacs, G.G., Bresjanac, M., 2010. Curcumin labeling of neuronal fibrillar tau inclusions in human brain samples. Journal of Neuropathology & Experimental Neurology 69(4), 405-414.

Mohseni, M., Sahebkar, A., Askari, G., Johnston, T.P., Alikiaii, B., Bagherniya, M., 2021. The clinical use of curcumin on neurological disorders: An updated systematic review of clinical trials. Phytotherapy Research 35(12), 6862-6882.

Momtazi-Borojeni, A.A., Mosafer, J., Nikfar, B., Ekhlasi-Hundrieser, M., Chaichian, S., Mehdizadehkashi, A., Vaezi, A., 2019. Curcumin in advancing treatment for gynecological cancers with developed drug- and radiotherapy-associated resistance. Reviews of Physiology, Biochemistry and Pharmacology 176, 107-129.

Morales, N.P., Sirijaroonwong, S., Yamanont, P., Phisalaphong, C., 2015. Electron paramagnetic resonance study of the free radical scavenging capacity of curcumin and its demethoxy and hydrogenated derivatives. Biological and Pharmaceutical Bulletin 38(10), 1478-1483.

Mosley, R.L., Benner, E.J., Kadiu, I., Thomas, M., Boska, M.D., Hasan, K., Laurie, C., Gendelman, H.E., 2006. Neuroinflammation, oxidative stress, and the pathogenesis of Parkinson's disease. Clinical neuroscience research 6(5), 261-281.

Moutinho, M.S.S., Aragao, S., Carmo, D., Casaca, F., Silva, S., Ribeiro, J., Sousa, H., Pires, I., Queiroga, F., Colaco, B., 2018. Curcumin and rutin down-regulate cyclooxygenase-2 and reduce tumor-associated inflammation in HPV16-transgenic mice. Anticancer research 38(3), 1461-1466.

Nakagawa, Y., Mukai, S., Yamada, S., Murata, S., Yabumoto, H., Maeda, T., Akamatsu, S., 2020. The Efficacy and Safety of Highly-Bioavailable Curcumin for Treating Knee Osteoarthritis: A 6-Month Open-Labeled Prospective Study. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 13, 1179544120948471.

Nasseri, E., Mohammadi, E., Tamaddoni, A., Qujeq, D., Zayeri, F., Zand, H., 2018. Benefits of curcumin supplementation on antioxidant status in β-thalassemia major patients: a double-blind randomized controlled clinical trial. Annals of Nutrition and Metabolism 71(3-4), 136-144.

Oglah, M.K., Mustafa, Y.F., Bashir, M.K., Jasim, M.H., Mustafa, Y.F., 2020. Curcumin and its derivatives: A review of their biological activities. Syst. Rev. Pharm 11(3), 472-481.

Ojo, O.A., Adeyemo, T.R., Rotimi, D., Batiha, G.E.-S., Mostafa-Hedeab, G., Iyobhebhe, M.E., Elebiyo, T.C., Atunwa, B., Ojo, A.B., Lima, C.M.G., 2022. Anticancer properties of

curcumin against colorectal cancer: a review. Frontiers in Oncology 12, 881641.

Osali, A., 2020. Aerobic exercise and nano-curcumin supplementation improve inflammation in elderly females with metabolic syndrome. Diabetology & Metabolic Syndrome 12, 1-7.

Panahi, Y., Hosseini, M.S., Khalili, N., Naimi, E., Simental-Mendía, L.E., Majeed, M., Sahebkar, A., 2016. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomedicine & pharmacotherapy 82, 578-582.

Pancholi, V., Smina, T.P., Kunnumakkara, A.B., Maliakel, B., Krishnakumar, I.M., 2021. Safety assessment of a highly bioavailable curcumin-galactomannoside complex (CurQfen) in healthy volunteers, with a special reference to the recent hepatotoxic reports of curcumin supplements: A 90-days prospective study. Toxicology Reports 8, 1255-1264.

Parsamanesh, N., Moossavi, M., Bahrami, A., Butler, A.E., Sahebkar, A., 2018. Therapeutic potential of curcumin in diabetic complications. Pharmacological research 136, 181-193.

Passildas-Jahanmohan, J., Eymard, J.-C., Pouget, M., Kwiatkowski, F., Van Praagh, I., Savareux, L., Atger, M., Durando, X., Abrial, C., Richard, D., Ginzac Couvé, A., Thivat, E., Monange, B., Chollet, P., Mahammedi, H., 2021. Multicenter randomized phase II study comparing docetaxel plus curcumin versus docetaxel plus placebo in first-line treatment of metastatic castration-resistant prostate cancer. Cancer Medicine 10(7), 2332-2340.

Pawar, K.S., Mastud, R.N., Pawar, S.K., Pawar, S.S., Bhoite, R.R., Bhoite, R.R., Kulkarni, M.V., Deshpande, A.R., 2021. Oral curcumin with piperine as adjuvant therapy for the treatment of COVID-19: a randomized clinical trial. Frontiers in pharmacology 12, 669362.

Peng, Y., Ao, M., Dong, B., Jiang, Y., Yu, L., Chen, Z., Hu, C., Xu, R., 2021. Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures. Drug Design, Development and Therapy 15(null), 4503-4525.

Perrone, D., Ardito, F., Giannatempo, G., Dioguardi, M., Troiano, G., Lo Russo, L., De Lillo, A., Laino, L., Lo Muzio, L., 2015. Biological and therapeutic activities, and anticancer properties of curcumin. Experimental and therapeutic medicine 10(5), 1615-1623.

Pivari, F., Mingione, A., Brasacchio, C., Soldati, L., 2019. Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment. Nutrients 11(8), 1837.

Pourbagher-Shahri, A.M., Farkhondeh, T., Ashrafizadeh, M., Talebi, M., Samargahndian, S., 2021. Curcumin and cardiovascular diseases: Focus on cellular targets and cascades. Biomedicine & Pharmacotherapy 136, 111214.

Prasad, S., Aggarwal, B.B., 2011. Turmeric, the golden spice. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition.

Priyadarsini, K.I., 2014. The chemistry of curcumin: from extraction to therapeutic agent. Molecules 19(12), 20091-20112.

Putri Laksmidewi, A.A.A., Mahendra, I.N.B., Soejitno, A., Vania, A., 2024. Improving cognitive function with intermittent dose escalation of curcumin extract in chemotherapy-induced cognitive impairment patients: a randomized controlled trial. Advances in Traditional Medicine.

Qin, S., Huang, L., Gong, J., Shen, S., Huang, J., Ren, H., Hu, H., 2017. Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. Nutrition journal 16, 1-10.

Rajitha, B., Belalcazar, A., Nagaraju, G.P., Shaib, W.L., Snyder, J.P., Shoji, M., Pattnaik, S., Alam, A., El-Rayes, B.F., 2016. Inhibition of NF-κB translocation by curcumin analogs induces G0/G1 arrest and downregulates thymidylate synthase in colorectal cancer. Cancer letters 373(2), 227-233.

Ramezani, V., Ghadirian, S., Shabani, M., Boroumand, M.A., Daneshvar, R., Saghafi, F., 2023. Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: a preliminary randomized controlled clinical trial. BMC cancer 23(1), 354.

Razavi, S.M., Khayatan, D., Arab, Z.N., Momtaz, S., Zare, K., Jafari, R.M., Dehpour, A.R., Abdolghaffari, A.H., 2021. Licofelone, a potent COX/5-LOX inhibitor and a novel option for treatment of neurological disorders. Prostaglandins & Other Lipid Mediators 157, 106587.

Recio, M.C., Andujar, I., 2012. L Rios. J. Anti-inflammatory agents from plants: Progress and potential. Curr. Med. Chem 19, 2088-2103.

Reis, D.C.M.V., Alvarenga, L., Cardozo, L.F.M.F., Baptista, B.G., Fanton, S., Paiva, B.R., Ribeiro-Alves, M., Fortunato, R.S., Vasconcelos, A.L., Nakao, L.S., Sanz, C.L., Berretta, A.A., Leite, M., Mafra, D., 2024. Can curcumin supplementation break the vicious cycle of inflammation, oxidative stress, and uremia in patients undergoing peritoneal dialysis? Clinical Nutrition ESPEN 59, 96-106.

Ribeiro, A.P.D., Pavarina, A.C., Dovigo, L.N., Brunetti, I.L., Bagnato, V.S., Vergani, C.E., de Souza Costa, C.A., 2013. Phototoxic effect of curcumin on methicillin-resistant Staphylococcus aureus and L929 fibroblasts. Lasers in medical science 28, 391-398.

Ringman, J.M., Frautschy, S.A., Teng, E., Begum, A.N., Bardens, J., Beigi, M., Gylys, K.H., Badmaev, V., Heath, D.D., Apostolova, L.G., 2012. Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alzheimer's research & therapy 4, 1-8.

Saber-Moghaddam, N., Salari, S., Hejazi, S., Amini, M., Taherzadeh, Z., Eslami, S., Rezayat, S.M., Jaafari, M.R., Elyasi, S., 2021. Oral nano-curcumin formulation efficacy in management of mild to moderate hospitalized coronavirus disease-19 patients: An open label nonrandomized clinical trial. Phytotherapy Research 35(5), 2616-2623.

Saberi-Karimian, M., Keshvari, M., Ghayour-Mobarhan, M., Salehizadeh, L., Rahmani, S., Behnam, B., Jamialahmadi, T., Asgary, S., Sahebkar, A., 2020. Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: A randomized controlled trial. Complementary Therapies in Medicine 49, 102322.

Saghatelyan, T., Tananyan, A., Janoyan, N., Tadevosyan, A., Petrosyan, H., Hovhannisyan, A., Hayrapetyan, L., Arustamyan, M., Arnhold, J., Rotmann, A.-R., 2020a. Efficacy and safety of curcumin in combination with paclitaxel in patients with advanced, metastatic breast cancer: A comparative, randomized, double-blind, placebo-controlled clinical trial. Phytomedicine 70, 153218.

Saghatelyan, T., Tananyan, A., Janoyan, N., Tadevosyan, A., Petrosyan, H., Hovhannisyan, A., Hayrapetyan, L., Arustamyan, M., Arnhold, J., Rotmann, A.-R., Hovhannisyan, A., Panossian, A., 2020b. Efficacy and safety of curcumin in combination with paclitaxel in patients with advanced, metastatic breast cancer: A comparative, randomized, double-blind, placebo-controlled clinical trial. Phytomedicine 70, 153218.

Sahebkar, A., Serban, M.-C., Ursoniu, S., Banach, M., 2015. Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. Journal of functional foods 18, 898-909.

Sankar, P., Gopal Telang, A., Kalaivanan, R., Karunakaran, V., Manikam, K., Sarkar, S.N., 2015. Effects of nanoparticle-encapsulated curcumin on arsenic-induced liver toxicity in rats. Environmental toxicology 30(6), 628-637.

Santosa, D., Suharti, C., Riwanto, I., Dharmana, E., Pangarsa, E.A., Setiawan, B., Suyono, S., Tobing, M.L., Suhartono, S., Hadisapurto, S., 2022. Curcumin as adjuvant therapy to improve remission in myeloma patients: A pilot randomized clinical trial. Caspian journal of internal medicine 13(2), 375-384.

Shabanian Boroujeni, Z., Heidari-Soureshjani, S., Sherwin, C.M.T., 2024. Effects of Curcuma longa (turmeric) and curcumin on the premenstrual syndrome and dysmenorrhea: A systematic review. Journal of Endometriosis and Pelvic Pain Disorders, 22840265231219331.

Sharifi Razavi, A., Mohajerani, F., Niksolat, F., Karimi, N., 2024. Efficacy of topical curcumin on mild to moderate carpal tunnel syndrome: a randomized double-blind, placebo-controlled clinical trial. Pain Medicine, pnae001.

Shehzad, A., Rehman, G., Lee, Y.S., 2013. Curcumin in inflammatory diseases. BioFactors 39(1), 69-77.

Sheikhzadeh, S., Alizadeh, M., Rezazad, M., Hamishehkar, H., 2015. Nanoencapsulation of curcumin: By sodium caseinate and gum Arabic. Agro Food Industry Hi-Tech 26(6), 49-52.

Shojaei, M., Sahebkar, A., Khorvash, F., Fallahpour, S., Askari, G., Bagherniya, M., 2023. The effects of phytosomal curcumin supplementation on clinical symptoms, and inflammatory and oxidative stress biomarkers in patients with migraine: A protocol for a randomized double-blind placebo-controlled trial. Avicenna J Phytomed 13(1), 45-57.

Sikora, E., Scapagnini, G., Barbagallo, M., 2010. Curcumin, inflammation, ageing and age-related diseases. Immunity & Ageing 7, 1-4.

Singh, M., Singh, N., 2011. Curcumin counteracts the proliferative effect of estradiol and induces apoptosis in cervical cancer cells. Molecular and cellular biochemistry 347, 1-11.

Singh, P.K., Kotia, V., Ghosh, D., Mohite, G.M., Kumar, A., Maji, S.K., 2013. Curcumin modulates α-synuclein aggregation and toxicity. ACS chemical neuroscience 4(3), 393-407.

Small, G.W., Siddarth, P., Li, Z., Miller, K.J., Ercoli, L., Emerson, N.D., Martinez, J., Wong, K.-P., Liu, J., Merrill, D.A., Chen, S.T., Henning, S.M., Satyamurthy, N., Huang, S.-C., Heber, D., Barrio, J.R., 2018. Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial. The American Journal of Geriatric Psychiatry 26(3), 266-277.

Soleimani, V., Sahebkar, A., Hosseinzadeh, H., 2018. Turmeric (Curcuma longa) and its major constituent (curcumin) as nontoxic and safe substances. Phytotherapy Research 32(6), 985-995.

Spanoudaki, M., Papadopoulou, S.K., Antasouras, G., Papadopoulos, K.A., Psara, E., Vorvolakos, T., Solovos, E., Chrysafi, M., Psallas, M., Mentzelou, M., Ourda, D., Giaginis, C., 2024. Curcumin as a Multifunctional Spice Ingredient against Mental Disorders in Humans: Current Clinical Studies and Bioavailability Concerns, Life.

Subramani, P.A., Cheeran, V., Munuswamy-Ramanujam, G., Narala, V.R., 2018. Clinical trials of curcumin, camptothecin, astaxanthin and biochanin. Natural Prod. Clin. Trials 1(79), 10-2174.

Sugimoto, K., Ikeya, K., Bamba, S., Andoh, A., Yamasaki, H., Mitsuyama, K., Nasuno, M., Tanaka, H., Matsuura, A., Kato, M., Ishida, N., Tamura, S., Takano, R., Tani, S., Osawa, S., Nishihira, J., Hanai, H., 2020. Highly Bioavailable Curcumin Derivative Ameliorates Crohn's Disease Symptoms: A Randomized, Double-Blind, Multicenter Study. Journal of Crohn's and Colitis 14(12), 1693-1701.

Taworntawat, C., Neeser, K.J., Somrongthong, R., O'Brien, T.E., 2022. Measuring Success of Meditation, Curcumin Supplementation and Sunlight Exposure among Office Workers with Mild Depression. Indian Journal of Forensic Medicine & Toxicology 16(3), 112-121.

Teow, S.-Y., Liew, K., Ali, S.A., Khoo, A.S.-B., Peh, S.-C., 2016. Antibacterial action of curcumin against Staphylococcus aureus: a brief review. Journal of tropical medicine 2016.

Thomas, J.V., Smina, T.P., Khanna, A., Kunnumakkara, A.B., Maliakel, B., Mohanan, R., Krishnakumar, I.M., 2021. Influence of a low-dose supplementation of curcumagalactomannoside complex (CurQfen) in knee osteoarthritis: A randomized, open-labeled, active-controlled clinical trial. Phytotherapy Research 35(3), 1443-1455.

Thong-Ngam, D., Choochuai, S., Patumraj, S., Chayanupatkul, M., Klaikeaw, N., 2012. Curcumin prevents indomethacin-induced gastropathy in rats. World Journal of Gastroenterology: WJG 18(13), 1479.

Tsai, J.-R., Liu, P.-L., Chen, Y.-H., Chou, S.-H., Cheng, Y.-J., Hwang, J.-J., Chong, I.-W., 2015. Curcumin inhibits non-small cell lung cancer cells metastasis through the adiponectin/NF-κb/MMPs signaling pathway. PloS one 10(12), e0144462.

Uchio, R., Kawasaki, K., Okuda-Hanafusa, C., Saji, R., Muroyama, K., Murosaki, S., Yamamoto, Y., Hirose, Y., 2021. Curcuma longa extract improves serum inflammatory markers and mental health in healthy participants who are overweight: a randomized, double-blind, placebo-controlled trial. Nutrition journal 20, 1-14.

Urošević, M., Nikolić, L., Gajić, I., Nikolić, V., Dinić, A., Miljković, V., 2022. Curcumin: Biological Activities and Modern Pharmaceutical Forms, Antibiotics.

Vasanthkumar, T., Hanumanthappa, M., Lakshminarayana, R., 2019. Curcumin and capsaicin modulates LPS induced expression of COX-2, IL-6 and TGF-β in human peripheral blood mononuclear cells. Cytotechnology 71, 963-976.

Verma, R., Rao, L., Nagpal, D., Yadav, M., Kumar, M., Mittal, V., Kaushik, D., 2024. Exploring the prospective of curcumin-loaded nanomedicine in brain cancer therapy: an overview of recent updates and patented nanoformulations. Recent Patents on Nanotechnology 18(3), 278-294.

Wang, J., Zhou, X., Li, W., Deng, X., Deng, Y., Niu, X., 2016. Curcumin protects mice from Staphylococcus aureus pneumonia by interfering with the self-assembly process of α-hemolysin. Scientific reports 6(1), 28254.

Wang, R., Zhang, J.Y., Zhang, M., Zhai, M.G., Di, S.Y., Han, Q.H., Jia, Y.P., Sun, M., Liang, H.L., 2018. Curcumin attenuates IR-induced myocardial injury by activating SIRT3. European Review for Medical & Pharmacological Sciences 22(4).

Wang, Y., Liang, L., Zhao, Y., 2024. Curcumin Delivery Systems: How Far from Clinical Application in Tumor Therapy? Natural Product Communications 19(2), 1934578X231222102.

Wang, Z., Jones, G., Winzenberg, T., Cai, G., Laslett, L.L., Aitken, D., Hopper, I., Singh, A., Jones, R., Fripp, J., Ding, C., Antony, B., 2020. Effectiveness of Curcuma longa Extract for the Treatment of Symptoms and Effusion–Synovitis of Knee Osteoarthritis. Annals of Internal Medicine 173(11), 861-869.

Wu, J., Cai, Z., Wei, X., Chen, M., Ying, S., Shi, L., Xu, R.-A., He, F., Liang, G., Zhang, X., 2015. Anti-lung cancer activity of the curcumin analog JZ534 in vitro. BioMed research international 2015.

Yallapu, M.M., Jaggi, M., Chauhan, S.C., 2012. Curcumin nanoformulations: a future nanomedicine for cancer. Drug Discovery Today 17(1), 71-80.

Yanagisawa, D., Taguchi, H., Yamamoto, A., Shirai, N., Hirao, K., Tooyama, I., 2011. Curcuminoid binds to amyloid-β 1-42 oligomer and fibril. Journal of Alzheimer's Disease 24(s2), 33-42.

Yuan, J., Liu, R., Ma, Y., Zhang, Z., Xie, Z., 2018. Curcumin attenuates airway inflammation and airway remolding by inhibiting NF-κB signaling and COX-2 in cigarette smoke-induced COPD mice. Inflammation 41, 1804-1814.

Zare'i, M., Rabieepour, M., Ghareaghaji, R., Zarrin, R., Faghfouri, A.H., 2024. Nanocurcumin supplementation improves pulmonary function in severe COPD patients: A randomized, double blind, and placebo-controlled clinical trial. Phytotherapy Research 38(3), 1224-1234.

Zhang, J., Ma, Y., Li, W., 2021. Curcumin reduces inflammation in mice with the psoriasis model by inhibiting NLRP3 inflammatory bodies. Cellular and Molecular Biology 67(6), 48-54.

Zhang, S., Wang, J., Liu, L., Sun, X., Zhou, Y., Chen, S., Lu, Y., Cai, X., Hu, M., Yan, G., 2022. Efficacy and safety of curcumin in psoriasis: Preclinical and clinical evidence and possible mechanisms. Frontiers in Pharmacology 13, 903160.

Zheng, J., Cheng, J., Zheng, S., Feng, Q., Xiao, X., 2018. Curcumin, a polyphenolic curcuminoid with its protective effects and molecular mechanisms in diabetes and diabetic cardiomyopathy. Frontiers in pharmacology 9, 472.